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The Feasibility of Performing Cumulative Risk Assessments for Mixtures of Disinfection By-Products in Drinking Water

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The Feasibility of Performing Cumulative Risk Assessments for Mixtures of Disinfection By-Products in Drinking Water

by

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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 technical feasibility of conducting cumulative risk assessments for mixtures of disinfection by-products (DBPs) in drinking water. Cumulative risk assessment is defined here as an evaluation involving multiple chemicals via multiple routes of exposure over time. This project was conducted in response to 42 USC § 300 of the Safe Drinking Water Act Amendments of 1996, where 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 and Office of Research and Development jointly 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 current results regarding the characterization of DBP mixtures via multiple route exposures.

Part of this effort is based on a report prepared by Wilkes Technologies, Inc. and Anteon Corporation under GSA Contract Number GS-10F-0154K, administered by the EPA's National Exposure Research Laboratory in Las Vegas. An external review of this document was conducted in July 2002 through peer review contract No. 68-C-99-237 with Eastern Research Group, Inc. External reviewers were Drs. Gunther F. Craun, Hisham El-Masri, and John Little.

EPA RESEARCHERS

This research was sponsored by the U.S. Environmental Protection Agency's (EPA), National Center for Environmental Assessment - Cincinnati Division (NCEA-Cin) Cumulative Risk Team. NCEA-Cin scientists conducted portions of this research and are the 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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LIST OF ABBREVIATIONS

AUC	Area under the concentration-time curve
BCA	Bromochloroacetic acid
BCAN	Bromochloroacetonitrile
BDCM	Bromodichloromethane
CAA	Chloroacetic acid
$CHBr_3$	Bromoform
$CHCl_3$	Chloroform
CRPF	Cumulative relative potency factor
DBA	Dibromoacetic acid
DBAN	Dibromoacetonitrile
DBCM	Dibromochloromethane
DBP	Disinfection by-product
DCA	Dichloroacetic acid
DCAN	Dichloroacetonitrile
DEEM	Dose estimating exposure model
ERDEM	Exposure related dose estimating model
HAA	Haloacetic acid
HAN	Haloacetonitrile
HED	Human equivalent dose
ICED	Index chemical equivalent dose
ILSI	International Life Sciences Institute
MBA	Bromoacetic acid
MLE	Maximum likelihood estimate
MOA	Mode of action
NCEA	National Center for Environmental Assessment
NHAPS	National Human Activity Patterns Survey
OPP	Office of Pesticides Programs
PBPK	Physiologically-based pharmacokinetic
QSAR	Quantitative structure activity relationship
RECS	Residential Energy Consumption Survey
REUWS	Residential End Use Water Survey
RfD	Reference dose
RPF	Relative potency factor
SF	Slope factor
TCA	Trichloroacetic acid
TCAN	Trichloroacetonitrile
TCE	Trichloroethylene
TEM	Total exposure model
THM	Trihalomethane

KEY DEFINITIONS

Absorbed Dose - the amount of a substance crossing a specific barrier through uptake processes.[1]

Additivity - When the "effect" of the combination is estimated by the sum of the exposure levels or the effects of the individual chemicals. The terms "effect" and "sum" must be explicitly defined. Effect may refer to the measured response or the incidence of adversely affected animals. The sum may be a weighted sum (see "dose addition") or a conditional sum (see "response addition").[2]

Bioavailability - The state of being capable of being absorbed and available to interact with the metabolic processes of an organism. Bioavailability is typically a function of chemical properties, physical state of the material to which an organism is exposed, and the ability of the individual organism to physiologically take up the chemical.[1]

Chemical Classes - Groups of components that exhibit similar biologic activities, and that frequently occur together in environmental samples, usually because they are generated by the same commercial process. The composition of these mixtures is often well controlled, so that the mixture can be treated as a single chemical. Dibenzo-dioxins are an example.[2] (Note: this is slightly modified from the original version).

Chemical Mixture - Any set of multiple chemical substances that may or may not be identifiable, regardless of their sources, that may jointly contribute to toxicity in the target population. May also be referred to as a "whole mixture" or as the "mixture of concern."[2]

Complex Mixture - mixture containing so many components that any estimation of its toxicity based on its components' toxicities contains too much uncertainty and error to be useful. The chemical composition may vary over time or with different conditions under which the mixture is produced. Complex mixture components may be generated simultaneously as by-products from a single source or process, intentionally produced as a commercial product, or may coexist because of disposal practices. Risk assessments of complex mixtures are preferably based on toxicity and exposure data on the complete mixture. Gasoline is an example.[2]

Components - Single chemicals that make up a chemical mixture that may be further classified as systemic toxicants, carcinogens, or both.[2]

Dose Additivity - When the effect of the combination is the effect expected from the equivalent dose of an index chemical. The equivalent dose is the sum of component doses scaled by their potency relative to the index chemical.[2]

Dose - The amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism.[1]

Dose-Response Assessment - A determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response. Response can be expressed as measured or observed incidence, percent response in groups of subjects (or populations), or as the probability of occurrence within a population.[3]

Dose-Response Relationship - The relationship between a quantified exposure (dose), and the proportion of subjects demonstrating specific, biological changes (response).[3] U.S. EPA's draft 1996 Cancer Guidelines further state: "Whether animal experiments or epidemiologic studies are the sources of data, questions need to be addressed in arriving at an appropriate measure of dose for the anticipated environmental exposure. Among these are:

- whether the dose is expressed as an environmental concentration, applied dose, or delivered dose to the target organ,
- whether the dose is expressed in terms of a parent compound, one or more metabolites, or both,
- the impact of dose patterns and timing where significant,
- conversion from animal to human doses, where animal data are used, and
- the conversion metric between routes of exposure where necessary and appropriate."

Effective Dose (ED_{10}) - The dose corresponding to a 10% increase in an adverse effect, relative to the control response.[3]

Exposure - Contact made between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut).[3] The NAS presents a similar definition for exposure defining it as "An event that occurs when there is contact at a boundary between a human and the environment with a contaminant of a specific concentration for an interval of time; the units of exposure are concentration multiplied by time." [4] These definitions are also closely related to the term "Potential Dose" which is used in this document and defined by NAS to imply "An exposure value multiplied by a contact rate (e.g., rates of inhalation, ingestion, or absorption through the skin) and assumes total absorption of the contaminant."

Exposure Assessment - An identification and evaluation of the human population exposed to a toxic agent, describing its composition and size, as well as the type, magnitude, frequency, route and duration of exposure.[3]

Extrapolation, Low Dose - An estimate of the response at a point below the range of the experimental data, generally through the use of a mathematical model.[3]

Human Equivalent Concentration (HEC) or Dose (HED) - The human concentration (for inhalation exposure) or dose (for other routes of exposure) of an agent that is believed to induce the same magnitude of toxic effect as the experimental animal species concentration or dose. This adjustment may incorporate toxicokinetic

information on the particular agent, if available, or use a default procedure, such as assuming that daily oral doses experienced for a lifetime are proportional to body weight raised to the 0.75 power.[3]

Index Chemical - The chemical selected as the basis for standardization of toxicity of components in a mixture. The index chemical must have a clearly defined dose-response relationship.[2]

Internal Dose - A more general term denoting the amount absorbed without regard to absorption process.[1]

Independence of Action - Mixture components that cause different kinds of toxicity, or effects in different target organs; the risk assessor may then combine the probabilities of toxic effects for the individual components.[2]

Model - A mathematical function with parameters that can be adjusted so the function closely describes a set of empirical data. A mechanistic model usually reflects observed or hypothesized biological or physical mechanisms, and has model parameters with real world interpretation. In contrast, statistical or empirical models selected for particular numerical properties are fitted to data; model parameters may or may not have real world interpretation. When data quality is otherwise equivalent, extrapolation from mechanistic models (e.g., biologically based dose-response models) often carries higher confidence than extrapolation using empirical models (e.g., logistic model).[3]

Physiologically Based Pharmacokinetic (PBPK) Model - Physiologically based compartmental model used to characterize pharmacokinetic behavior of a chemical. Available data on blood flow rates, and metabolic and other processes which the chemical undergoes within each compartment are used to construct a mass-balance framework for the PBPK model.[3]

Point of Departure - The dose-response point that marks the beginning of a low-dose extrapolation. This point is most often the upper bound on an observed incidence or on an estimated incidence from a dose-response model.[3]

Potential Dose - An exposure value multiplied by a contact rate (e.g., rates of inhalation, ingestion, or absorption through the skin) and assumes total absorption of the contaminant.[4]

Response Additivity - When the response (rate, incidence, risk, or probability) of effects from the combination is equal to the conditional sum of component responses as defined by the formula for the sum of independent event probabilities.[2]

Similar Components - Single chemicals that cause the same biologic activity or are expected to cause a type of biologic activity based on chemical structure. Evidence of similarity may include parallel log-probit dose-response curves and same mechanism of action or toxic endpoint. These components are expected to have comparable characteristics for fate, transport, physiologic processes, and toxicity.[2]

Similar Mixtures - Mixtures that are slightly different, but are expected to have comparable characteristics for fate, transport, physiologic processes, and toxicity. These mixtures may have the same components but in slightly different proportions, or have most components in nearly the same proportions with only a few different (more or fewer) components. Similar mixtures cause the same biologic activity or are expected to cause the same type of biologic activity due to chemical composition. Similar mixtures act by the same mechanism of action or affect the same toxic endpoint. Diesel exhausts from different engines are an example.[2]

Simple Mixture - A mixture containing two or more identifiable components, but few enough that the mixture toxicity can be adequately characterized by a combination of the components' toxicities and the components' interactions.[2]

Target Organ - The biological organ(s) most adversely effected by exposure to a chemical substance.[3]

Uptake - The process by which a substance crosses an absorption barrier and is absorbed into the body.[1]

Sources

[1]U.S. EPA. 1992. Guidelines for Exposure Assessment; Notice. Federal Register. 57(104):22888-22938.

[2]U.S. EPA. 2000. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC. EPA/630/R-00/002.

[2]U.S. EPA. 2002. Integrated Risk Information System. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris

[4]NRC (National Research Council). 1991. Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities. National Academy of Sciences, Washington, DC.

EXECUTIVE SUMMARY

Assessment of potential human health risk(s) from disinfection by-products (DBPs) in drinking water is needed because of widespread oral, dermal and inhalation exposures to this complex mixture and because positive data from both epidemiologic and toxicologic studies of DBPs raise concern for human health (U.S. EPA, 2000a). Although these data suggest human health effects are possible, human exposures are complex, making the interpretation of positive results difficult. Occurrence information shows that the mix of DBPs may vary considerably with geographic location and water treatment process. Furthermore, for the more volatile DBPs, inhalation exposures may be greater than ingestion; for highly lipophilic DBPs, dermal exposures may also be important. Information from toxicologic studies has focused primarily on single DBPs administered orally at doses far above finished drinking water concentrations. *Information from positive epidemiologic studies suggests that exposures to different* mixtures of DBPs in various geographic locations may pose quite different health risks. Thus, to develop a regulatory and risk reduction strategy, there is a need to consider the health risks associated with DBP mixtures and the various exposures from contact with finished drinking water.

Several risk assessment issues are of concern to managers responsible for ensuring safe drinking water for the public. The first issue is to evaluate the association between DBP mixture exposures and human health outcomes and thereby establish whether or not human health risks are a significant concern. Because the evaluations of this association are inconclusive and human health effects from DBP exposures are possible, some drinking water regulations have been promulgated and others posed with the goal of controlling levels of DBPs in the drinking water (e.g., U.S. EPA, 1979,

1994a, 1998b). As rules go into effect, alternative drinking water treatment technologies are developed to meet these new standards. Thus, a second important issue is to choose among treatment options by evaluating whether changes in exposure impact health risk(s) across various drinking water treatment systems and source waters. A third issue for evaluation of DBP mixtures is that approximately 50% of the DBP mass consists of unidentified total organic halide material, the toxicity of which is largely unknown (Weinberg, 1999). By comparing whole mixture toxicity data with data on the mixture components, the toxicity of the unknown fraction of the DBP complex mixture can be evaluated.

U.S. EPA's National Center for Environmental Assessment - Cincinnati has conducted research for assessing DBP health risks using a cumulative risk assessment approach, defined here as multiple chemical exposures via multiple exposure routes over time (U.S. EPA, 2000a). The evaluation of human health risks as a cumulative risk assessment problem requires consideration of the following factors:

- Exposure to multiple chemicals at low environmental concentrations,
- Knowledge of toxic mode of action (MOA) and judgment regarding similarity of MOA among DBPs, and extrapolation of animal bioassay results from high to low doses
- Dermal, oral and inhalation routes of exposure,
- Measures of internal absorbed dose,
- Human activity patterns that affect the types of water use and the amount of contact time with the drinking water,
- Physicochemical properties of the DBPs,
- Physical properties of the indoor environment, and
- Sensitive subpopulations.

Incorporating many of these factors, research has been conducted to develop human exposure estimates for individual DBPs from multiple exposure routes; whole body and organ-specific internal doses are estimated for all three exposure routes for each individual DBP. This report describes how these data can be used to assess DBP risks using a newly developed risk assessment method, the Cumulative Relative Potency Factors (CRPF) approach.

In this document two different mathematical models are employed to evaluate human exposures. An *Exposure Assessment Model* generates estimates of exposures at the body boundaries through human contact with the media, influenced by human activity patterns. A *Physiologically-Based Pharmacokinetic (PBPK) Model* predicts doses of DBPs experienced by relevant organs or target tissues. Three different measures of dose are presented with respect to possible application of the CRPF approach (see Figure E-1):

1) Exposures. The amount of a chemical available at the exchange boundaries (e.g., skin, lungs, intestinal tract).

2) *Total Absorbed Doses (e.g., blood concentrations).* The amount of a contaminant that is absorbed from all exposure routes without regard to specific absorption processes.

3) *Organ or Tissue Doses.* The amount of a contaminant in an organ or tissue, estimated from all exposure routes based on pharmacokinetic information.

The actual choice of dose metric, as well as the temporal element of each dose measure, is influenced by available dose-response data. Oral dose-response animal data exist for most of the major DBPs identified in the drinking water for cancer,

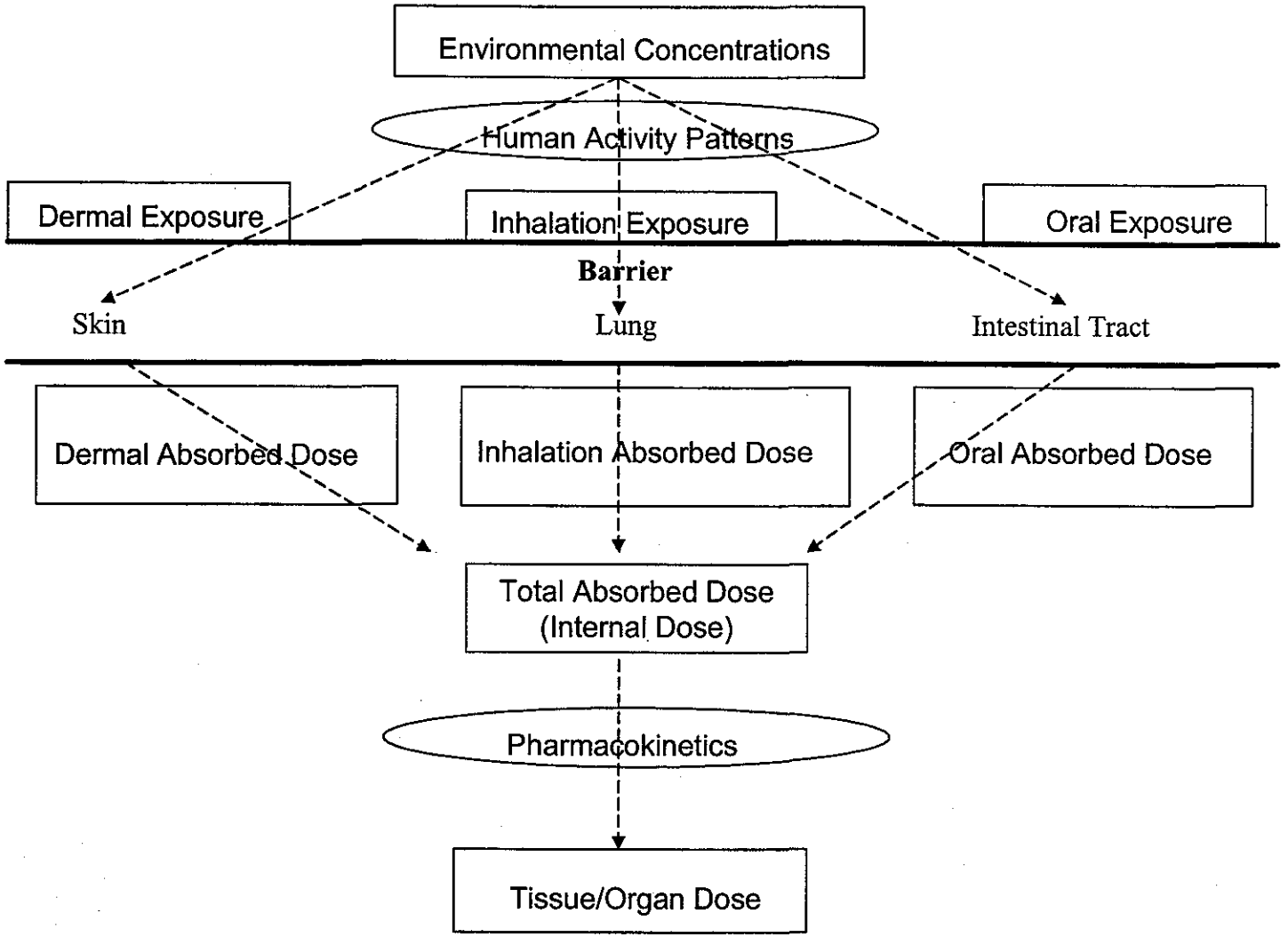

FIGURE E-1

Dose Metrics for Environmental Contaminants

developmental and reproductive effects, and a number of systemic effects. Dermal and inhalation dose-response animal data are relatively sparse. Thus, the development of the CRPF approach that can be based primarily on the use of oral dose-response information is a plausible research direction.

The goal of this document is to examine the feasibility of conducting a cumulative risk assessment for drinking water DBP mixtures by combining exposure modeling results with the CRPF risk assessment approach. Discussions within the document include: presentation of the CRPF approach; exposure modeling results that provide multiple route human exposure estimates for 13 DBPs; explanation of how these newly developed exposure estimates may be used in the CRPF approach; and details regarding the uncertainties and data gaps that define future research needs and feasibility of completing a cumulative risk assessment for DBP mixtures.

THEORY OF THE CRPF APPROACH

The CRPF approach is a new method that combines the principles of dose addition and response addition into one method to assess mixtures risk for multiple route exposures (U.S. EPA, 2000a). (Using two subclasses, Figure E-2 illustrates how the CRPF approach estimates risk from exposure to the mixture.) The CRPF approach groups DBPs with a common MOA into subclasses. The MOA differ across the subclasses, but the toxicological endpoint (or outcome) is the same. For each subclass, an index chemical is selected to be representative of that subclass, and *Index Chemical Equivalent Doses (ICED)* are calculated using the Relative Potency Factor (RPF) approach (U.S. EPA, 2000b). The ICED is an important concept for the CRPF method that is employed at two levels:

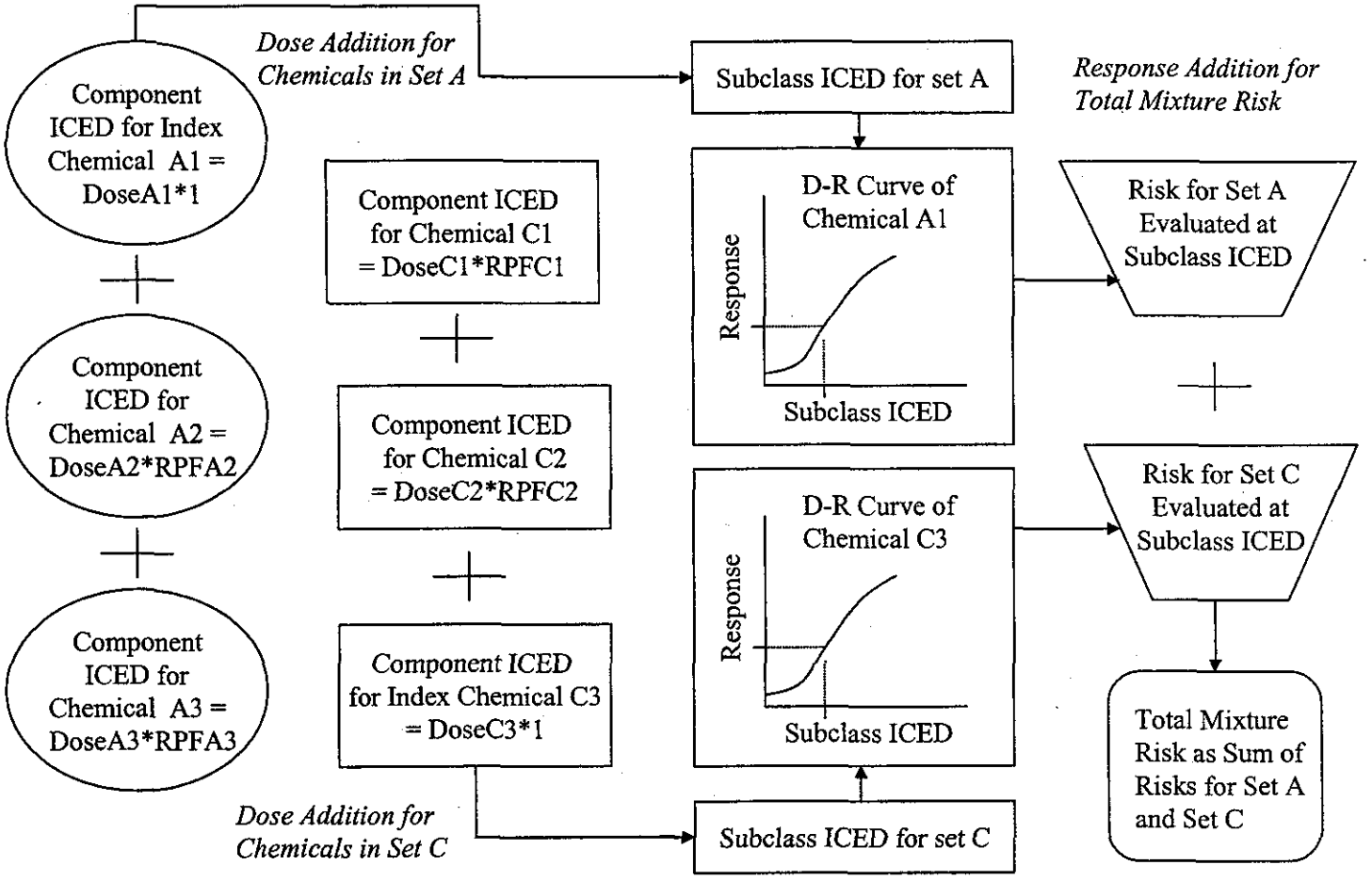

FIGURE E-2

CRPF Approach : Integration of Dose Addition and Response Addition to Estimate Mixture Risk

1) **Component ICED** - refers to the ICED for an individual chemical within a subclass.

2) **Subclass ICED** - refers to the ICED for all chemicals within the subclass, computed by summing their Component ICEDs.

The RPF approach has been proposed for characterizing health risks associated with mixtures of chemical compounds that are toxicologically similar (U.S. EPA, 2000b). To develop an RPF-based risk estimate for a class of chemicals, good toxicological data are needed for at least for one component of the mixture (referred to as the index chemical). Scientific judgment and analysis of available data are used to assess the relative toxicity of the other individual components in the mixture. The exposure levels of the components in the mixture are scaled by their toxicities relative to that of the index chemical resulting in Component ICEDs which are then summed to generate a Subclass ICED. The risk posed by the subclass can be estimated using the dose-response curve of the index chemical. For each subclass, the RPF approach uses dose-addition to estimate risk for the toxicologic outcome common across the subclasses. However, these subclass risks are independent of each other (i.e., the toxicity caused by one subclass does not influence the toxicity caused by the other subclass because their respective MOA are different), thus meeting the criteria required to apply response addition; the subclass risk estimates are added to yield a risk estimate for the total DBP mixture.

EXPOSURE MODELING

A comprehensive exposure modeling effort was implemented to estimate population-based exposures and absorbed doses for 15 DBPs, incorporating parameters for chemical volatilization, human activity patterns, water use behaviors, ingestion characteristics, building characteristics, physiological measurements, and

chemical concentrations in the water supply. The DBPs targeted for evaluation are listed in Table E-1. In the final modeling exercise, data were insufficient to estimate chemical properties for BCAN and Bromate; thus, exposure estimates were not modeled for these two DBPs. Estimates were made for a three person family based on data from women and men of reproductive age (ages 15-45) and children (age 6).

The exposure assessment model for this effort was the Total Exposure Model (TEM) developed by Wilkes Technologies (Wilkes, 1998). The PBPK Model used was the Exposure Related Dose Estimating Model (ERDEM). This model, formerly known as DEEM (Dose Estimating Exposure Model), was developed by Anteon Corporation in collaboration with the Human Exposure Research Branch of EPA's National Environmental Research Laboratory in Las Vegas. Combining these two models into one analysis provided the ability to evaluate target tissue dose (estimated using ERDEM) as a function of a variety of behaviors, environmental factors, and other exposure related parameters (estimated by TEM). Figures E-3, E-4 and E-5 illustrate the flow of information in and out of the two models. Of particular note is that TEM is used to develop 24-hour exposure time histories for the demographic groups of interest; this output data set becomes input data to the PBPK model. Also, both models are capable of producing estimates of total absorbed dose, although the ERDEM model does so using more specific physiological functions than TEM. Only ERDEM produces organ and tissue doses. The research report showing all details of the DBP analysis (Appendix 1) includes the following information:

- Detailed Information on the model parameter inputs for both TEM and ERDEM

TABLE E-1

List of Chemicals for Exposure and Internal Dose Assessment

DBP Subclass	Chemical Name	CAS Number
Trihalomethanes	Chloroform ($CHCl_3$)	67-66-3
(THMs)	Bromodichloromethane (BDCM)	75-27-4
	Dibromochloromethane (DBCM)	124-48-1
	Bromoform ($CHBr_3$)	75-25-2
Haloacetic Acids	Chloroacetic acid (CAA)	79-11-8
(HAAs)	Dichloroacetic acid (DCA)	79-43-6
	Trichloroacetic acid (TCA)	76-03-9
	Bromoacetic acid (MBA)	79-08-3
	Dibromoacetic acid (DBA)	631-64-1
	Bromochloroacetic acid (BCA)	5589-96-8
Haloacetonitriles (HANs)	Dichloroacetonitrile (DCAN)	3018-12-0
	Trichloroacetonitrile (TCAN)	545-06-2
	Bromochloroacetonitrile (BCAN)	83463-62-1
	Dibromoacetonitrile (DBAN)	3252-43-5
Miscellaneous	Bromate	15541-45-4

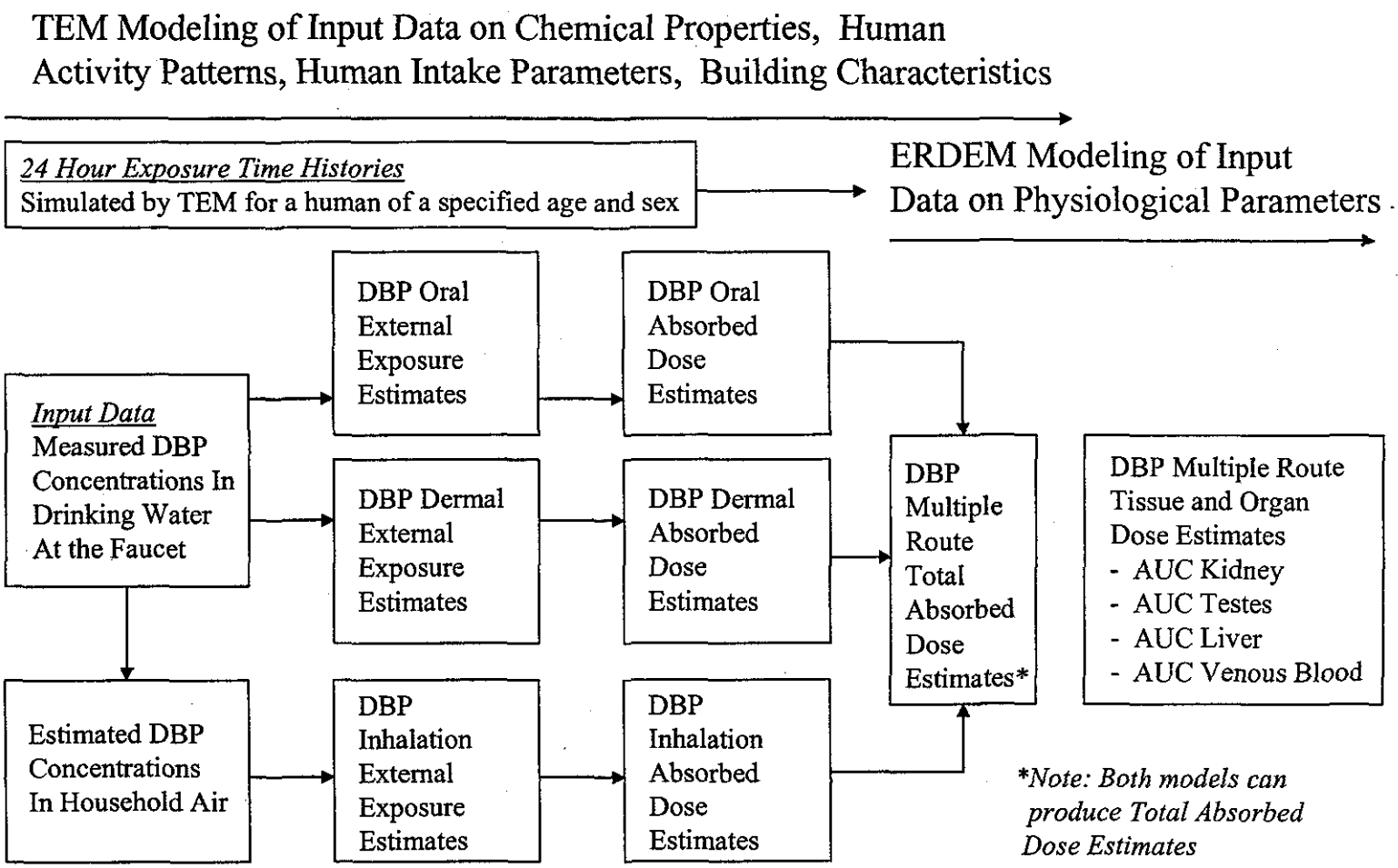

FIGURE E-3

Linking TEM Exposure Assessment Modeling with ERDEM PBPK Modeling

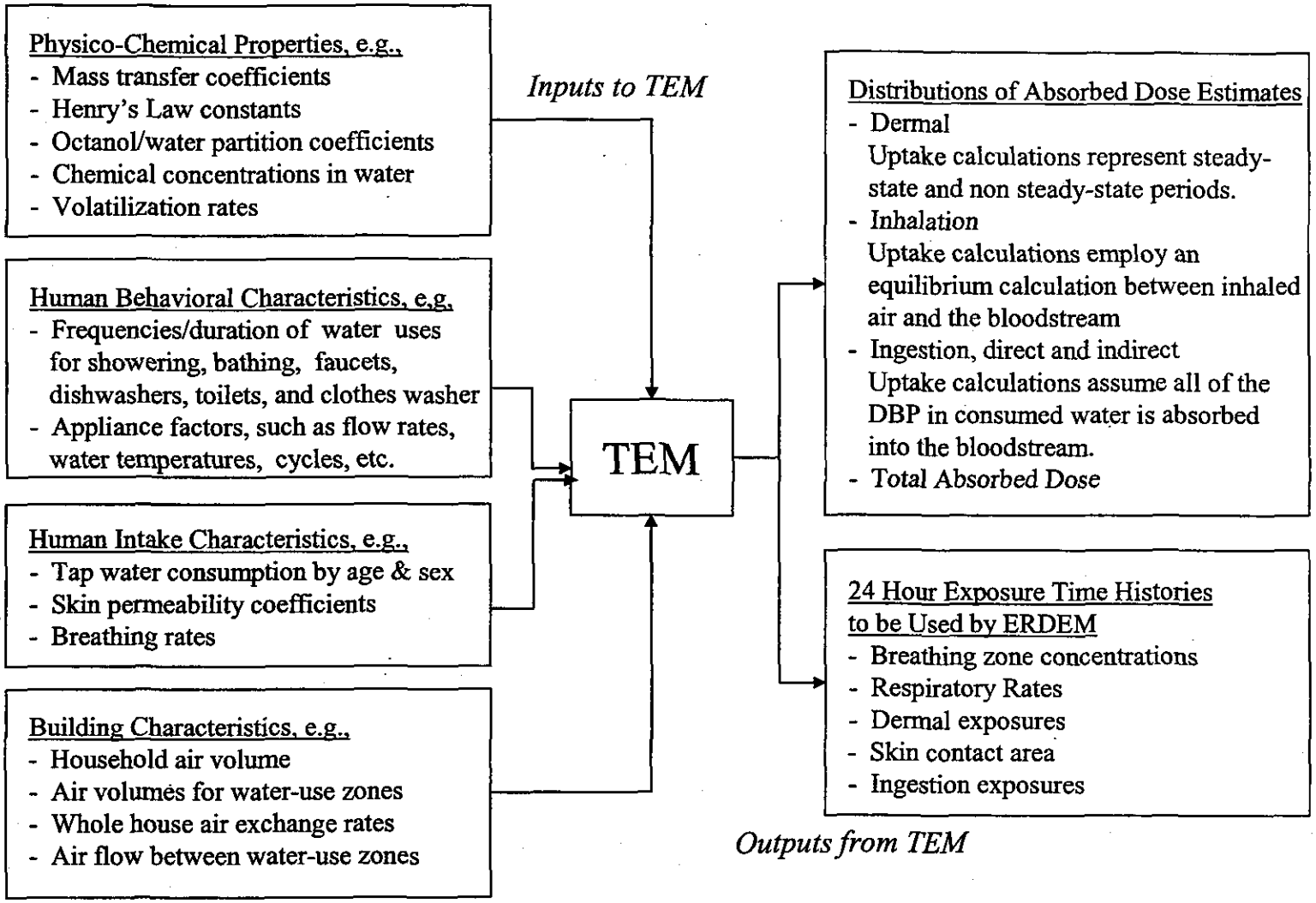

FIGURE E-4

TEM Modeling of Indoor Air Concentrations, Exposure and Absorbed Dose Estimates

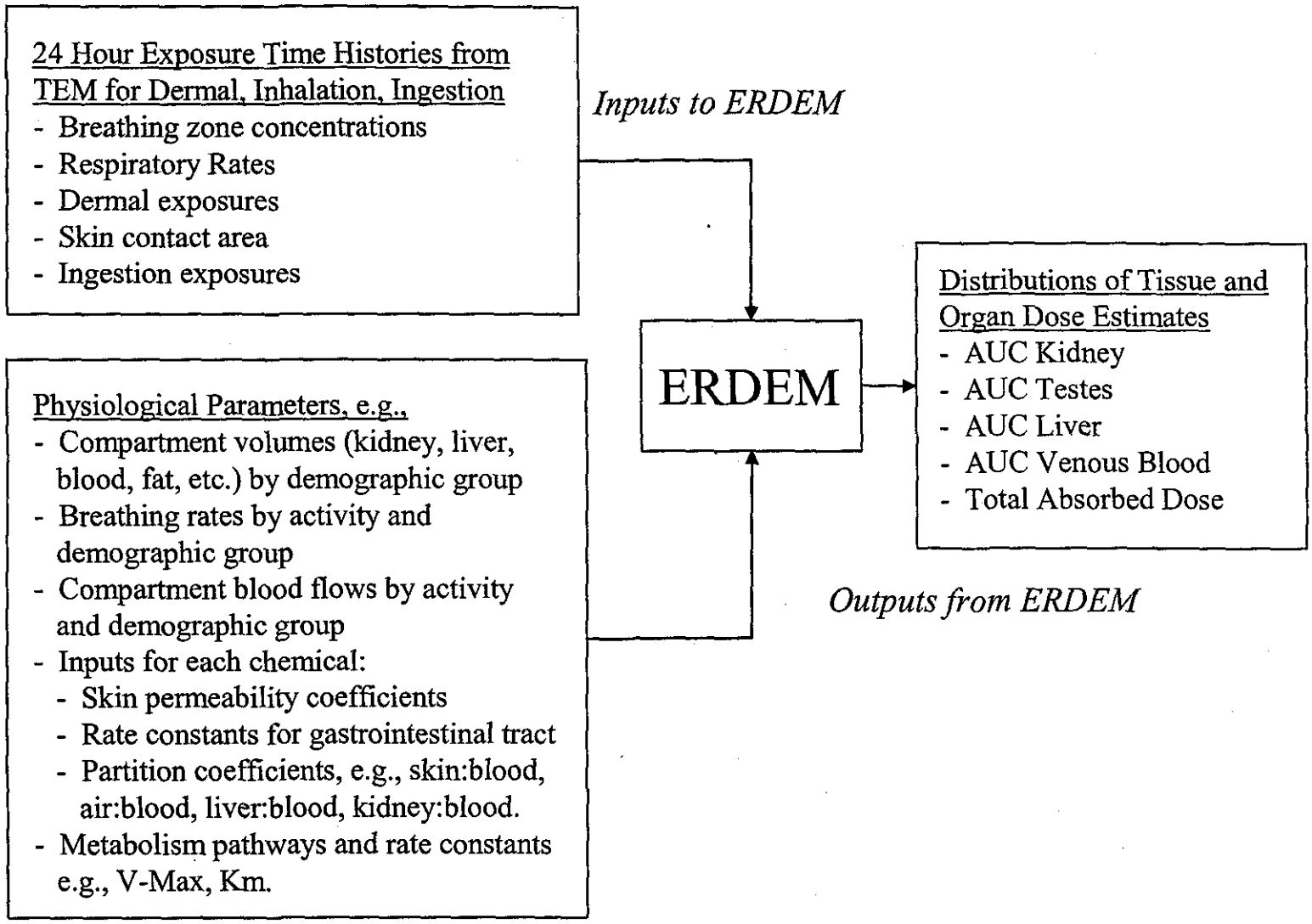

FIGURE E-5

ERDEM Modeling of Tissue and Organ Level Absorbed Dose Estimates

- Estimates of absorbed dose for oral, dermal, and inhalation routes of exposure and total absorbed dose for 13 (of 15) DBPs using TEM
- Estimates of total absorbed dose and tissue doses for the kidney, liver, venous blood and testes/ovaries for 4 (of 15) DBPs using the PBPK model, ERDEM.
- A sensitivity analysis of the combined models for a selected set of parameters.

Simulation results of the TEM modeling include distributions of absorbed dose estimates for the dermal, ingestion (direct and indirect), and inhalation exposure routes and total absorbed dose. In Appendix 1, a table is presented for each of the 13 DBPs, containing the absorbed doses for a 24-hour period as a function of route, population group, and percentile of the population. Table E-2 shows an example of the absorbed dose estimates for BDCM. Table E-3 shows the 50th percentile absorbed dose estimates for all 13 DBPs. In addition to these tables for the 13 DBPs, Appendix 1 provides plots of their respective cumulative distribution functions and histograms for the dose estimates (see Section 4.2.2., Appendix 1).

The results of the uptake modeling provide information for comparing and contrasting uptake as a function of the chemical, the population group and behavior, and the route of exposure. General conclusions about the importance of each route for a given chemical can be made by comparing the chemical uptake across each route. However, specific conclusions can be problematic due to large uncertainties in some of the model parameters, most notably the dermal permeability coefficient. A large range of uncertainty exists in the dermal estimates that make it difficult to compare the dermal route to the inhalation and ingestion routes. This is because the skin permeability rates (Section 3.6.5. of Appendix 1) are generally poorly quantified. As a result, the uncertainty in this parameter is quite large. The impact of this uncertainty is examined

TABLE E-2

TEM Output for BDCM: Absorbed Dose Estimates (mg) for a 24-Hour Exposure

Percentile	Total[a]	Dermal	Ingestion			Inhalation
			Direct	Indirect	Total[a]	
Female, Age 15-45						
1	7.20E-03	0[b]	1.03E-03	5.64E-04	2.49E-03	1.12E-04
5	1.35E-02	0[b]	1.83E-03	7.64E-04	3.51E-03	2.66E-03
10	1.92E-02	1.54E-04	2.46E-03	8.86E-04	4.14E-03	8.78E-03
25	3.96E-02	3.71E-04	4.19E-03	1.23E-03	6.05E-03	2.35E-02
50	8.00E-02	2.70E-03	7.73E-03	1.71E-03	9.72E-03	6.12E-02
75	1.66E-01	5.21E-03	1.51E-02	2.37E-03	1.69E-02	1.42E-01
90	2.79E-01	8.67E-03	2.76E-02	3.18E-03	2.95E-02	2.64E-01
95	4.13E-01	1.21E-02	3.50E-02	3.61E-03	3.70E-02	3.88E-01
99	2.41E+00	1.87E-02	8.49E-02	5.05E-03	8.60E-02	2.38E+00
Male, Age 15-45						
1	6.25E-03	0[b]	7.64E-04	2.79E-04	2.18E-03	1.01E-04
5	1.27E-02	0[b]	1.55E-03	4.95E-04	3.42E-03	2.64E-03
10	1.97E-02	0[b]	2.14E-03	6.49E-04	4.35E-03	6.07E-03
25	3.88E-02	3.09E-04	4.05E-03	1.05E-03	6.52E-03	1.89E-02
50	8.43E-02	2.90E-03	7.98E-03	1.85E-03	1.11E-02	6.05E-02
75	1.64E-01	5.57E-03	1.55E-02	3.37E-03	1.86E-02	1.46E-01
90	2.95E-01	8.73E-03	2.91E-02	5.67E-03	3.19E-02	2.74E-01
95	4.36E-01	1.13E-02	4.31E-02	7.93E-03	4.68E-02	4.23E-01
99	1.93E+00	1.84E-02	7.14E-02	1.31E-02	7.28E-02	1.91E+00

TABLE E-2 cont.						
Percentile	Total[a]	Dermal	Ingestion			Inhalation
			Direct	Indirect	Total[a]	
Child, Age 6						
1	3.51E-03	0[b]	4.66E-04	1.13E-04	1.10E-03	5.71E-05
5	6.98E-03	0[b]	8.66E-04	2.26E-04	1.73E-03	1.13E-03
10	1.00E-02	0[b]	1.17E-03	3.28E-04	2.27E-03	2.98E-03
25	1.95E-02	9.26E-05	2.07E-03	6.03E-04	3.50E-03	1.07E-02
50	4.38E-02	2.66E-04	4.02E-03	1.07E-03	6.03E-03	3.36E-02
75	9.48E-02	2.67E-03	7.68E-03	2.17E-03	9.89E-03	8.56E-02
90	1.81E-01	4.48E-03	1.32E-02	3.80E-03	1.53E-02	1.73E-01
95	2.29E-01	5.63E-03	1.75E-02	5.37E-03	1.88E-02	2.19E-01
99	3.58E-01	8.03E-03	3.25E-02	8.16E-03	3.54E-02	3.51E-01

[a]Note that total absorbed dose (by ingestion or by all three routes) is not equal to the sum of the doses in each row. This occurs because each simulation provides a new data point to each of the dose estimates represented in the columns; the percentiles are then produced for each dose estimate (column) independently of each other. Furthermore, because the total absorbed dose is the sum of independent random variables, its variance is less than what is obtained when specific percentiles are summed.

[b]The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

TABLE E-3

50th Percentile 24-Hour Absorbed Dose Estimates (mg) Output by TEM

Chemical	Total*	Dermal	Ingestion			Inhalation
			Direct	Indirect	Total*	
Female, Age 15-45						
$CHCl_3$	3.00E-01	2.51E-02	2.09E-02	3.76E-03	2.52E-02	2.19E-01
BDCM	8.00E-02	2.70E-03	7.73E-03	1.71E-03	9.72E-03	6.12E-02
DBCM	5.12E-02	2.47E-03	5.33E-03	1.40E-03	7.03E-03	3.73E-02
$CHBr_3$	2.65E-02	1.60E-03	2.88E-03	3.00E-03	6.55E-03	1.63E-02
MCA	4.45E-01	1.16E-04	1.91E-03	1.99E-03	4.34E-03	1.15E-06
DCA	2.73E-02	1.05E-05	1.20E-02	1.25E-02	2.72E-02	5.46E-06
TCA	2.90E-02	1.71E-05	1.27E-02	1.32E-02	2.89E-02	9.27E-06
MBA	8.73E-03	2.32E-04	3.74E-03	3.89E-03	8.51E-03	1.79E-06
DBA	3.76E-03	1.06E-04	1.61E-03	1.67E-03	3.66E-03	4.33E-07
BCA	7.95E-03	2.18E-04	3.40E-03	3.54E-03	7.74E-03	2.09E-06
DCAN	1.83E-03	4.08E-05	7.48E-04	7.79E-04	1.70E-03	4.39E-05
TCAN	1.26E-04	4.18E-06	5.23E-05	5.45E-05	1.19E-04	9.73E-07
DBAN	7.09E-04	1.79E-05	3.03E-04	3.15E-04	6.89E-04	1.88E-06
Male, Age 15-45						
$CHCl_3$	3.02E-01	2.62E-02	2.16E-02	4.00E-03	2.84E-02	2.13E-01
BDCM	8.43E-02	2.90E-03	7.98E-03	1.85E-03	1.11E-02	6.05E-02
DBCM	5.49E-02	2.64E-03	5.50E-03	1.52E-03	8.10E-03	3.79E-02
$CHBr_3$	3.00E-02	1.70E-03	2.97E-03	3.24E-03	7.55E-03	1.68E-02
MCA	5.09E-03	1.25E-04	1.97E-03	2.14E-03	5.00E-03	1.33E-06
DCA	3.14E-02	1.16E-05	1.23E-02	1.35E-02	3.14E-02	6.20E-06
TCA	3.34E-02	1.88E-05	1.31E-02	1.43E-02	3.33E-02	1.09E-05
MBA	9.97E-03	2.50E-04	3.86E-03	4.20E-03	9.81E-03	1.99E-06
DBA	4.29E-03	1.14E-04	1.66E-03	1.81E-03	4.22E-03	5.04E-07

TABLE E-3 cont.						
Chemical	Total*	Dermal	Ingestion			Inhalation
			Direct	Indirect	Total*	
Male, Age 15-45						
BCA	9.08E-03	2.35E-04	3.51E-03	3.82E-03	8.93E-03	2.35E-06
DCAN	2.09E-03	4.46E-05	7.72E-04	8.41E-04	1.96E-03	4.26E-05
TCAN	1.45E-04	4.47E-06	5.40E-05	5.88E-05	1.37E-04	1.00E-06
DBAN	8.13E-04	1.94E-05	3.12E-04	3.40E-04	7.94E-04	1.99E-06
Child, Age 6						
$CHCl_3$	1.56E-01	1.87E-03	1.09E-02	9.19E-04	1.26E-02	1.19E-01
BDCM	4.38E-02	2.66E-04	4.02E-03	1.07E-03	6.03E-03	3.36E-02
DBCM	2.91E-02	2.59E-04	2.77E-03	7.72E-04	4.18E-03	2.21E-02
$CHBr_3$	1.34E-02	1.73E-04	1.50E-03	7.42E-03	2.70E-03	8.77E-03
MCA	1.84E-03	1.35E-05	9.92E-04	4.92E-04	1.79E-03	6.29E-07
DCA	1.12E-02	1.26E-06	6.22E-03	3.08E-03	1.12E-02	3.01E-06
TCA	1.19E-02	2.06E-06	6.61E-03	3.28E-03	1.19E-02	5.22E-06
MBA	3.61E-03	2.70E-05	1.95E-03	9.64E-04	3.50E-03	1.01E-06
DBA	1.56E-03	1.22E-05	8.36E-04	4.14E-04	1.51E-03	2.37E-07
BCA	3.29E-03	2.53E-05	1.77E-03	8.77E-04	3.19E-03	1.26E-06
DCAN	7.72E-04	4.84E-06	3.89E-04	1.93E-04	7.01E-04	2.57E-05
TCAN	5.20E-05	4.76E-07	2.72E-05	1.35E-05	4.91E-05	5.57E-07
DBAN	2.94E-04	2.10E-06	1.58E-04	7.81E-05	2.84E-04	1.07E-06

[a]Note that total absorbed dose (by ingestion or by all three routes) is not equal to the sum of the doses in each row. This occurs because each simulation provides a new data point to each of the dose estimates represented in the columns; the percentiles are then produced for each dose estimate (column) independently of each other. Furthermore, because the total absorbed dose is the sum of independent random variables, its variance is less than what is obtained when specific percentiles are summed.

by calculating the dermal uptake at the minimum and maximum values of the identified range (Section 4.2.3. of Appendix 1).

Exposure patterns simulated by TEM were used as input values upon which ERDEM based the exposure scenarios for simulations of tissue doses. The estimation of tissue doses was accomplished by programming and operating a previously validated PBPK model for each chemical, BDCM, $CHCl_3$, DCA and TCA. These models were standardized, so that flows and tissue volumes were consistent across the different chemicals. ERDEM was constructed to simulate tissue doses of parent chemical in several different tissues, identified as potential target organs of toxicity. ERDEM estimated exposure metrics as area under the concentration-time curve (AUC) for liver, kidney, venous blood, ovaries and testes averaged over 2 days. This differs from the TEM modeling, in which results are presented as AUC averaged over a single 24-hour exposure period. Table E-4 shows the ERDEM results for BDCM for three different age-dependent models: the adult male, the adult female and the 6-year-old male child.

APPLICATION OF THE CRPF APPROACH

Because animal dose-response data are typically available for only a single exposure route (usually oral), practical implementation of the CRPF approach for multiple exposure routes requires route extrapolations. Few inhalation or dermal toxicity data are available for the DBPs. Thus, although the CRPF analysis may be conducted using separate exposures for each route, it is more logical to develop the approach so it can be implemented using dose-response information on the oral route only. (PBPK models may also be useful in constructing physiologically-based extrapolations across different exposure routes.) The text that follows in this section focuses on the use of

TABLE E-4

48-Hour PBPK Modeled Absorbed Doses for BDCM for the Adult Male, Adult Female and Male Child

Demographic Group	Average	Standard Deviation	Skewness	Max	Min	5th	10th	50th	90th	95th
Adult Male										
AUC Kidney (mg/L*hr)	0.00230	0.00681	9.98	0.0919	8.56E-06	6.72E-05	9.58E-05	0.000884	0.00386	0.00643
AUC Testes (mg/L*hr)	0.00450	0.0134	9.98	0.180	1.68E-05	0.000132	0.000188	0.00173	0.00757	0.0126
Absorbed Dose (mg)	0.455	1.31	10.0	17.7	0.00730	0.0201	0.0340	0.184	0.732	1.25
AUC Liver (mg/L*hr)	0.00043	0.00119	9.95	0.0161	1.11E-05	2.73E-05	4.26E-05	0.000188	0.000714	0.00114
AUC Venous Blood	0.00176	0.00517	9.96	0.0698	9.04E-06	5.52E-05	8.11E-05	0.000682	0.00294	0.00490
Adult Female										
AUC Kidney (mg/L*hr)	0.00269	0.00721	6.23	0.0640	1.02E-05	5.36E-05	0.00013	0.00103	0.00424	0.00723
AUC Ovaries (mg/L*hr)	0.00372	0.00995	6.22	0.0883	1.4E-05	7.39E-05	0.00018	0.00142	0.00584	0.00994
Absorbed Dose (mg)	0.457	1.20	6.24	10.6	0.00793	0.0206	0.0328	0.177	0.703	1.22
AUC Liver (mg/L*hr)	0.000525	0.00133	6.23	0.0118	1.51E-05	3.33E-05	4.41E-05	0.000217	0.000794	0.00135
AUC Venous Blood	0.00203	0.00540	6.22	0.0479	1.11E-05	4.85E-05	0.000107	0.000778	0.00319	0.00539
Demographic Group	Average	Standard	Skewness	Max	Min	5th	10th	50th	90th	95th
Child Male										
AUC Kidney (mg/L*hr)	0.00132	0.00149	2.18	0.00899	3.86E-06	4.85E-05	0.000142	0.000815	0.00342	0.00440
AUC Testes (mg/L*hr)	0.00258	0.00291	2.18	0.0176	7.57E-06	9.52E-05	0.000279	0.00160	0.00670	0.00864
Absorbed Dose (mg)	0.175	0.190	2.19	1.16	0.00174	0.0126	0.0232	0.113	0.437	0.567
AUC Liver (mg/L*hr)	0.000377	0.000392	2.20	0.00244	6.51E-06	4.3E-05	5.94E-05	0.000251	0.000921	0.00118
AUC Venous Blood	0.00104	0.00117	2.19	0.00710	4.38E-06	4.54E-05	0.000119	0.000653	0.00268	0.00345

internal doses based on human exposures to all three routes. Working with the 13 DBPs for which example exposure and dose estimates have been developed (Appendix 1), it is envisioned that the following steps may be followed to conduct the CRPF-based assessment.

Group DBPs into Subclasses by Common MOA

Collect, evaluate and select the highest quality MOA and dose-response toxicology data; determine the best measure of a biologically effective dose (i.e., exposures, total absorbed doses, organ/tissue doses); identify subclasses of the 13 DBPs, grouping them by similar toxic MOA; determine the appropriate dose metric (e.g., area under the curve for absorbed and tissue doses or the maximum concentration).

Conduct Dose Response Modeling of Toxicology Data

Adjust administered animal doses to internal animal doses using bioavailability factors; adjust the internal animal doses to internal human equivalent doses using allometric scaling or PBPK modeling; develop dose-response curves for individual DBPs; re-evaluate subclass groupings based on similarly shaped dose-response curves within the exposure region of interest.

Develop RPF Estimates for Each Subclass and Combine Using the CRPF Approach

For each subclass, choose an index chemical and estimate RPFs; multiply each component dose by its RPF to obtain the Component ICED; sum the Component ICEDs to generate a Subclass ICEDs; Use the dose-response curve for the index chemical to estimate risk for its subclass; sum the subclass risks to estimate the total mixtures risk; develop a full risk characterization for the analysis, including an analysis of uncertainty.

CRPF ILLUSTRATION FOR DBPS

This procedure for applying the CRPF approach is illustrated for the cancer endpoint only, utilizing two DBP subclasses, carcinogens that are that are thought to be genotoxic and non-genotoxic. The basic schematic for this illustration is shown in Figure E-6; the calculations for the illustration are shown in Table E-5.

For each subclass, an index chemical is chosen. (Figure E-6 indicates that BDCM and DCA are the index chemicals for the genotoxic subclass and non-genotoxic subclasses, respectively.) RPFs are then calculated for each member of the subclass relative to the index chemical using the dose-response functions generated for the individual DBPs. (Table E-5 shows the RPFs for each DBP, where the calculation was conducted using a ratio of slope factors.) Then, within each subclass, the absorbed dose for each DBP is multiplied by its RPF to calculate a Component ICED for each member of the subclass; these estimates are summed to yield a total Subclass ICED. The dose-response curve for the index chemical is used to estimate risk for that subclass at the Subclass ICED.

Table E-5 provides an illustration of the cancer risk calculations that could be made for a 70 kg adult male by combining the dose-response information with the TEM total absorbed dose estimates shown in Table E-3. The 50th percentile doses (mg/day) from Table E-3 are converted to mg/kg/day doses (dividing by 70 kg) and then multiplied by the RPF for each DBP to obtain Component ICEDs. The sum of the Component ICEDs form the Subclass ICEDs. The product of the Subclass ICEDs and the MLE slope factor for the subclass index chemical provides an estimate of the average cancer risk for that subclass. The subclass risks are then added to obtain the final total average cancer risk for the whole mixture.

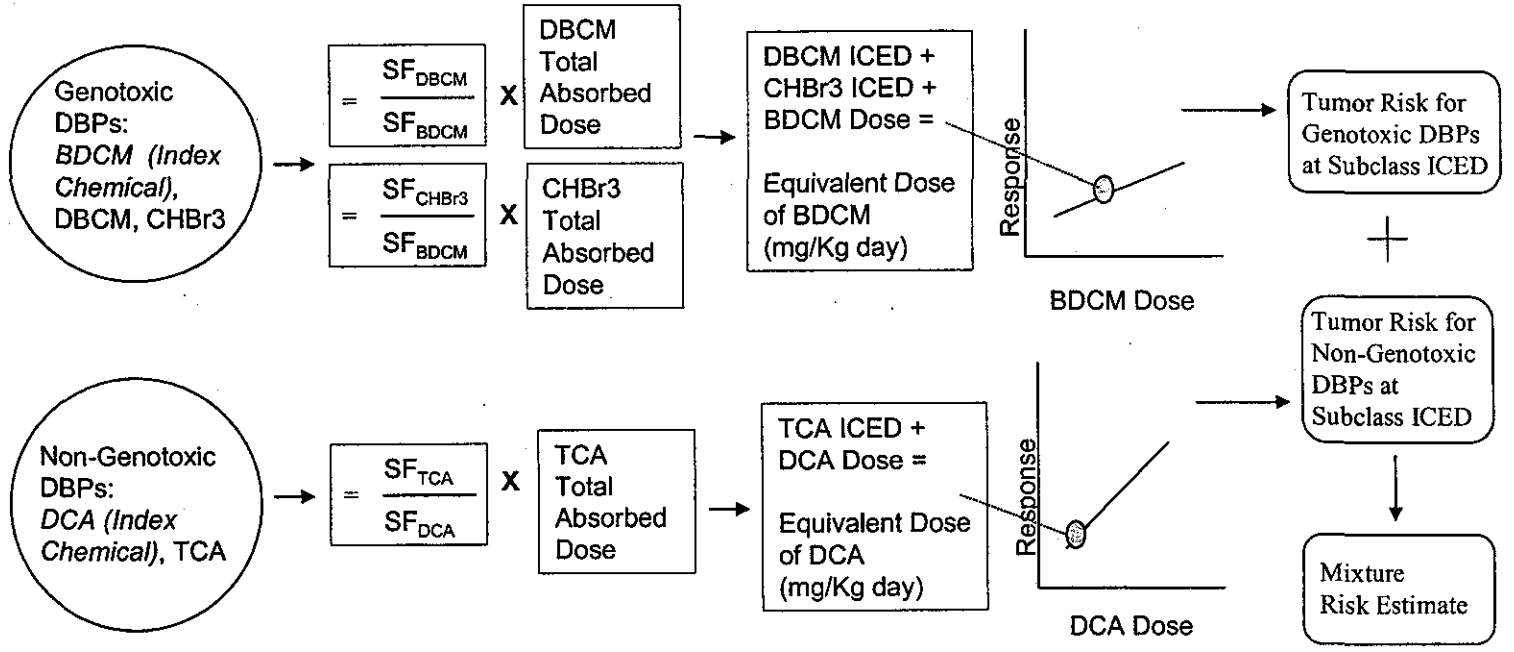

FIGURE E-6

Schematic of CRPF Approach for Illustration of DBP Mixture Cancer Risk

TABLE E-5

Illustration of CRPF Approach for Average Cancer Risk Calculations
(Includes assumption of 100% bioavailability)

DBP	95% Upper Bound Slope Factor (SF)[a]	RPF (SF_i/SF_1)[b]	Total Absorbed Dose for 70 kg Male		Component ICED mg/kg/day	Subclass ICED mg/kg/day	Subclass Risk
			50% mg/day	50% mg/kg/day			MLE Slope Factor times Subclass ICED
Genotoxic Subclass							
BDCM[c]	6.20E-02	1.00	8.43E-02	1.20E-03	1.20E-03	2.32E-03	1.32E-05
DBCM	8.40E-02	1.35	5.49E-02	7.84E-04	1.06E-03		
$CHBr_3$	7.90E-03	0.13	3.00E-02	4.29E-04	5.46E-05		
Non-Genotoxic Subclass							
DCA[d]	1.00E-01	1.00	3.14E-02	4.49E-04	4.49E-04	8.49E-04	1.19E-06
TCA	8.40E-02	0.84	3.34E-02	4.77E-04	4.01E-04		
$CHCl_3$	RfD=0.01	--	3.02E-01	4.31E-03	--		
						Total Mixture Average Cancer Risk	1.44E-05

[a]Slope factors for BDCM, DBCM, $CHBr_3$ are from IRIS, (U.S. EPA, 2002c). MLE slope factors are from the same dose-response model as the 95% upper bound slope factors. Slope factors for DCA and TCA, derived from data presented in Bull and Kopfler (1991) are included here to illustrate the CRPF approach only and are not representative of EPA peer-reviewed, endorsed values. This illustration assumes exposures below the $CHCl_3$ Reference Dose (RfD) of 0.01 mg/kg/day do not contribute to carcinogenicity.

[b]SF_1 is slope factor for index chemical; SF_i is slope factor for i^{th} chemical in the subclass.

[c]Genotoxic Subclass Index Chemical, Maximum Likelihood Estimate (MLE) of Cancer Slope Factor (SF) = 5.7E-3

[d]Non-Genotoxic Subclass Index Chemical, MLE SF = 1.4E-3

It is noteworthy that a strength of the CRPF approach is that it can be applied more broadly and expanded beyond this simple illustration using only six well-studied DBPs. In this hypothetical example, the toxicity of each chemical was well characterized. However, this approach can accommodate other DBPs for which fewer toxicity data exist. For example, other genotoxic carcinogens exhibiting similar MOA to BDCM may be present in the mixture. Although *in vivo* data may not be available, RPFs can be derived using other measures of potency (e.g., *in vitro* genotoxicity data), providing these data are relevant to the endpoint of interest and also exist for the index chemical. Clearly, exposure estimates would also need to be developed for the CRPF approach to be implemented.

The final step of such an effort is to fully characterize the uncertainties that exist as a product of the analysis. This risk characterization should include uncertainties in the CRPF process, including discussions regarding subclass development, choice of index chemical, and the strength of the exposure assessment.

CONCLUSIONS

Exposure modeling techniques and risk assessment methods are available to formulate CRA estimates for specified groups of DBPs. This analysis illustrates that multiple route exposure estimates can be developed that account for human activity patterns affecting contact time with identified DBPs in tap water by developing internal dose estimates for selected DBPs. Although important data gaps still exist (e.g., chemical properties of some DBPs such as bromate, MOA data for appropriately assigning DBPs into subclasses), additional data on these chemicals continue to be developed by many researchers. Application of this approach may provide a more scientific basis for evaluating risks posed by different mixtures of DBPs than

comparisons developed based on concentrations of individual DBPs and single route risk analyses. With sufficient data, applications of this approach should provide a more useful comparison to epidemiologic studies than analyses based on concentrations of individual DBPs and single routes of exposure. Cumulative risk estimates developed using these approaches can be compared across different types of treatments of the same source water or across geographic areas. These estimates of risk should be compared on a relative basis, rather than an absolute basis. For example, a Hazard Index or other component based mixtures risk assessment approach may be applied (see U.S. EPA, 2000b) using cumulative dose estimates. For more difficult problems, such as predicting actual risks from exposure to chlorinated drinking water (e.g., number of cases of cancer for a population served by a particular system), additional research will be required before credible CRAs can be implemented. To improve upon the current effort, the following information still needs to be developed:

1) A careful treatment is needed to determine MOA for the major DBPs of concern for health risk assessment. At a minimum, MOA should be determined for cancer, developmental effects and reproductive effects.

2) Dose response models need to be developed for the major DBPs of concern for all relevant endpoints. Although some initial work has been done in the 1990's (U.S. EPA, 2000a), this research should be updated to include the current literature base. In addition, issues to be carefully considered in the development of new dose response models include consideration of vehicle effects, non-linear responses at low doses, different MOA at low and high doses, background response rates, and litter effects.

3) The exposure and PBPK model predictions used in this analysis need to be further evaluated against independent data sets.

4) Improved quantitative skin permeability rates need to be developed. A large range of uncertainty exists in the dermal estimates that make it difficult to compare the dermal route to the inhalation and ingestion routes. Similarly, much uncertainty associated with inhalation exposures could be reduced through better estimation of volatilization.

5) A factor that limited the exposure modeling results to 13 of the 15 chemicals was lack of data on chemical properties, e.g., Henry's law constant, Kow, boiling point, vapor pressure, liquid and gas phase diffusivities (see section 3. for a chemical-specific detailed list). This is a important data gap, particularly because bromate was not included in the exposure modeling estimates. (Bromate, a suspected carcinogen, is of concern for high bromide source waters where ozonation is the primary disinfectant for the treatment system.)

6) Some physiological parameters are still needed for improved PBPK modeling. The sensitivity analysis (based on $CHCl_3$ and DCA) indicated that certain parameters could produce relatively large changes in the exposure estimates. These included: alveolar ventilation rates, blood flow in the kidney, volume in the liver, liver metabolism Vmax, volume in the body, the partition coefficient for testes/blood, and stomach to portal blood rate.

7) Future exposure modeling efforts should ensure that a complete uncertainty analysis be conducted and that the sensitivity analyses include all modeled chemicals and demographic groups in the study.

8) Research needs to be conducted to determine whether populations sensitive to particular DBPs or DBP classes exist. Sensitivity may arise through different activity patterns among people (e.g., long vs. short shower durations), toxicokinetic differences among individuals, and toxicodynamic differences between individuals.

9) Approximately 50% of DBPs in the finished drinking water consists of unidentified material. EPA has conducted research to identify these DBPs (Richardson, 1998), to estimate the potential toxicity of these chemicals (Moudgal et al., 2000; Woo et al., 2002), and to estimate the additional health risk from exposure to this unknown fraction of DBPs (Teuschler et al., 2001; U.S. EPA, 2000a). Research needs to be conducted to enhance the CRPF approach to account for the potential toxicity of the unknown fraction.

While comprehensive lists of needed research are useful, they generally provide little insight as to which of the research needs are of the highest priority. The current understanding of the risks that DBPs pose through multiple exposure routes would be improved ultimately through the successful conduct of any research listed here. To determine which areas of research would be most useful in refining risk estimates, quantitative human health risk estimates for DBPs need to be developed, including detailed analyses of uncertainly and variability. The research needs could be evaluated based on the expected improvement in the confidence in estimated DBP risks. This evaluation could serve as a ranking approach for DBP research needs.

1. INTRODUCTION

1.1. BACKGROUND

Assessment of potential human health risk(s) from disinfection by-products (DBPs) in drinking water is needed because of widespread oral, dermal and inhalation exposures to this complex mixture and because positive data from both epidemiologic and toxicologic studies of DBPs raise concern for human health (U.S. EPA, 2000a). Although these data suggest human health effects are possible, human exposures are complex, making the interpretation of positive results difficult. Occurrence information shows that the mix of DBPs may vary considerably with geographic location and water treatment process. Furthermore, for the more volatile DBPs, inhalation exposures may be greater than ingestion; for highly lipophilic DBPs, dermal exposures may also be important. Information from toxicologic studies has focused primarily on single DBPs at doses far above finished drinking water concentrations. Information from positive epidemiologic studies suggests that exposures to different mixtures of DBPs in various geographic locations may pose quite different health risks. Thus, to develop a regulatory and risk reduction strategy, there is a need to consider the health risks associated with DBP mixtures and the various exposures from contact with finished drinking water. Given this need, the U.S. Environmental Protection Agency (EPA) has conducted research for assessing DBP health risks using a cumulative risk assessment approach, defined here as multiple chemical exposures via multiple exposure routes over time (U.S. EPA, 2000a).

The need to conduct a risk assessment for DBP mixtures arose both as a legal 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 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 produced a report, identifying the major issues for consideration to conduct scientifically credible and comprehensive DBP mixtures risk assessments (U.S. EPA, 2000a). The report concludes that the evaluation of human health risks from exposure to DBPs is a cumulative risk assessment problem and recommends consideration of the following factors:

- Exposure to multiple chemicals at low environmental concentrations,
- Knowledge of toxic mode of action (MOA)[1] and judgment regarding similarity of MOA among DBPs,
- Dermal, oral and inhalation routes of exposure,
- Measures of internal absorbed dose,
- Human activity patterns that affect the types of water use and the amount of contact time with the drinking water,
- Physicochemical properties of the DBPs,
- Physical properties of the indoor environment, and
- Sensitive subpopulations.[2]

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[1]Mode of Action (MOA) is defined as the set of biological events at the target tissue or target organ leading to a toxicologic outcome. A toxicologic outcome is considered to be damage to the organism at any level of biological organization (i.e., molecular, cellular, tissue,...).

[2]Sensitive subpopulations are groups of individuals in a population with increased likelihood over the average population to express an adverse health effect resulting from exposure to a contaminant. The reasons for this sensitivity may be unknown, but could include factors such as age, sex, genetic predisposition, nutritional status, immune system deficiencies, etc.

Incorporating many of these factors, research has been conducted to develop human exposure estimates for individual DBPs from multiple exposure routes; whole body and organ-specific internal doses are estimated for all three exposure routes for each individual DBP. This report describes how these data can be used to assess DBP risks using a newly developed risk assessment method, the Cumulative Relative Potency Factors (CRPF) approach, that combines the principles of dose addition[3] and response addition[4] into one method to assess mixtures risk for multiple route exposures (U.S. EPA, 2000a).

The CRPF approach is a component-based method for assessing health risks that combines dose-response and exposure data for each individual chemical in the mixture to estimate risk, as opposed to using data on the whole mixture. Oral dose-response animal data exist for most of the major DBPs identified in the drinking water for cancer, developmental and reproductive effects, and a number of systemic effects. These data are too numerous to include here; numerous journal publications exist on DBP toxicologic studies, as well as reviews of the literature (e.g., IPCS, 2000; Klinefelter et al., 2001; U.S. EPA, 2000a). In contrast to the oral data, dermal and inhalation dose-response animal data are relatively sparse. Thus, the development of

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[3]Dose Addition is a chemical mixtures risk assessment method in which doses are summed (after scaling for relative potency) across chemicals that have a similar MOA; risk is then estimated using the combined total dose.

[4]Response addition is a chemical mixtures risk assessment method applied to chemicals whose MOA are independent of each other (i.e., the presence of one chemical in the body does not influence the effects caused by another chemical); risk of a whole body effect (e.g., non-specific cancer), is then estimated by summing the risks (e.g., skin cancer, liver cancer) of the individual chemicals.

DBP mixture risk assessment approaches based primarily on the use of oral dose-response information is a plausible research direction.

Three different measures of dose are presented with respect to possible application of the CRPF approach (see Figure 1-1). The actual choice of dose metric, as well as the temporal element of each exposure measure, is influenced by available dose-response data. Contaminant exposures may be evaluated in one of three ways:

1) *Exposures.* In this measure, exposure is quantified separately for each exposure route as the amount of an agent available at the exchange boundaries (e.g., skin, lungs, intestinal tract). Exposure estimates are based on environmental concentrations in the media and human activity patterns that affect the types of water use and the amount of contact time with the drinking water.

2) *Total Absorbed Doses (e.g., blood concentrations).* Internal dose estimates are developed based on the amount of a contaminant that is absorbed from all exposure routes without regard to specific absorption processes.

3) *Organ or Tissue Doses.* In this measure, organ doses (e.g., doses experienced by the kidney, liver, etc.) or tissue doses are estimated from all exposure routes based on pharmacokinetic information.

The goal of this document is to examine the feasibility of conducting a cumulative risk assessment for drinking water DBP mixtures by combining exposure modeling results with the CRPF risk assessment approach. Section 2 of this document presents the new CRPF approach, developed for application to the DBP complex mixture risk problem (U.S. EPA, 2000a). To provide additional detail, Appendix 2 reproduces Chapter 4 of the U.S. EPA (2000a) report that presents the CRPF approach as a

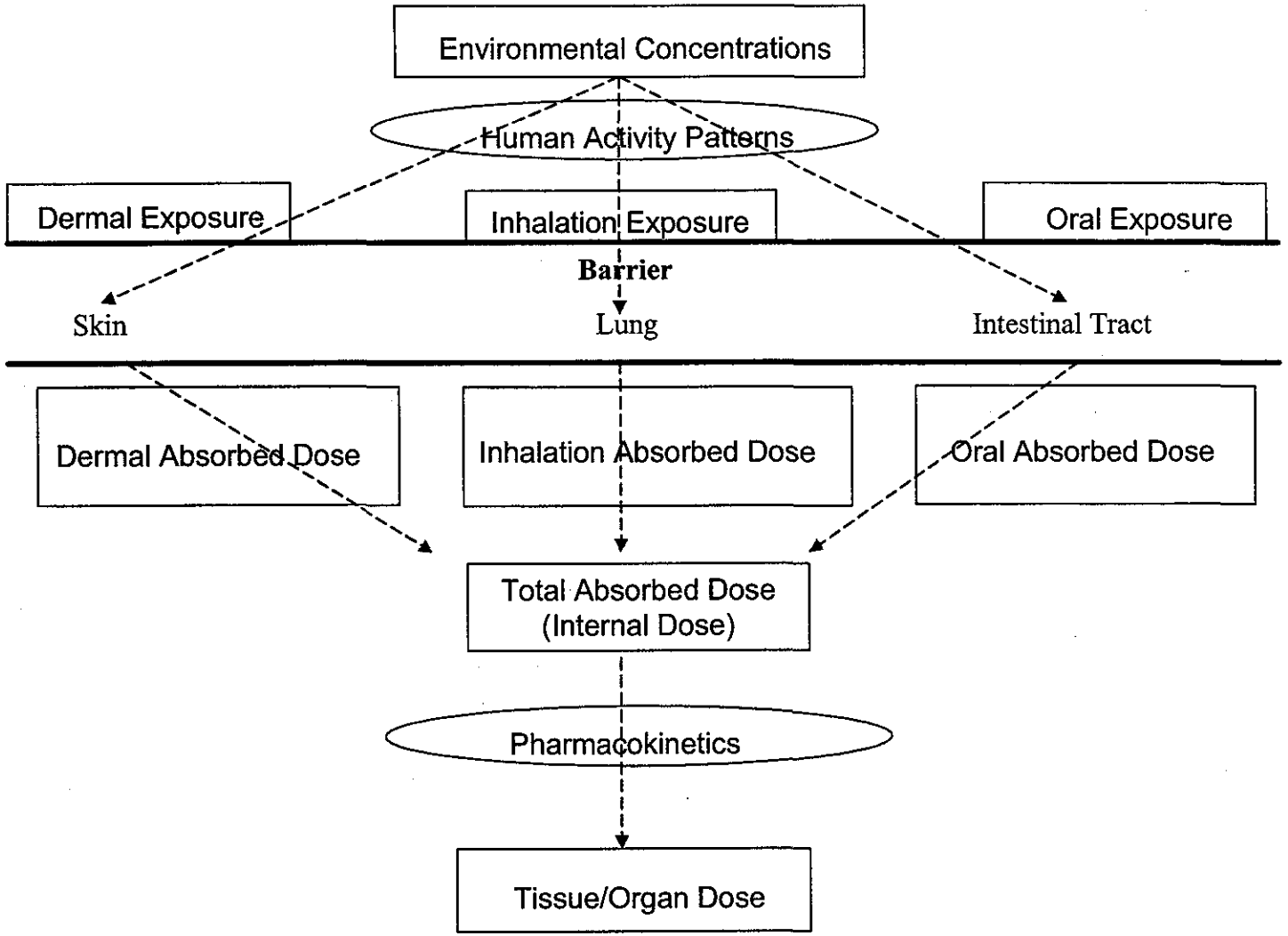

FIGURE 1-1

Dose Metrics for Environmental Contaminants

conceptual model. Section 3 presents a summary of the DBP exposure research results (detailed report in Appendix 1) that provide human exposure estimates for 13 DBPs, accounting for oral, dermal and ingestion routes of exposure as well as human activity patterns. Section 4 discusses the use of these newly developed exposure estimates in the CRPF approach. Section 5 details the uncertainties and data gaps that define future research needs and discusses the technical feasibility of completing a cumulative risk assessment for DBP mixtures.

1.2. EXPOSURE MODELS

Different approaches exist for evaluating human exposures to environmental contaminants. In this document two different mathematical models are employed to evaluate human exposures. An *Exposure Assessment Model* generates estimates of exposures at the body boundaries through human contact with the media, influenced by human activity patterns. A *Physiologically-Based Pharmacokinetic (PBPK) Model* predicts doses of DBPs experienced by relevant organs or target tissues.

Exposure assessment models are used in conjunction with exposure scenario analyses to estimate contaminant concentrations in the media surrounding sources. Exposure scenarios detail the assumptions concerning how humans might contact a contaminant or a mixture of contaminants (Paustenbach, 2000). In the context of drinking water contaminants analysis, exposure assessment models characterize contaminant contact with body membranes (e.g., the tissues lining the gastrointestinal tract, the lungs, and the dermis). An exposure scenario is constructed to characterize sources of human exposure, physical properties of a building or room that influence the dispersion of the contaminants from their sources into the indoor environment, and human behavioral patterns that bring individuals into contact with the contaminated

media. For example, an exposure assessment model can quantify the human exposures that occur through the inhalation route due to a volatile drinking water contaminant both during and following a shower.

PBPK models predict doses of contaminants that occur at the tissue or organ level. PBPK models employ a series of mathematical formulae that quantify pharmacokinetic processes. PBPK models predict the contaminant doses that pass through the body's exterior membranes, the distribution of these contaminants through body tissues, the metabolism of the contaminants, and their elimination. The rates at which these processes occur change in part due to variations in predicted contaminant absorbed doses in the tissues and organs modeled. Because PBPK models account for the different rates at which these physiological and biochemical processes occur, changes in tissue or organ doses can be predicted through extrapolation across species based on measurements in a test species. PBPK models predict tissue doses based on changes in exposures, changes in exposure routes, changes in exposure duration, and interindividual variations (e.g., enzyme activity levels). These capabilities are significant in the conduct of risk assessments because they quantify uncertain aspects of extrapolation: across species (e.g., from test species to human); from high experimental doses to lower environmental exposures; from experimental to environmental exposure durations; and across different exposure routes (Clewell et al., 2002).

PBPK models are useful not only for assessing individual chemicals, but also for conducting cumulative risk assessments. Cumulative risk assessments, as defined in this effort, evaluate human exposures to multiple contaminants through multiple exposure routes. Mumtaz et al. (1993) noted that PBPK models can be used to

estimate absorbed doses of chemicals and their metabolites (a mixture) through multiple exposure routes, to evaluate competition of different chemicals for a specific receptor (e.g., glutathione) or target, and to examine increases or decreases in metabolic enzyme activity due to the presence of a second contaminant.

1.3. GUIDANCE ON CUMULATIVE RISK

The EPA is developing a number of approaches for conducting cumulative risk assessments. The Risk Assessment Forum, under the Office of Research and Development, is currently drafting a *Framework for Cumulative Risk Assessment* (U.S. EPA, 2002a) that will serve as the basis for a future cumulative risk assessment guidelines document. The Office of Pesticides Programs (OPP) has also been actively involved in response to a mandate within the Food Quality Protection Act of 1996 which calls for the multiple route risk assessment of pesticide mixtures that act by a common mechanism of toxicity. OPP has produced guidance in this area as well as a preliminary cumulative assessment of the organophosphorous pesticides using Relative Potency Factors (U.S. EPA, 2001, 2002b). A general definition of cumulative risk is, "the combined risks from multiple routes of exposure to multiple agents or stressors", which can include non-chemical stressors (U.S. EPA, 2002a). For the DBP complex mixture, cumulative risk is defined for use in this document in a more limited way as "the combined risks from exposure to multiple chemicals via multiple exposure routes over time." Other stressors, such as smoking, that could influence outcomes associated with DBPs (e.g., gastrointestinal cancer, adverse pregnancy outcomes) are not evaluated. The starting point for approaching this cumulative risk problem is to apply the premises put forth in existing Agency guidelines and guidance documents on chemical mixtures risk assessment.

The U.S. EPA has published methods to perform health risk assessments of chemical mixtures (U.S. EPA, 1986, 2000b), in which three approaches to quantifying health risk are recommended depending on the type of data available to the risk assessor: data on the complex mixture of concern; data on a sufficiently similar mixture; or, data on the individual components of the mixture or on their interactions. Figure 1-2 shows that different aspects of the risk actually posed can be evaluated using these three types of data; data collection efforts can be targeted for use in these risk assessment approaches (Teuschler and Simmons, 2002). In the top row of Figure 1-2, data are available on the complex mixture of concern, in this case, real-world drinking water samples. The quantitative risk assessment is done directly from these data, including either epidemiologic or toxicologic data. In the middle row of Figure 1-2, data are available on a "sufficiently similar" mixture, e.g., finished drinking water samples created in the laboratory that are representative of specified treatment processes and source waters. Two mixtures are thought to be sufficiently similar for use in risk assessment when differences in their major chemical components and their relative proportions are small (U.S. EPA, 2000b). In practice, existing toxicity data on a sufficiently similar mixture may be used to estimate the expected toxicity of finished drinking water produced by the same treatment process and source water.

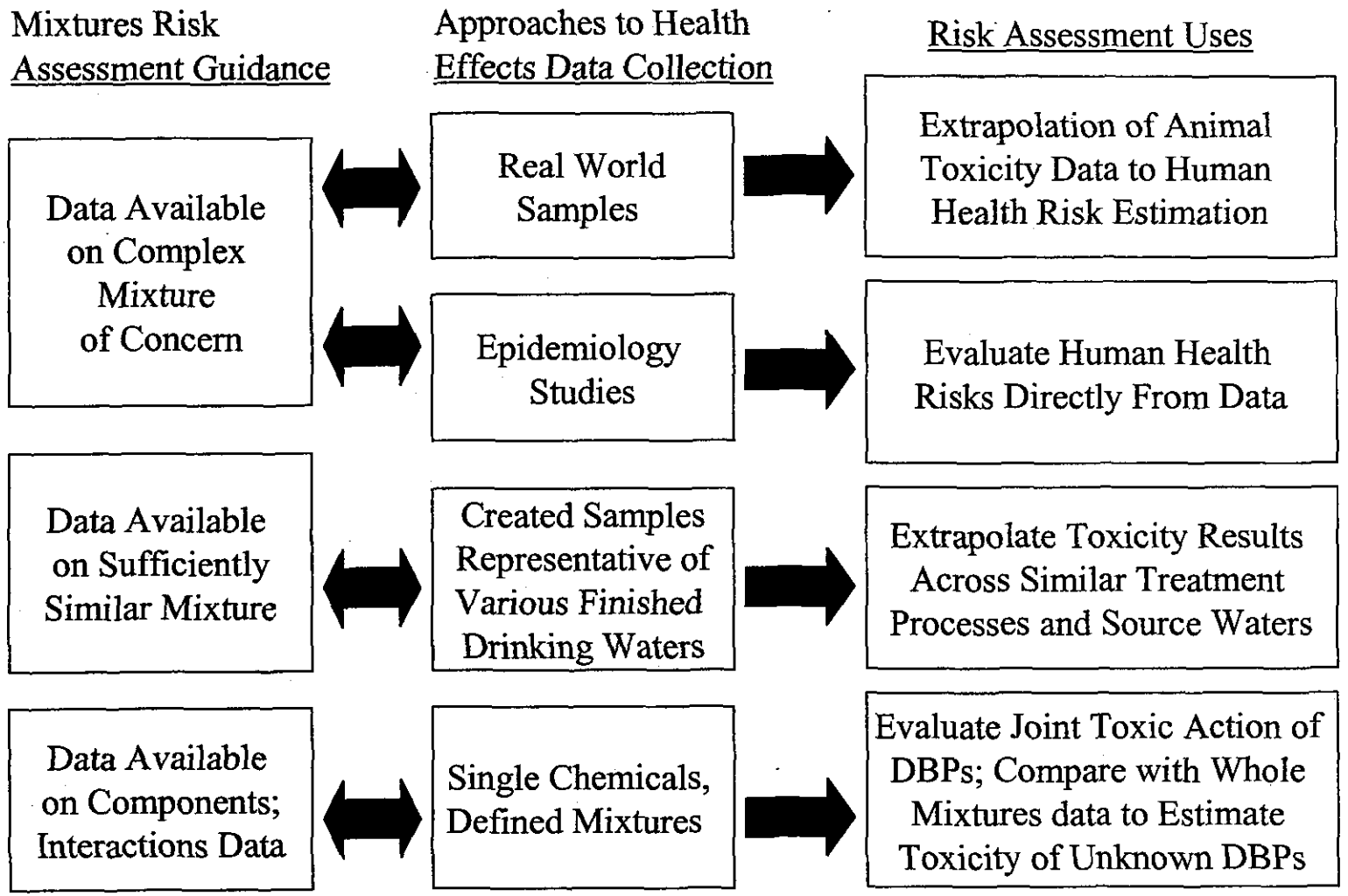

FIGURE 1-2

Mapping of Risk Assessment Approaches to Drinking Water Studies

In the bottom row of Figure 1-2, data are available on single chemicals and defined mixtures of DBPs to evaluate the mixture through an analysis of its components. For example, there is precedent for using dose addition to estimate the risk of systemic effects and response addition for estimates of cancer risk (U.S. EPA, 1989, 2000b). These particular procedures include a general assumption that interaction effects (i.e., effects that are greater than or less than those expected under additivity) at low exposure levels either do not occur at all or are small enough to be insignificant to the risk characterization.[5] For DBPs, toxicity and exposure data on the components of a mixture can be combined and added (depending on the assumption used) to estimate mixtures risk.

Thus, Figure 1-2 highlights several risk assessment issues of concern to managers responsible for ensuring safe drinking water for the public. The first issue is to evaluate the association between DBP mixture exposures and human health outcomes and thereby establish whether or not human health risks are a significant concern. Because the evaluations of this association are inconclusive and human health effects from DBP exposures are possible, some drinking water regulations have been promulgated and others posed with the goal of controlling levels of DBPs in the drinking water (e.g., U.S. EPA, 1979, 1994a, 1998b). As rules go into effect, alternative drinking water treatment technologies are developed to meet these new standards.

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[5]For exposures at low doses with low component risks, the likelihood of significant interaction is usually considered to be low. Interaction arguments based on saturation of metabolic pathways or competition for cellular sites usually imply an increasing interaction effect with dose, so that the importance at low doses is probably small. The default component procedure at low exposure levels is then to assume response addition when the component toxicological processes are assumed to act independently, and dose (or concentration) addition when the component toxicological processes are similar (U.S. EPA, 2000b).

Thus, a second important issue is to choose among treatment options by evaluating potential changes in exposure and health risk(s) across various drinking water treatment systems and source waters. A third issue for evaluation of DBP mixtures is that approximately 50% of the DBP mass consists of unidentified total organic halide material, the toxicity of which is largely unknown (Weinberg, 1999). By comparing whole mixture toxicity data with data on the mixture components, the toxicity of the unknown fraction of the DBP complex mixture can be evaluated.

In a preliminary health risk assessment of DBPs, toxicity and exposure data on the components of a mixture were combined and added, assuming response addition, to estimate mixtures risk (Teuschler et al., 2001; U.S. EPA, 2000a). To perform a cumulative risk assessment, however, the DBP assessment must be broadened to take into account dermal, oral, and inhalation exposure routes and patterns of human behavior that affect water usage and contact time with the drinking water. The method proposed in this document using the CRPF approach is a component based approach, based on Agency guidance, and incorporates improved exposure information on the DBPs.

2. CUMULATIVE RELATIVE POTENCY FACTORS

This section describes the CRPF approach (U.S. EPA, 2000a) as it may be applied to DBP mixture exposures. (A detailed description of the CRPF approach is given in Appendix 2.) Section 4 will discuss how the exposure estimates presented in Section 3 can be used to conduct a DBP cumulative risk assessment by applying the CRPF approach. As discussed in Section 1.1, application of the CRPF approach will vary depending on the choice of dose metric for the analysis (i.e., external exposures, total absorbed doses, and tissue or organ doses). The use of these dose metrics is discussed below and further developed in Section 4.

2.1. RELATIVE POTENCY FACTORS

U.S. EPA developed the Relative Potency Factor (RPF) approach to assess risks posed by mixtures that are comprised of chemical components exhibiting a common mode of action[6] (MOA) for a toxic effect (U.S. EPA, 2000b). The RPF approach is based on the concept of dose addition. Mixture components are grouped for the purpose of developing an *RPF Set* by factors such as membership in a chemical class (relating to observed toxicity), and common toxicologic effects, exposure routes, exposure durations, or dose ranges. To implement the approach, the toxicity of each component is predicted by scaling its exposure level by a measure of the component's

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[6]The terms *mechanism* of toxicity (or mechanism of toxic action) and *mode* of action represent a continuum of understanding regarding a toxicodynamic process. Knowledge of a chemical's **mechanism of toxicity or mechanism of toxic action** implies that the molecular and cellular events leading to a toxicologic outcome are described and well-understood. A toxicologic outcome is considered to be damage to the organism at any level of biological organization (i.e., molecular, cellular, tissue,...). Knowledge of a chemical's **mode of action** implies a general understanding of the key toxicodynamic events that occur at a tissue level, but not a detailed description of these events at the cellular or molecular level.

relative toxicity. This scaling factor, the RPF, is based on a comparison of a component's toxicity with similar measures of toxicity for a selected index chemical, a toxicologically well-studied component of the mixture (i.e., of the RPF Set). The product of the measured exposure dose of each mixture component and its RPF is defined as an Index Chemical Equivalent Dose (ICED). The ICEDs of all the mixture components are summed to express the total mixture exposure in terms of an equivalent exposure to the index chemical. The risk posed by the mixture is quantified by comparing a mixture's total ICED to the dose-response assessment of the index chemical. (The mathematical formulae for the RPF are detailed in Text Box 2-1.)

Appropriate application of the RPF method requires a judgment that the mixture components share a common mechanism of action or a common mode of action and evidence that the components have similarly shaped dose response curves. For the first

TEXT BOX 2-1

Mathematical Representations and RPF Formulas

d_1 = dose of chemical 1 present in a mixture (units not specified)

d_2 = dose of chemical 2 present in a mixture (units not specified; must be consistent with those of d_1)

pot_1 = potency estimate (e.g., a slope factor) for chemical 1 (risk per unit of dose specified for d_1)

pot_2 = potency estimate (e.g., a slope factor) for chemical 2 (risk per unit of dose specified for d_2)

ICED = index chemical equivalent dose based on relative potency estimates (units consistent with d_1 and d_2)

$f_1(*)$ = dose-response function of the index chemical for the response(s) common to chemical 1 and chemical 2 (units consistent with d_1 and d_2)

$h(d_1,d_2)$ = mixture hazard or risk from joint exposure of dose d_1 to chemical 1 and dose d_2 to chemical 2

$[ED_{10}]_1$ = dose of chemical 1 that results in a 10% response, either as a fraction of exposed test animals that respond, or as a fractional change in a measured physiological value.

$[ED_{10}]_2$ = dose of chemical 2 that also results in the same 10% response

Then, designating chemical 1 as the index chemical in the RPF approach,

$RPF_2 \approx [ED_{10}]_1 / [ED_{10}]_2$,
(or equivalently = pot_2 / pot_1)

$ICED \approx d_1 + (RPF_2 * d_2)$

$h(d_1,d_2) = f_1(ICED)$

assumption, the term *Common Mechanism of Action* implies that the chemicals in a mixture exhibit a common toxicologic outcome when tested and that the underlying molecular and cellular toxicodynamic events leading to this outcome are the same for each chemical, after they reach the target site. (Toxicodynamic events include the initial interaction of a toxicant with its molecular or cellular target and subsequent responses to the toxic insult.) The term *Common Mode of Action* implies that chemicals in a mixture exhibit a common toxicologic outcome when tested but that the toxicodynamic events leading to this common outcome after the chemicals reach the target site are not well understood. Because detailed toxicodynamic data are not abundant for most chemical mixtures, analysts typically must judge whether or not the chemicals in a mixture exhibiting a common toxicologic outcome share a common MOA. The second assumption of similarly shaped dose-response functions includes their expected shape in the low dose region *including* the region that may lie below the lowest dose tested in the relevant toxicological bioassay. Evidence that a chemical class fulfills one of these requirements does *not* necessarily imply that the second requirement is fulfilled.

RPFs are based on comparisons with an index chemical, and the mixture risk is estimated using the dose response function of the index chemical. Criteria pertaining to the inclusion of compounds in an RPF Set apply to the index chemical. The index chemical should be a well-studied member of the RPF Set; studies on the index chemical need to provide exposure data for routes of interest and health assessment data for health endpoints of interest. To estimate *relative* potency, toxicity studies of compounds in the RPF Set need to be comparable to studies conducted on the index chemical. (See Appendix 2 for a quantitative example of the RPF process.)

2.2. THE CRPF APPROACH

The CRPF approach groups DBPs with a common MOA into RPF Sets called subclasses. The MOA differ across the subclasses, but the toxicological endpoint (or outcome) is the same. A dose-addition analysis is conducted within each subclass for the toxicologic outcome common across subclasses using the RPF approach (U.S. EPA, 2000b). Each resulting subclass risk estimate represents the risk for this common endpoint. However, these subclass risks are independent of each other (i.e., the toxicity caused by one subclass does not influence the toxicity caused by the other subclass because their respective MOA are different), thus meeting the criteria required to apply response addition; the subclass risk estimates are added to yield a risk estimate for the total DBP mixture.

Figure 2-1 illustrates this integration of dose addition and response addition using two subclasses to estimate risk from exposure to the mixture. Based on available data, the components are considered to have two different MOA and are subdivided into two subclasses for development of RPFs. For each subclass, an index chemical is determined and an ICED is calculated using RPFs. The ICED is an important concept for the CRPF method that is employed at two levels:

1) **Component ICED** - refers to the ICED for an individual chemical within a subclass.

2) **Subclass ICED** - refers to the ICED for all chemicals within the subclass, computed by summing their Component ICEDs.

Figure 2-1 is illustrated in this paragraph using a hypothetical non-cancer example. In this example, the presence of amino acids in urine of test animals during separate chronic rodent bioassays of two chemicals indicates that chronic exposure to

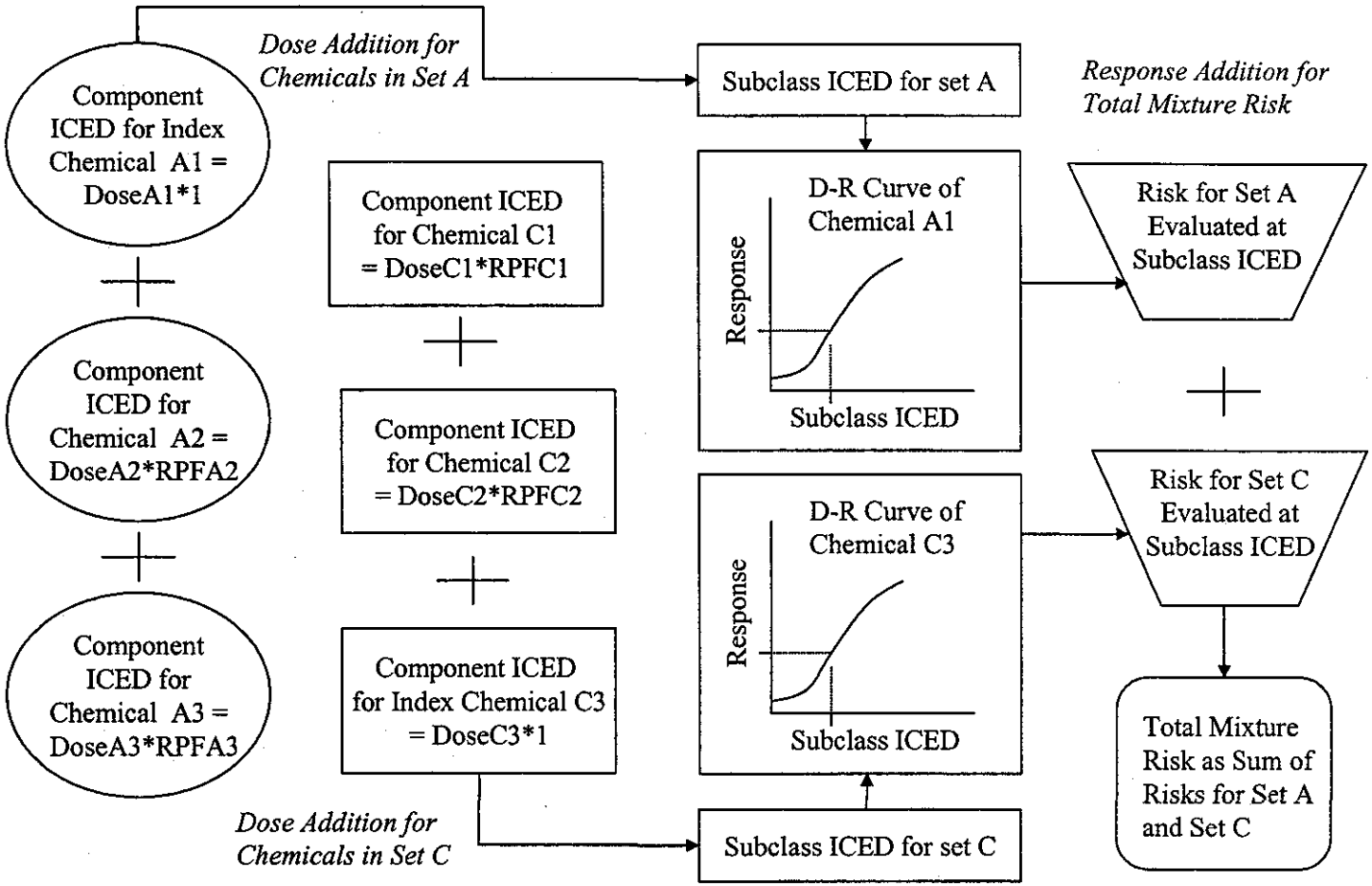

FIGURE 2-1

CRPF Approach : Integration of Dose Addition and Response Addition to Estimate Mixture Risk

each chemical alters renal function. Additional toxicologic evidence indicates that the two renal toxicants exhibit different MOA. The first chemical causes cellular injury to glomerular endothelial cells through an MOA similar to that of cyclosporine. The second causes cellular injury to proximal tubule segments 3 and 4 of the nephron through an MOA similar to that of mercuric chloride. Each chemical is selected as an index chemical for a subclass; limited evidence suggests that members of each subclass share a common MOA with their respective index chemicals. Low environmental concentrations of the mixture of chemicals in the two subclasses result in predicted human exposures in the low dose region where component interactions are not significant (i.e., synergistic or antagonistic interactions among components are not expected to occur, so the RPF approach based on dose-addition within each subclass of renal toxicant is appropriate). Because the MOA data indicate independence of toxicologic action between the subclasses, response addition is appropriate for combining risks across the subclasses. A risk estimate for adverse renal effects is made for each subclass from its index chemical's dose-response curve at the Subclass ICED. The subclass risks are added using the assumption of response addition to estimate the total mixture risk of adverse renal effects.

2.2.1. Theory of the RPF Approach. The RPF approach has been proposed for characterizing health risks associated with mixtures of chemical compounds that have data indicating they are toxicologically similar (U.S. EPA, 2000b). To develop an RPF-based risk estimate for a class of chemicals, good toxicological data are needed for at least for one component of the mixture (referred to as the index chemical). Scientific judgment and analysis of available data are used to assess the relative toxicity of the other individual components in the mixture. Based on available data, the RPF Set can

be limited to specific exposure routes, specific health endpoints, or specific members of a class of compounds that have similar pharmacodynamic and possibly pharmacokinetic 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 Pharmacodynamic 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. To the extent that data are available, division of the DBPs into RPF Sets called subclasses is 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 RPF method requires that a *quantitative uncertainty analysis or qualitative description of uncertainty be included in* the risk characterization.

2.2.2. RPF Calculations Using Exposures from Exposure Assessment Models. Human exposures may be estimated using exposure assessment models that take into account concentrations of chemicals in the media, human activity patterns, physical properties of the chemicals, etc. (see Section 1.1. and Figure 1-1). To apply the RPF approach to one subclass (m) of DBPs and one exposure route (w) using these exposure estimates, the basic model is as follows:

$$R_{mw}(k) = f_{kw}\left(C_{mw}(k)\right) \qquad (2\text{-}1)$$

where:

$R_{mw}(k)$ = subclass m risk (unitless) for a specified endpoint and exposure route w as a function of index chemical k

f_{kw} = dose response function of index chemical k for the specified endpoint and exposure route w

$C_{mw}(k)$ = Subclass ICED of index chemical k for the specified endpoint and exposure route w.

The Subclass ICED is developed when the component exposures are expressed as Component ICEDs by developing scaling factors, i.e., RPFs. Then, the Subclass ICED is estimated as:

$$C_{mw}(k) = \sum_{i=1}^{n} \left(RPF_{iw} * C_{iw} \right) \qquad (2\text{-}2)$$

where:

$C_{mw}(k)$ = Subclass ICED of index chemical k for the specified endpoint and exposure route w.

n = number of components in the subclass

RPF_{iw} = proportionality constant (unitless) relative to the toxic potency of the index chemical, k, for the ith mixture component, exposure route w

C_{iw} = exposure estimate of the ith mixture component by exposure route w

$RPF_{iw} * C_{iw}$ = Component ICED for the ith mixture component, exposure route w.

Calculation of an RPF_i involves estimating the relative potency of each component compared with the index chemical (see Appendix 2 for an example calculation). To illustrate, one method is to calculate the ratio of effective dose levels, e.g., the ratio of the index chemical's ED_{10} to the ith chemical's ED_{10} to estimate an RPF_i for that chemical (see Text Box 2-1). A second method is to calculate the ratio of

potency estimates (e.g., cancer slope factors). The calculation of the RPF_i requires that the chemicals in the subclass have similarly shaped dose-response curves, at least in the region of exposures relevant to the risk assessment.

2.2.3. RPF Calculations Using Internal Doses from PBPK Models. Internal doses (e.g., blood, tissue and organ doses) may be estimated using PBPK models that take into account exposures and pharmacokinetic processes (see Section 1.1. and Figure 1-1). RPFs can be applied to a DBP subclass for multiple exposure routes using measures of total absorbed dose or total tissue/organ doses from PBPK modeling for evaluating risks posed to internal organs, *providing that no portal-of-entry effects are involved*. For chemicals exhibiting portal of entry effects, PBPK models may be used to refine the tissue dosimetry estimates. The basic model for subclass m for internal dose across multiple route exposures is as follows:

$$R_m(k) = f_k\left(C_m(k)\right) \tag{2-3}$$

where:

$R_m(k)$ = subclass risk (unitless) of a specified endpoint as a function of index chemical k

f_k = oral dose response function of index chemical k for the specified endpoint (adjusted to be relevant to internal doses using a bioavailability factor for index chemical k)

$C_m(k)$ = Subclass ICED of chemical k for internal doses accumulated across multiple route exposures.

The Subclass ICED is developed when the internal doses of the components are expressed as Component ICEDs by developing scaling factors, i.e., RPFs. Then, the Subclass ICED is estimated as:

$$C_m(k) = \sum_{i=1}^{n}\left(RPF_i * C_i\right) \tag{2-4}$$

where:

$C_m(k)$ = Subclass ICED of chemical k for internal doses accumulated across multiple route exposures

n = number of components in the subclass

RPF_i = proportionality constant (unitless) relative to the toxic potency of the index chemical, k, for the ith mixture component and the oral exposure route

C_i = internal dose of the ith mixture component accumulated across multiple route exposures.

$RPF_i * C_i$ = Component ICED for the ith mixture component

Calculation of an RPF_i for internal doses representing multiple route exposures involves making an estimate of relative potency for each chemical compared with the index chemical from oral dose-response information that is adjusted to internal doses using bioavailability factors. Using the adjusted oral dose-response information, one method is to calculate the ratio of the ED_{10} (or other effect level relevant to the risk assessment) of the index chemical to the ith chemical's ED_{10} to provide an RPF_i for that chemical. A second method is to calculate the ratio of potency estimates (e.g., cancer slope factors). The calculation of the RPF_i requires that the chemicals in the subclass have similarly shaped dose-response curves, at least in the region of exposures relevant to the risk assessment.

2.3. CRPF CALCULATIONS

The CRPF combines the RPF-based risk estimates under response addition based on the assumption that the subclasses were accurately formed and independence of action holds. The RPF approach yields a single risk estimate for each subclass of toxicologically similar chemicals for a specified endpoint and time frame.

The total mixture risk for endpoint h (expressed as R_{Th}) is calculated as a sum of the subclass risks (expressed as R_m):

$$R_{Th} = \sum_m R_m \qquad (2\text{-}5)$$

When exposures are estimated using exposure assessment models, Equation 2-5 sums subclass risks that represent not only different MOA, but also different exposure routes. A dose-response curve for each exposure route, or at least some minimal effect level information, is required for each mixture component to develop RPFs.

When internal doses (e.g., blood, tissue or organ doses) are estimated using PBPK models, Equation 2-5 sums subclass risks that represent different MOA and account for exposures from multiple routes. Only oral dose-response information is required for each mixture component, along with bioavailability factors to adjust laboratory administered doses to internal doses (see Section 4).

3. DEVELOPMENT OF DBP MULTIPLE ROUTE EXPOSURE ESTIMATES

The research presented in this document suggests that both exposures and internal doses can be estimated through modeling procedures, incorporating chemical properties of the DBPs, physical characteristics of the indoor environment, and behavioral and physiological characteristics of the exposed individuals relative to the occurrence of the contaminant in the indoor environment. Such estimates may be combined with dose-response data to estimate cumulative risk using the CRPF approach (Section 2). This section describes the results of a research project to develop multiple route exposures and internal dose estimates for DBPs. The full report is provided in Appendix 1. It should be noted that some of the text in this chapter has been taken directly from Appendix 1, but has been reorganized and edited to provide the reader with a summary of the information provided in that report.

3.1. BACKGROUND ON DBP EXPOSURE ESTIMATION

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.

Occurrence data for routinely measured DBPs are available as concentration measurements in drinking water samples taken at water treatment plants, at the consumer's tap or simulated in laboratory studies (e.g., Krasner et al., 1989; Richardson, 1998; U.S. EPA, 1996a). In-home concentrations 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.

Exposure assessment 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 rate estimates 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.

PBPK 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. In an oral exposure model, DBP exposure is a function of the concentration in water and the daily quantity of water ingested; a bioavailability parameter may also be included (U.S. EPA, 2000b) (See Key Definitions). Both U.S. EPA (1994b) and Wilkes (1998), among others, describe inhalation exposure models. Wilkes (1998) describes a model for estimating the absorbed dose of drinking water contaminants including DBPs. The model estimates absorbed doses 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 of relevant DBPs.

Further development of these (or similar) models and extensions to other trihalomethanes (THMs) as well as to other DBP classes such as the haloacetic acids (HAAs) and haloacetonitriles (HANs) is useful both in refining human exposure and absorbed dose estimates and in obtaining more relevant information from epidemiological studies. The development of DBP exposure data derived from exposure assessment and PBPK models of human exposures from multiple exposure routes will provide contextual support for both toxicology data and epidemiology data. This research need has been described in two EPA reports. *The Risk Assessment of Mixtures of Disinfectant Byproducts (DBPs) for Drinking Water Treatment Systems* (U.S. EPA, 2000a) and *Feasibility of Attaining/Constructing Refined DBP Exposure Information for Extant Cancer Epidemiologic Studies* (U.S. EPA, 2000c). The goal of

this research effort is to develop exposure and internal dose estimates for several DBPs using exposure assessment and PBPK models.

3.2. RESEARCH RESULTS REGARDING MULTIPLE ROUTE DBP ESTIMATES

A comprehensive exposure modeling effort was implemented to estimate population-based exposures and absorbed doses for 15 DBPs, incorporating parameters for chemical volatilization, human activity patterns, water use behaviors, ingestion characteristics, building characteristics, physiological measurements, and chemical concentrations in the water supply. The DBPs targeted for evaluation are listed in Table 3-1. Estimates were made for a three person family based on data from women and men of reproductive age (ages 15-45) and children (age 6).

The exposure assessment model for this effort was the Total Exposure Model (TEM) developed by Wilkes Technologies (Wilkes, 1998). The PBPK Model used was the Exposure Related Dose Estimating Model (ERDEM) (Blancato et al., 2000, 2002; Knaak et al., 2002; U.S. EPA, 2002d). This model, formerly known as DEEM (Dose Estimating Exposure Model), was developed by Anteon Corporation in collaboration with the Human Exposure Research Branch of EPA's National Environmental Research Laboratory in Las Vegas. Combining these two models into one analysis provided the ability to evaluate target tissue dose (estimated using ERDEM) as a function of a variety of behaviors, environmental factors, and other exposure related parameters (estimated by TEM). Figure 3-1 illustrates the flow of information in and out of the two models. Of particular note is that TEM is used to develop 24-hour exposure time histories for the demographic groups of interest; this output data set becomes input data to the PBPK model. Also, both models are capable of producing estimates of total absorbed dose, although the ERDEM model does so using more specific physiological functions than

TABLE 3-1

List of Chemicals for Exposure and Internal Dose Assessment

DBP Subclass	Chemical Name	CAS Number
Trihalomethanes (THMs)	Chloroform ($CHCl_3$)	67-66-3
	Bromodichloromethane (BDCM)	75-27-4
	Dibromochloromethane (DBCM)	124-48-1
	Bromoform ($CHBr_3$)	75-25-2
Haloacetic Acids (HAAs)	Chloroacetic acid (CAA)	79-11-8
	Dichloroacetic acid (DCA)	79-43-6
	Trichloroacetic acid (TCA)	76-03-9
	Bromoacetic acid (MBA)	79-08-3
	Dibromoacetic acid (DBA)	631-64-1
	Bromochloroacetic acid (BCA)	5589-96-8
Haloacetonitriles (HANs)	Dichloroacetonitrile (DCAN)	3018-12-0
	Trichloroacetonitrile (TCAN)	545-06-2
	Bromochloroacetonitrile (BCAN)	83463-62-1
	Dibromoacetonitrile (DBAN)	3252-43-5
Miscellaneous	Bromate	15541-45-4

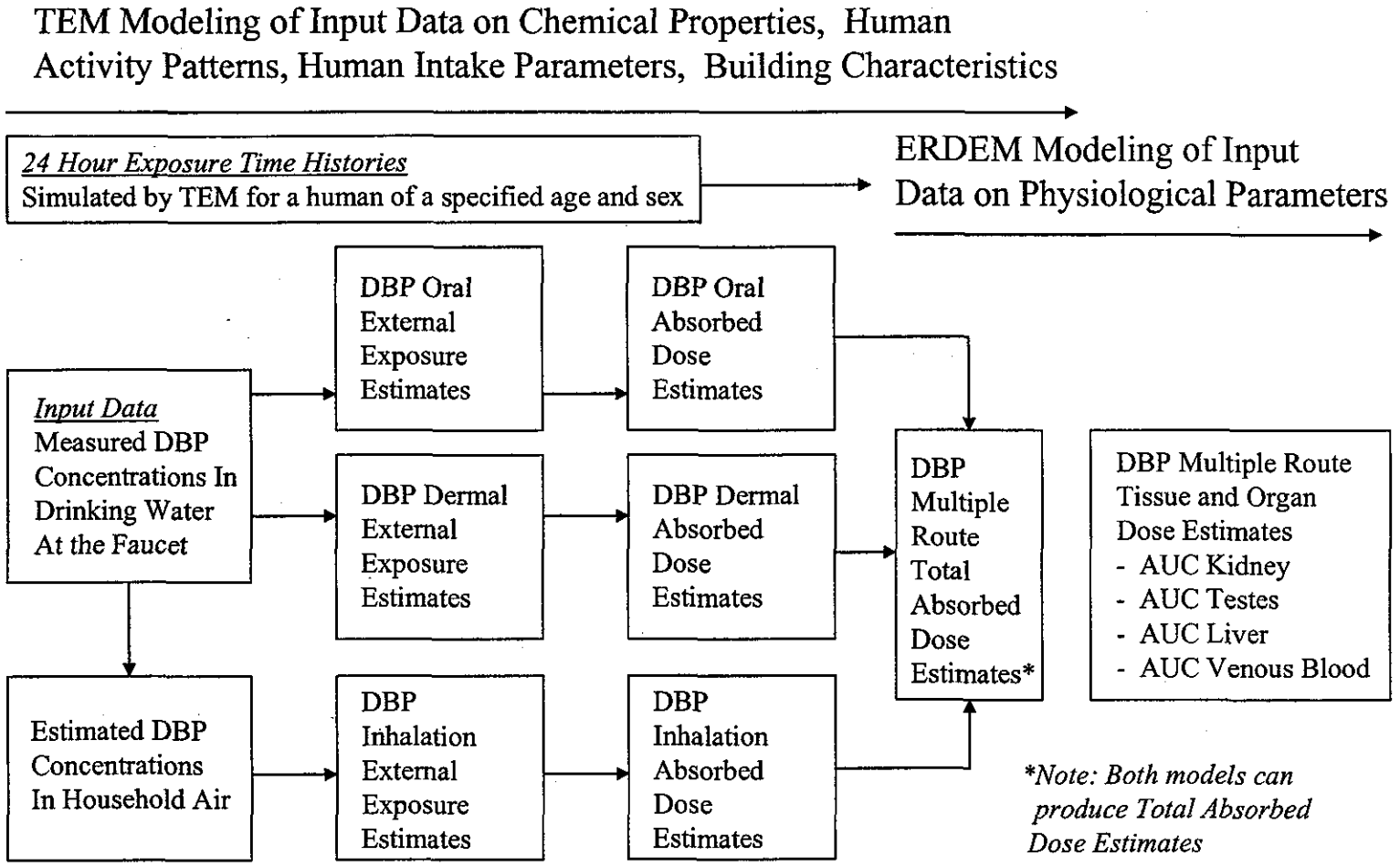

FIGURE 3-1

Linking TEM Exposure Assessment Modeling with ERDEM PBPK Modeling

TEM. Only ERDEM produces the organ and tissue doses. The research report showing all details of the DBP analysis (Appendix 1) includes the following information:

- Detailed Information on the model parameter inputs for both TEM and ERDEM
- Estimates of absorbed dose for oral, dermal, and inhalation routes of exposure and total absorbed dose for 13 (of 15) DBPs using TEM
- Estimates of total absorbed dose and tissue doses for the kidney, liver, venous blood and testes/ovaries for 4 (of 15) DBPs using the PBPK model ERDEM.
- A sensitivity analysis of the combined models for a selected set of parameters.

In the TEM analysis, oral ingestion is subdivided into direct and indirect consumption. Direct consumption of drinking water represents the number of drinks and volumes consumed, either assuming that the contaminant level remains constant from tap to glass to body, or considering that some contaminant volatilized during air contact. Indirect water consumption represents the quantity found in foods or reconstituted drinks and also considers whether the fraction of the contaminant remaining in the drink or food after volatilization and preparation is still significant enough to be included in the exposure calculation.

3.2.1. Model Inputs for TEM. TEM has been applied to several modeling studies examining the exposure and dose to waterborne contaminants as a result of household water use. Wilkes et al. (1992) examined typical exposures for a three person family to trichloroethylene (TCE) from normal water uses. An analysis of behavioral factors leading to inhalation exposure quantified the importance of time spent in the bathroom and in showering and bathing activities (Wilkes et al., 1996). A study comparing the

exposure to DBPs to that of TCE as a result of constructing a municipal treatment facility analyzed whether the remediation lowered the carcinogenic risk to the community (Wilkes and Giardino, 1999; Giardino and Wilkes, 1999). As part of an International Life Sciences Institute (ILSI/RSI) working group entitled "Working Group on Estimation of Dermal and Inhalation Exposures to Contaminants in Drinking Water", a modeling study demonstrating the application of TEM to produce multiple route, population-based estimates of exposure and uptake to three contaminants ($CHCl_3$, methyl parathion, and chromium) was conducted and presented as a case study (Wilkes, 1998).

TEM is an indoor-air-quality human exposure model that combines probabilistic and deterministic principles in a single framework[7]. The input and output data for the TEM application to DBPs are shown in Figure 3-2. This framework combines a Monte Carlo simulation of variable parameters, such as water use behaviors and other behaviors affecting exposure, with point estimates of parameters representing physical and chemical processes, resulting in a prediction of the air and water concentrations at the interface with the exposed individuals. The deterministic framework uses the activities generated by the probabilistic algorithms to predict the release of contaminants, the fate and transport of the contaminants within the building, and finally, the resulting exposures. In the case of volatilization of DBPs during water use, the

[7]Probabilistic analysis is conducted using simulation techniques, randomly sampling values for parameters that have natural variability or uncertainty using distributional data for those parameters. Deterministic analysis is conducted by solving equations, calculating parameter values from known relationships (i.e., calculations based on physical and chemical processes) and using point estimates for various parameters.

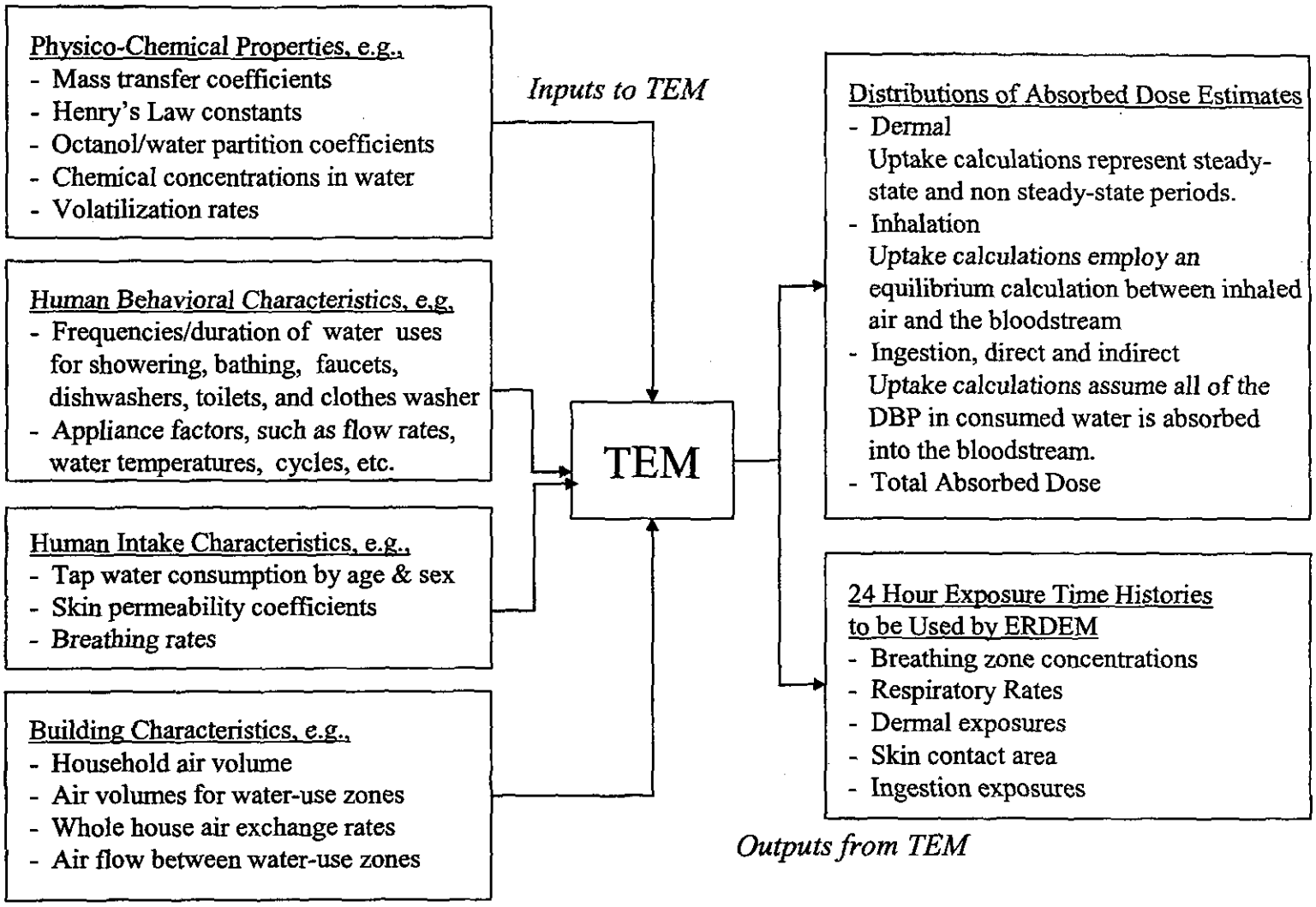

FIGURE 3-2

TEM Modeling of Indoor Air Concentrations, Exposure and Absorbed Dose Estimates

deterministic framework incorporates realistic models for predicting the transfer from the liquid phase to the gas phase during household water uses. Additionally, route specific uptake models are used to estimate the transfer of the chemical to the exposed individual. The TEM model input parameters, shown here with an indication of where they are discussed in Appendix 1, include the following:

- Parameters needed for implementation of volatilization model (Section 3.1., Appendix 1)
- Human behavior characteristics that drive the activity model, including location and water use behaviors (Section 3.2., Appendix 1)
- Ingestion characteristics (Section 3.3., Appendix 1)
- Building characteristics (Section 3.4., Appendix 1)
- Chemical concentrations in water supply (Section 3.5., Appendix 1)

Not all of these parameters are discussed here; the reader is referred to the appropriate section of Appendix 1 for additional details.

One factor that limited the exposure modeling results to 13 of the 15 chemicals was lack of data on specific chemical properties. A literature search was performed to identify reliable values for the desired chemical properties (Section 3.1.2., Appendix 1). For those with data gaps, prediction methods were employed to estimate parameter values (Section 3.1.3., Appendix 1). The properties of interest were Henry's law constant, liquid phase diffusivity, gas phase diffusivity, octanol/water partition coefficient, and molecular weight. Boiling point and volatility were additional properties of value for the study. A number of DBP-specific data gaps were identified as follows:

- Bromochloroacetic Acid (BCA) - Henry's law constant, vapor pressure, liquid and gas phase diffusivities
- Dichloroacetic Acid (DCA) - Liquid and gas phase diffusivities

- Trichloroacetic Acid (TCA) - Liquid and gas phase diffusivities
- Bromoacetic Acid (MBA) - Liquid and gas phase diffusivities
- Dibromoacetic Acid (DBA) - Vapor pressure, liquid and gas phase diffusivities
- Bromochloroacetonitrile (BCAN) - Henry's law constant, Kow, boiling point, vapor pressure, liquid and gas phase diffusivities
- Bromodichloromethane (BDCM) - Henry's law constant for the desired temperatures
- Dichloroacetonitrile (DCAN) - Liquid and gas phase diffusivities
- Trichloroacetonitrile (TCAN) - Liquid and gas phase diffusivities
- Dibromoacetonitrile (DBAN) - Liquid and gas phase diffusivities
- Bromate - Henry's law constant, Kow, boiling point, vapor pressure, liquid and gas phase diffusivities

Prediction methods were used to supplement the literature review for chemical properties that were not found. Values for the dermal permeability coefficients (Kp) were calculated based on biological and physicochemical characteristics of human skin and test chemicals, respectively. Computations were based on the method published by Poulin and Krishnan (2001), in which the value for the partition coefficient of the chemical for human skin and the value for the diffusion coefficient of the chemical for lipid are combined with the fractional lipid and water composition of human skin. Separate values were calculated based on the range of lipid and water contents for human skin, accounting for the range of Kp values demonstrated. Values for the liquid and gas phase diffusivity, the dimensionless Henry's Law Constant, and the overall mass transfer coefficient were predicted for many of the DBPs. However, data were insufficient to estimate chemical properties for BCAN and bromate; thus, exposure estimates were not modeled for these two DBPs.

The water-use behavior parameters needed for TEM were developed from the data presented in the National Human Activity Patterns Survey (NHAPS), the Residential End Use Water Survey (REUWS), Residential Energy Consumption Survey (RECS), in appliance manufacturer data, and supplemented, as necessary, by best judgment. (See Section 3.2.1. of Appendix 1 for additional details on these data bases.)

3.2.2. Model Inputs for ERDEM. ERDEM is a PBPK model consisting of compartments representing different tissue types within the body (Figure 3-3). Rather than make individual compartments for every organ in the body, the models are constructed to include groups of tissues, which are grouped based on the similarity of their tissue composition, metabolic activity and blood flows. These are often the lung (where inhalation exposures occur at the blood:air interface in the alveolus), the liver (modeled usually as the site of chemical metabolism), the richly perfused tissue group, the poorly perfused tissue group and fat (adipose tissue). When the model is developed to account for concentrations of toxicants in specific organs or tissues not usually modeled separately, their tissue mass and blood flow is subtracted from their typical compartment placement, and a new compartment is added to the model and is given descriptions of tissue mass, blood flow, blood:tissue partition coefficient value, and, where appropriate, metabolic activity. The present model exemplifies this, as the compartments for ovaries and testes were isolated from the richly perfused tissue group. Just as in the intact system (the whole body), these compartments differ in biochemical composition, reflected in their being assigned different blood:tissue partition coefficients (unique for each chemical), representing the ability of chemicals to move from blood into tissue perfused with that blood, and the compartments are tied together with blood flow. Thus, PBPK models are developed to accommodate

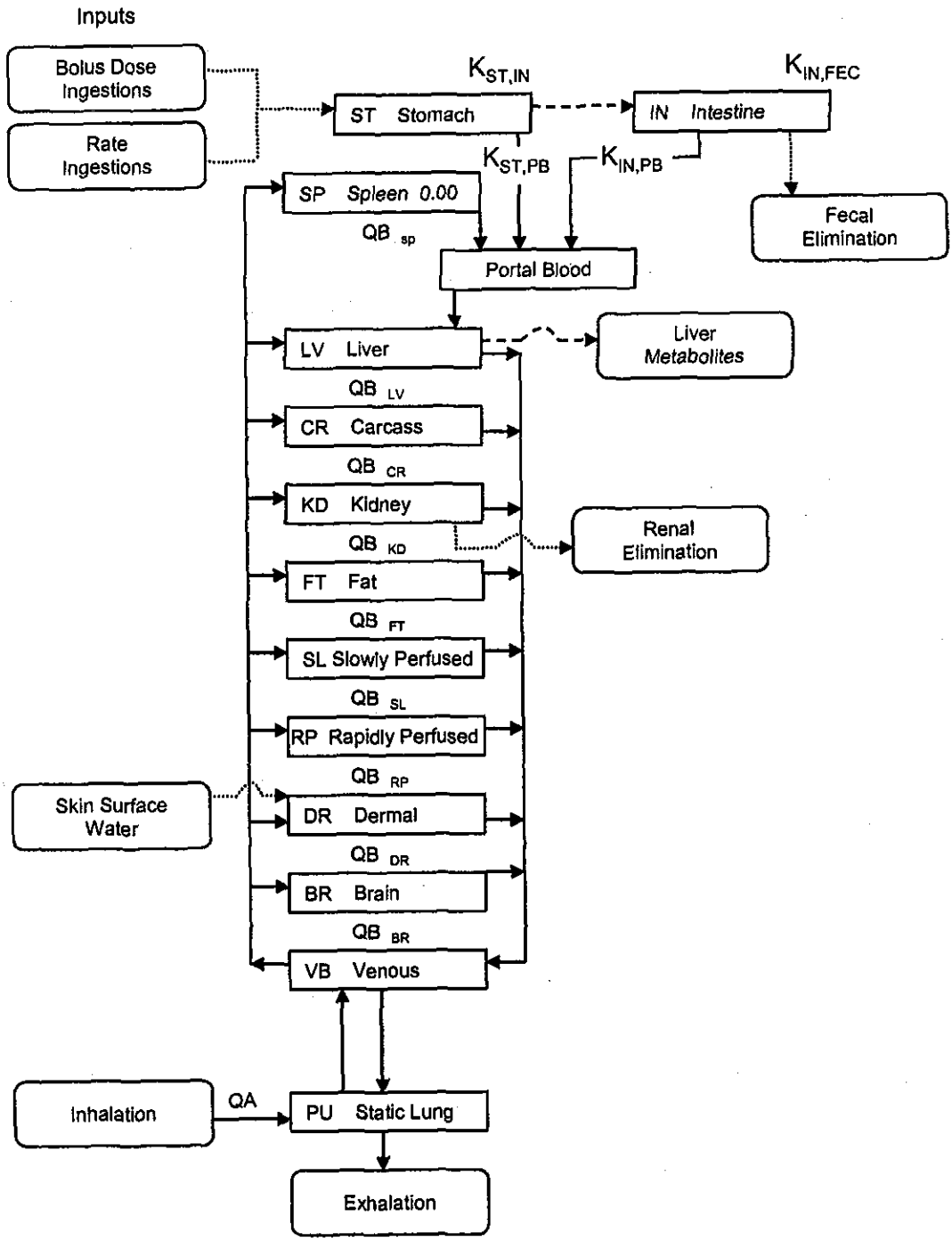

FIGURE 3-3

Compartmental Design of ERDEM PBPK Model

differences in chemical transport between blood and various tissues across dose ranges, and to accurately simulate tissue doses of chemicals resulting from exposures via the oral, dermal, and inhalation routes.

Chemicals are encountered by experimental animals and humans through the oral, dermal and inhalation routes. These routes are each important, and previously, PBPK models have been developed, validated and published accounting for exposure for each of these routes. In the case of ERDEM, the models have discrete input portals for each of the three exposure pathways, with systemic blood then serving as an internal exposure conduit to tissues removed from the portal of entry (lung, GI tract, skin). Within the PBPK model, each compartment is linked with the others via the blood compartment, which is described by both blood:air and blood:tissue partition coefficients and flow to the various tissue groups, proportionate to the flow to various tissues in the body. For instance, the lung compartment gets 100% of the cardiac output, while the liver compartment gets approximately 20% of the cardiac output.

PBPK models are comprised of a series of differential equations which describe the movement of a chemical into blood and from blood into tissues over the course of chemical exposure. Models such as this are constructed so that they accurately portray route-specific absorption of chemical across the skin by including biochemical constants governing dermal transport, absorption into the blood in the alveolus by including the blood:air partition coefficient value and rates of alveolar ventilation, and absorption from the gut into the blood by including specific information on water solubility, lipid solubility and ionization characteristics. Once in the systemic circulation, these models are constructed to describe the partitioning of the chemical from blood into the various tissue types of the body, the metabolism of the chemical, urinary elimination of the

chemical as parent chemical and/or metabolite, and the exhalation of the chemical or metabolite in expired air. This is accomplished by developing several chemical-specific biochemical measures in vitro (tissue:air partition coefficients and/or blood:tissue partition coefficients). These values are integrated with values describing blood flow to the various tissue compartments and estimates of metabolic rate constants, and through an iterative process, fitting PBPK model predictions to a set of values for measured tissue time-course doses.

The input and output data for the ERDEM application to DBPs are shown in Figure 3-4. Input parameters are treated in the analysis as point estimates. The volumes and blood flows are required for each compartment or sub-section of a compartment. The breathing rates, the gastrointestinal absorption rates, and the skin permeation coefficients, in part, determine the absorbed dose of chemical into the body. Partition coefficients for tissue to blood, tissue to air, and blood to air, determine how much of the chemical remains and how much passes to the next state. Metabolic constants determine the amount of chemical that is converted to metabolites. The greatest difficulty is determining values for the various parameters needed for a species and chemical; generic values for volumes and blood flows for a set of compartments or sub-compartments is not adequate. Each type of chemical that is modeled may require the use of a different set of compartments. Some compartments may be combined, or others may be broken up into multiple subcompartments. The chemically-dependent parameters are determined from many sources, or are estimated using various techniques, such as QSARs (Quantitative Structure-Activity Relationships). The choices are made based on the state of the science for the chemicals, their metabolism pathways, and the type of chemical. The ERDEM model input parameters are

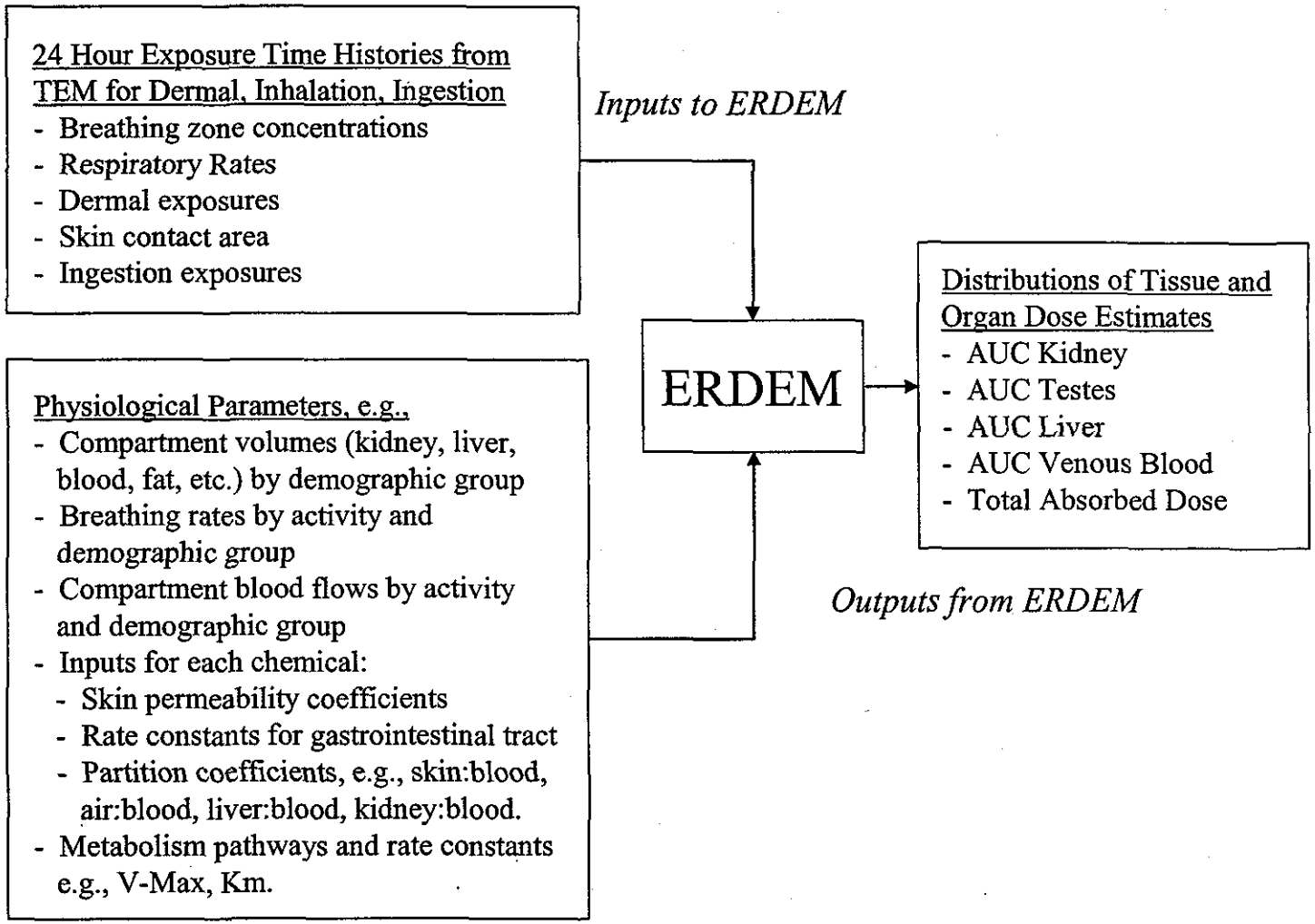

FIGURE 3-4

ERDEM Modeling of Tissue and Organ Level Absorbed Dose Estimates

developed in Section 3.6. of Appendix 1. These input parameters, with an indication of where they are discussion in Appendix 1, include the following:

- Compartment volumes by demographic group (Section 3.6.1., Appendix 1)
- Breathing rates by activity and demographic group (Section 3.6.2., Appendix 1)
- Compartment blood flows by activity and demographic group (Section 3.6.3., Appendix 1)
- Definition of the exposure scenarios for each exposure route (Section 3.6.4., Appendix 1) (24-hour exposure time histories supplied by TEM)
- Skin permeability coefficients for each chemical (Section 3.6.5., Appendix 1)
- Rate constants for the gastrointestinal model for each chemical (Section 3.6.6., Appendix 1)
- Compartment-to-blood partition coefficients (Section 3.6.7., Appendix 1)
- Metabolism pathways for each parent chemical (Section 3.6.8., Appendix 1)
- The metabolism rate constants, or the V-Max and the Michaelis Menten constants for each metabolism to be modeled (Section 3.6.8., Appendix 1)
- The elimination rate constants for the urine, feces, and any other required compartments, by chemical (Section 3.6.9., Appendix 1)

Data for these parameters were found using a number of sources including the peer reviewed literature, the EPA's Exposure Factors Handbook (U.S. EPA, 1997b), personal communications from scientists working in this scientific area, estimates from modeling predictions, and estimates extrapolated using values from other compounds in the same class. Of particular note for the DBP analysis, however, is that the definition of the exposure scenarios for each exposure route (Section 3.6.4., Appendix 1) is the set of parameters that is supplied by TEM in the form of 24-hour exposure time

histories. Study size limitations for this effort resulted in the selection of four DBPs for PBPK modeling, $CHCL_3$, BDCM, DCA and TCA.

3.2.3. Modeling Results. TEM was initiated using the inputs on chemical specific properties, building-related model parameters and water-use behaviors, identifying the structure of the household, the characteristics and locations of the water appliances, and the population groups for the three-person household. For each simulated period of 24 hours, activity patterns were sampled from the NHAPS for the three defined population groups, the activities were mapped into the household, and the appropriate water uses were simulated consistent with the activity patterns. The model was executed for 1000 simulations.

Subsequent to executing the exposure model, the results were interfaced with the PBPK model, ERDEM (Figures 3-2 and 3-4). This was accomplished by creating 24-hour exposure time histories containing information on breathing zone concentrations, respiratory rates, dermal exposures, skin contact area, ingestion exposures as a function of time for each of the simulations. These results were input into ERDEM for 250 of the simulations to predict blood and organ concentrations.

3.2.3.1. TEM Modeling Results — Simulation results of the TEM modeling include distributions of absorbed dose estimates for the dermal, ingestion (direct and indirect), and inhalation exposure routes and total absorbed dose. In Appendix 1, a table is presented for each of the 13 DBPs, containing the absorbed doses for a 24-hour period as a function of route, population group, and percentile of the population. Table 3-2 shows an example of the absorbed dose estimates for BDCM. Table 3-3 shows the 50th percentile absorbed dose estimates for all 13 DBPs. In addition to these tables for the 13 DBPs, Appendix 1 provides plots of their respective

TABLE 3-2

TEM Output for BDCM: Absorbed Dose Estimates (mg) for a 24-Hour Exposure

Percentile	Total[a]	Dermal	Ingestion			Inhalation
			Direct	Indirect	Total[a]	
Female, Age 15-45						
1	7.20E-03	0[b]	1.03E-03	5.64E-04	2.49E-03	1.12E-04
5	1.35E-02	0[b]	1.83E-03	7.64E-04	3.51E-03	2.66E-03
10	1.92E-02	1.54E-04	2.46E-03	8.86E-04	4.14E-03	8.78E-03
25	3.96E-02	3.71E-04	4.19E-03	1.23E-03	6.05E-03	2.35E-02
50	8.00E-02	2.70E-03	7.73E-03	1.71E-03	9.72E-03	6.12E-02
75	1.66E-01	5.21E-03	1.51E-02	2.37E-03	1.69E-02	1.42E-01
90	2.79E-01	8.67E-03	2.76E-02	3.18E-03	2.95E-02	2.64E-01
95	4.13E-01	1.21E-02	3.50E-02	3.61E-03	3.70E-02	3.88E-01
99	2.41E+00	1.87E-02	8.49E-02	5.05E-03	8.60E-02	2.38E+00
Male, Age 15-45						
1	6.25E-03	0[b]	7.64E-04	2.79E-04	2.18E-03	1.01E-04
5	1.27E-02	0[b]	1.55E-03	4.95E-04	3.42E-03	2.64E-03
10	1.97E-02	0[b]	2.14E-03	6.49E-04	4.35E-03	6.07E-03
25	3.88E-02	3.09E-04	4.05E-03	1.05E-03	6.52E-03	1.89E-02
50	8.43E-02	2.90E-03	7.98E-03	1.85E-03	1.11E-02	6.05E-02
75	1.64E-01	5.57E-03	1.55E-02	3.37E-03	1.86E-02	1.46E-01
90	2.95E-01	8.73E-03	2.91E-02	5.67E-03	3.19E-02	2.74E-01
95	4.36E-01	1.13E-02	4.31E-02	7.93E-03	4.68E-02	4.23E-01
99	1.93E+00	1.84E-02	7.14E-02	1.31E-02	7.28E-02	1.91E+00

TABLE 3-2 cont.

Percentile	Total[a]	Dermal	Ingestion			Inhalation
			Direct	Indirect	Total[a]	
Child, Age 6						
1	3.51E-03	0[b]	4.66E-04	1.13E-04	1.10E-03	5.71E-05
5	6.98E-03	0[b]	8.66E-04	2.26E-04	1.73E-03	1.13E-03
10	1.00E-02	0[b]	1.17E-03	3.28E-04	2.27E-03	2.98E-03
25	1.95E-02	9.26E-05	2.07E-03	6.03E-04	3.50E-03	1.07E-02
50	4.38E-02	2.66E-04	4.02E-03	1.07E-03	6.03E-03	3.36E-02
75	9.48E-02	2.67E-03	7.68E-03	2.17E-03	9.89E-03	8.56E-02
90	1.81E-01	4.48E-03	1.32E-02	3.80E-03	1.53E-02	1.73E-01
95	2.29E-01	5.63E-03	1.75E-02	5.37E-03	1.88E-02	2.19E-01
99	3.58E-01	8.03E-03	3.25E-02	8.16E-03	3.54E-02	3.51E-01

[a]Note that total absorbed dose (by ingestion or by all three routes) is not equal to the sum of the doses in each row. This occurs because each simulation provides a new data point to each of the dose estimates represented in the columns; the percentiles are then produced for each dose estimate (column) independently of each other. Furthermore, because the total absorbed dose is the sum of independent random variables, its variance is less than what is obtained when specific percentiles are summed.

[b]The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

TABLE 3-3

50th Percentile 24-Hour Absorbed Dose Estimates (mg) Output by TEM

Chemical	Total*	Dermal	Ingestion			Inhalation
			Direct	Indirect	Total*	
Female, Age 15-45						
$CHCl_3$	3.00E-01	2.51E-02	2.09E-02	3.76E-03	2.52E-02	2.19E-01
BDCM	8.00E-02	2.70E-03	7.73E-03	1.71E-03	9.72E-03	6.12E-02
DBCM	5.12E-02	2.47E-03	5.33E-03	1.40E-03	7.03E-03	3.73E-02
$CHBr_3$	2.65E-02	1.60E-03	2.88E-03	3.00E-03	6.55E-03	1.63E-02
MCA	4.45E-01	1.16E-04	1.91E-03	1.99E-03	4.34E-03	1.15E-06
DCA	2.73E-02	1.05E-05	1.20E-02	1.25E-02	2.72E-02	5.46E-06
TCA	2.90E-02	1.71E-05	1.27E-02	1.32E-02	2.89E-02	9.27E-06
MBA	8.73E-03	2.32E-04	3.74E-03	3.89E-03	8.51E-03	1.79E-06
DBA	3.76E-03	1.06E-04	1.61E-03	1.67E-03	3.66E-03	4.33E-07
BCA	7.95E-03	2.18E-04	3.40E-03	3.54E-03	7.74E-03	2.09E-06
DCAN	1.83E-03	4.08E-05	7.48E-04	7.79E-04	1.70E-03	4.39E-05
TCAN	1.26E-04	4.18E-06	5.23E-05	5.45E-05	1.19E-04	9.73E-07
DBAN	7.09E-04	1.79E-05	3.03E-04	3.15E-04	6.89E-04	1.88E-06
Male, Age 15-45						
$CHCl_3$	3.02E-01	2.62E-02	2.16E-02	4.00E-03	2.84E-02	2.13E-01
BDCM	8.43E-02	2.90E-03	7.98E-03	1.85E-03	1.11E-02	6.05E-02
DBCM	5.49E-02	2.64E-03	5.50E-03	1.52E-03	8.10E-03	3.79E-02
$CHBr_3$	3.00E-02	1.70E-03	2.97E-03	3.24E-03	7.55E-03	1.68E-02
MCA	5.09E-03	1.25E-04	1.97E-03	2.14E-03	5.00E-03	1.33E-06
DCA	3.14E-02	1.16E-05	1.23E-02	1.35E-02	3.14E-02	6.20E-06
TCA	3.34E-02	1.88E-05	1.31E-02	1.43E-02	3.33E-02	1.09E-05
MBA	9.97E-03	2.50E-04	3.86E-03	4.20E-03	9.81E-03	1.99E-06
DBA	4.29E-03	1.14E-04	1.66E-03	1.81E-03	4.22E-03	5.04E-07

TABLE 3-3 cont.

Chemical	Total*	Dermal	Ingestion			Inhalation
			Direct	Indirect	Total*	
Male, Age 15-45						
BCA	9.08E-03	2.35E-04	3.51E-03	3.82E-03	8.93E-03	2.35E-06
DCAN	2.09E-03	4.46E-05	7.72E-04	8.41E-04	1.96E-03	4.26E-05
TCAN	1.45E-04	4.47E-06	5.40E-05	5.88E-05	1.37E-04	1.00E-06
DBAN	8.13E-04	1.94E-05	3.12E-04	3.40E-04	7.94E-04	1.99E-06
Child, Age 6						
$CHCl_3$	1.56E-01	1.87E-03	1.09E-02	9.19E-04	1.26E-02	1.19E-01
BDCM	4.38E-02	2.66E-04	4.02E-03	1.07E-03	6.03E-03	3.36E-02
DBCM	2.91E-02	2.59E-04	2.77E-03	7.72E-04	4.18E-03	2.21E-02
$CHBr_3$	1.34E-02	1.73E-04	1.50E-03	7.42E-03	2.70E-03	8.77E-03
MCA	1.84E-03	1.35E-05	9.92E-04	4.92E-04	1.79E-03	6.29E-07
DCA	1.12E-02	1.26E-06	6.22E-03	3.08E-03	1.12E-02	3.01E-06
TCA	1.19E-02	2.06E-06	6.61E-03	3.28E-03	1.19E-02	5.22E-06
MBA	3.61E-03	2.70E-05	1.95E-03	9.64E-04	3.50E-03	1.01E-06
DBA	1.56E-03	1.22E-05	8.36E-04	4.14E-04	1.51E-03	2.37E-07
BCA	3.29E-03	2.53E-05	1.77E-03	8.77E-04	3.19E-03	1.26E-06
DCAN	7.72E-04	4.84E-06	3.89E-04	1.93E-04	7.01E-04	2.57E-05
TCAN	5.20E-05	4.76E-07	2.72E-05	1.35E-05	4.91E-05	5.57E-07
DBAN	2.94E-04	2.10E-06	1.58E-04	7.81E-05	2.84E-04	1.07E-06

[a]Note that total absorbed dose (by ingestion or by all three routes) is not equal to the sum of the doses in each row. This occurs because each simulation provides a new data point to each of the dose estimates represented in the columns; the percentiles are then produced for each dose estimate (column) independently of each other. Furthermore, because the total absorbed dose is the sum of independent random variables, its variance is less than what is obtained when specific percentiles are summed.

cumulative distribution functions and histograms for the dose estimates (see Section 4.2.2., Appendix 1).

The results of the uptake modeling provide information for comparing and contrasting uptake as a function of the chemical, the population group and behavior, and the route of exposure. General conclusions about the importance of each route for a given chemical can be made by comparing the uptake for each route. However, specific conclusions can be problematic due to large uncertainties in some of the model parameters, most notably the dermal permeability coefficient. A large range of uncertainty exists in the dermal estimates that make it difficult to compare the dermal route to the inhalation and ingestion routes. This is because the skin permeability rates (Section 3.6.5. of Appendix 1) are generally poorly quantified. The values presented in the table are estimated based on correlation with other chemical properties, and there are few measured values for this parameter to serve as a validation. As a result, the uncertainty in this parameter is quite large. The impact of this uncertainty is examined by calculating the dermal uptake at the minimum and maximum values of the identified range (Section 4.2.3. of Appendix 1).

The THMs are the most volatile class of chemicals in this study, and the inhalation route clearly dominates the absorbed dose estimates. The contribution of the ingestion and dermal routes are similar, and given the uncertainty of the parameters, it is unclear which route provides the larger dose. The contribution of the dose by route of exposure/uptake is presented for each chemical for the 50th and 95th percentiles of each population group (Tables 3-4 and 3-5). The relative contribution of the inhalation pathway to the total absorbed dose for BDCM is higher than that for chloroform. This may be attributed to the significantly higher blood:air partition coefficient of BDCM

TABLE 3-4

Summary of 24-Hour Absorbed Dose by Route for 50th Percentile of the Population

Chemical	Total Absorbed Dose (mg/day)	Contribution to Total by Route		
		Dermal	Ingestion	Inhalation
Female, Age 15-45				
$CHCl_3$	3.00E-01	9%	9%	81%
BDCM	8.00E-02	4%	13%	83%
DBCM	5.12E-02	5%	15%	80%
$CHBr_3$	2.65E-02	7%	27%	67%
MCA	4.45E-01	3%	97%	0%
DCA	2.73E-02	0%	100%	0%
TCA	2.90E-02	0%	100%	0%
MBA	8.73E-03	3%	97%	0%
DBA	3.76E-03	3%	97%	0%
BCA	7.95E-03	3%	97%	0%
DCAN	1.83E-03	2%	95%	2%
TCAN	1.26E-04	3%	96%	1%
DBAN	7.09E-04	3%	97%	0%
Male, Age 15-45				
$CHCl_3$	3.02E-01	10%	11%	80%
BDCM	8.43E-02	4%	15%	81%
DBCM	5.49E-02	5%	17%	78%
$CHBr_3$	3.00E-02	7%	29%	64%
MCA	5.09E-03	2%	98%	0%
DCA	3.14E-02	0%	100%	0%
TCA	3.34E-02	0%	100%	0%
MBA	9.97E-03	2%	97%	0%
DBA	4.29E-03	3%	97%	0%

TABLE 3-4 cont.

Chemical	Total Absorbed Dose (mg/day)	Contribution to Total by Route		
		Dermal	Ingestion	Inhalation
BCA	9.08E-03	3%	97%	0%
DCAN	2.09E-03	2%	96%	2%
TCAN	1.45E-04	3%	96%	1%
DBAN	8.13E-04	2%	97%	0%
Child, Age 6				
$CHCl_3$	1.56E-01	1%	9%	89%
BDCM	4.38E-02	1%	15%	84%
DBCM	2.91E-02	1%	16%	83%
$CHBr_3$	1.34E-02	1%	23%	75%
MCA	1.84E-03	1%	99%	0%
DCA	1.12E-02	0%	100%	0%
TCA	1.19E-02	0%	100%	0%
MBA	3.61E-03	1%	99%	0%
DBA	1.56E-03	1%	99%	0%
BCA	3.29E-03	1%	99%	0%
DCAN	7.72E-04	1%	96%	4%
TCAN	5.20E-05	1%	98%	1%
DBAN	2.94E-04	1%	99%	0%

TABLE 3-5

Summary of 24-Hour Absorbed Dose by Route for 95th Percentile of the Population

Chemical	Total Absorbed Dose (mg/day)	Contribution to Total by Route		
		Dermal	Ingestion	Inhalation
Female, Age 15-45				
$CHCl_3$	1.52E+00	8%	6%	86%
BDCM	4.13E-01	3%	8%	89%
DBCM	2.56E-01	4%	10%	87%
$CHBr_3$	1.12E-01	5%	14%	81%
MCA	1.13E-02	3%	97%	0%
DCA	7.03E-02	0%	100%	0%
TCA	7.48E-02	0%	100%	0%
MBA	2.22E-02	3%	97%	0%
DBA	9.54E-03	4%	96%	0%
BCA	2.02E-02	4%	96%	0%
DCAN	4.53E-03	3%	92%	5%
TCAN	3.13E-04	5%	94%	2%
DBAN	1.80E-03	3%	96%	1%
Male, Age 15-45				
$CHCl_3$	1.56E+00	7%	7%	86%
BDCM	4.36E-01	2%	10%	88%
DBCM	2.68E-01	3%	11%	85%
$CHBr_3$	1.20E-01	4%	18%	78%
MCA	1.66E-02	2%	98%	0%
DCA	1.03E-01	0%	100%	0%
TCA	1.10E-01	0%	100%	0%
MBA	3.25E-02	2%	98%	0%
DBA	1.40E-02	3%	97%	0%

TABLE 3-5 cont.				
Chemical	Total Absorbed Dose (mg/day)	Contribution to Total by Route		
		Dermal	Ingestion	Inhalation
BCA	2.95E-02	2%	97%	0%
DCAN	6.51E-03	2%	94%	4%
TCAN	4.55E-04	3%	96%	1%
DBAN	2.63E-03	2%	97%	0%
Child, Age 6				
$CHCl_3$	8.63E-01	7%	5%	88%
BDCM	2.29E-01	2%	8%	90%
DBCM	1.55E-01	3%	8%	89%
$CHBr_3$	6.28E-02	4%	12%	84%
MCA	5.51E-03	3%	97%	0%
DCA	3.38E-02	0%	100%	0%
TCA	3.60E-02	0%	100%	0%
MBA	1.08E-02	3%	97%	0%
DBA	4.65E-03	4%	96%	0%
BCA	9.85E-03	4%	96%	0%
DCAN	2.26E-03	3%	90%	7%
TCAN	1.54E-04	4%	93%	2%
DBAN	8.76E-04	3%	96%	1%

(6.11) versus that for chloroform (3.94). These values indicate that for equal amounts of BDCM and chloroform in inspired air, blood will absorb 55% more BDCM than chloroform.

The HAAs and HANs are much less volatile, and therefore the inhalation route has the least contribution to the absorbed dose. Given the large uncertainty in the dermal parameters, it is unclear whether ingestion or dermal is the largest contributor to the total absorbed dose. In general, for less volatile compounds, dermal absorption is less than ingestion, but is generally within an order of magnitude. This summary further illustrates that multiple exposure route analysis is important because exposures are dependent upon chemical properties, particularly a chemical's volatility. In addition, this summary further underscores the importance of understanding the uncertainties associated with individual exposure routes relative to the predicted exposures. In the case of the dermal route, the summary also shows the importance of understanding this uncertainty to identify the importance of the dermal route. Given the large uncertainty in the dermal parameters, the dermal route cannot be dismissed as unimportant even though the results indicate it is of lesser importance. Other analyses not conducted as a part of this research could have benefits. A very intensive evaluation of the results would allow an understanding of the impact of each activity and the range of behavior across a population. An analysis of the relationship between water-use behavior and resultant exposure and dose would be useful in identifying and potentially modifying exposure related behaviors. In addition, the impact of a multitude of other factors, such as air exchange rates, water use rates, and water temperature, could be evaluated.

3.2.3.2. ERDEM Modeling Results — TEM was used to produce 24-hour exposure time histories for use by ERDEM; 250 simulations of exposure conditions

were generated. These exposure conditions were the results of Monte Carlo simulations of individual water-related activity. For instance, if hand washing occurred at a finite frequency between 3 and 7 times per day, and for a duration of between 30 seconds and three minutes, the model would randomly select a frequency and a duration 250 times, and pair that exposure with random selections from data describing exposures from other water-related activities. Water use patterns were separately developed for the adult male, the adult female and the male child. Each of these exposures was combined in TEM to produce a total of 250 individual daily exposure patterns. This same panel of exposure patterns was used with chemical-specific physicochemical characteristics to determine "secondary" measures of water exposure, e.g., the concentration of chloroform in air following showering activity. Once completed, the 250 individual exposure patterns developed from simulations of water use activities were used as an "input" for the PBPK modeling of internal dose (Figure 3-3), accomplished via ERDEM. In the next phase, the chemical of interest was selected, and exposure patterns simulated by TEM were used as input values upon which ERDEM based the exposure scenarios for simulations of tissue doses. The estimation of tissue doses was accomplished by programming and operating a previously validated PBPK model for each chemical of interest. These models were standardized, so that flows and tissue volumes were consistent across the different chemicals. ERDEM was constructed to simulate tissue doses of parent chemical in several different tissues, identified as potential target organs of toxicity. ERDEM estimated exposure metrics as area under the concentration-time curve (AUC) for liver, kidney, venous blood, ovaries and testes averaged over two days. This differs from the TEM modeling, in which results are presented as AUC averaged over a single 24-hour

exposure period. Differences, if any, between the AUC values calculated by TEM and separately by ERDEM, thus, will reflect "carry-over", or the residual chemical present from the first 24-hour period at the time the second 24-hour exposure period was initiated. Results for BDCM (Table 3-6), $CHCl_3$ (Table 3-7), DCA (Table 3-8) and TCA (Table 3-9) are presented for three different age-dependent models: the adult male, the adult female and the 6-year-old male child. Results are configured so that variance in water use patterns governing exposure via the oral, dermal and inhalation routes is demonstrated as variance in the AUC for a given tissue or organ. While TEM identified 250 independent exposure scenarios, the PBPK models employed by ERDEM utilized point estimates for partition coefficients and metabolic parameters taken from within distributions of values, either previously determined or developed through professional judgment. A sensitivity analysis (Section 3.2.4.) demonstrated the impact of variance of these values with respect to different pharmacokinetic outcomes of interest. For the pharmacokinetic outcome of interest (determined by the results of toxicity studies: for instance, if kidney toxicity is the result of a metabolite, the appropriate pharmacokinetic outcome would be the amount of the metabolite present in kidney), the sensitivity of that outcome was measured and is presented as a function of variance of the parameter (e.g., blood:kidney partition coefficient) being investigated. AUC values are presented as mg/L*hr. In this simulation, the model was not constructed to simulate water use patterns in the form necessary to capture peak exposures, as these are highly influenced by the placement of an individual in juxtaposition to a water use portal and the timing of discrete and often independent water uses. Instead, the model does capture AUC values, which are useful in estimating toxicity, and are based on the

TABLE 3-6

48-Hour PBPK Modeled Absorbed Doses for BDCM for the Adult Male, Adult Female and Male Child

Demographic Group	Average	Standard Deviation	Skewness	Max	Min	5th	10th	50th	90th	95th
Adult Male										
AUC Kidney (mg/L*hr)	0.00230	0.00681	9.98	0.0919	8.56E-06	6.72E-05	9.58E-05	0.000884	0.00386	0.00643
AUC Testes (mg/L*hr)	0.00450	0.0134	9.98	0.180	1.68E-05	0.000132	0.000188	0.00173	0.00757	0.0126
Absorbed Dose (mg)	0.455	1.31	10.0	17.7	0.00730	0.0201	0.0340	0.184	0.732	1.25
AUC Liver (mg/L*hr)	0.00043	0.00119	9.95	0.0161	1.11E-05	2.73E-05	4.26E-05	0.000188	0.000714	0.00114
AUC Venous Blood	0.00176	0.00517	9.96	0.0698	9.04E-06	5.52E-05	8.11E-05	0.000682	0.00294	0.00490
Adult Female										
AUC Kidney (mg/L*hr)	0.00269	0.00721	6.23	0.0640	1.02E-05	5.36E-05	0.00013	0.00103	0.00424	0.00723
AUC Ovaries (mg/L*hr)	0.00372	0.00995	6.22	0.0883	1.4E-05	7.39E-05	0.00018	0.00142	0.00584	0.00994
Absorbed Dose (mg)	0.457	1.20	6.24	10.6	0.00793	0.0206	0.0328	0.177	0.703	1.22
AUC Liver (mg/L*hr)	0.000525	0.00133	6.23	0.0118	1.51E-05	3.33E-05	4.41E-05	0.000217	0.000794	0.00135
AUC Venous Blood	0.00203	0.00540	6.22	0.0479	1.11E-05	4.85E-05	0.000107	0.000778	0.00319	0.00539
Demographic Group	Average	Standard	Skewness	Max	Min	5th	10th	50th	90th	95th
Child Male										
AUC Kidney (mg/L*hr)	0.00132	0.00149	2.18	0.00899	3.86E-06	4.85E-05	0.000142	0.000815	0.00342	0.00440
AUC Testes (mg/L*hr)	0.00258	0.00291	2.18	0.0176	7.57E-06	9.52E-05	0.000279	0.00160	0.00670	0.00864
Absorbed Dose (mg)	0.175	0.190	2.19	1.16	0.00174	0.0126	0.0232	0.113	0.437	0.567
AUC Liver (mg/L*hr)	0.000377	0.000392	2.20	0.00244	6.51E-06	4.3E-05	5.94E-05	0.000251	0.000921	0.00118
AUC Venous Blood	0.00104	0.00117	2.19	0.00710	4.38E-06	4.54E-05	0.000119	0.000653	0.00268	0.00345

TABLE 3-7

48-Hour PBPK Modeled Absorbed Doses for $CHCL_3$ for the Adult Male, Adult Female, and Male Child

Demographic Group	Average	Standard Deviation	Skewness	Max	Min	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
Adult Male										
AUC Kidney mg/L*hr)	0.01118	0.0319	9.70	0.426	1.68E-05	0.000251	0.000552	0.00445	0.0187	0.0316
AUC Testes (mg/L*hr)	0.0141	0.0407	9.70	0.544	2.14E-05	0.000321	0.000704	0.00568	0.0239	0.0403
Absorbed Dose (mg)	1.57	4.43	9.74	59.2	0.0175	0.0650	0.1070	0.658	2.560	4.61
AUC Liver (mg/L*hr)	0.00120	0.00331	9.71	0.0443	2.24E-05	6.32E-05	0.000106	0.000522	0.00194	0.00339
AUC Venous Blood (mg/L*hr)	0.00576	0.0163	9.67	0.218	1.07E-05	0.000142	0.000325	0.00234	0.00960	0.0164
Adult Female										
AUC Kidney (mg/L*hr)	0.0117	0.0311	6.16	0.275	1.39E-05	0.000194	0.000532	0.00448	0.0183	0.0314
AUC Ovaries (mg/L*hr)	0.0114	0.0302	6.16	0.267	1.35E-05	0.000189	0.000519	0.00436	0.0178	0.0305
Absorbed Dose (mg)	1.58	4.10	6.18	36.4	0.0214	0.0622	0.104	0.609	2.45	4.24
AUC Liver (mg/L*hr)	0.001428	0.00362	6.17	0.0321	3.17E-05	7.74E-05	0.000116	0.000585	0.00219	0.00366
AUC Venous Blood (mg/L*hr)	0.00629	0.0164	6.15	0.145	1.119E-05	0.000117	0.000311	0.00241	0.00980	0.0166
Child Male										
AUC Kidney (mg/L*hr)	0.00586	0.00666	2.23	0.0422	5.19E-06	0.000137	0.000622	0.00364	0.0152	0.0201
AUC Testes (mg/L*hr)	0.00772	0.00878	2.23	0.0556	6.84E-06	0.000180	0.000821	0.00480	0.0201	0.0265
Absorbed Dose (mg)	0.601	0.657	2.24	4.20	0.00466	0.0354	0.0796	0.391	1.5	1.99
AUC Liver (mg/L*hr)	0.0010	0.00117	2.26	0.00758	1.43E-05	9.92E-05	0.000165	0.000738	0.00272	0.00354
AUC Venous Blood (mg/L*hr)	0.00319	0.00358	2.24	0.0229	4.19E-06	9.23E-05	0.000347	0.00198	0.00823	0.0108

TABLE 3-8

48-Hour PBPK Modeled Absorbed Doses for DCA for the Adult Male, Adult Female, and Male Child

Demographic Group	Average	Standard Deviation	Skewness	Max	Min	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
Adult Male										
AUC Kidney mg/L*hr)	0.00399	0.00318	3.54	0.0310	0.000392	0.00123	0.00141	*0.00317*	0.00733	0.00983
AUC Testes (mg/L*hr)	0.00493	0.00393	3.54	0.0384	0.000485	0.00152	0.00174	0.00392	0.00907	0.0122
Absorbed Dose (mg)	0.0693	0.0542	3.26	0.509	0.00633	0.0217	0.0242	0.0544	0.127	0.175
AUC Liver (mg/L*hr)	0.00404	0.00322	3.52	0.0313	0.000396	0.001248	0.001426	0.00321	*0.00743*	0.00997
AUC Venous Blood (mg/L*hr)	0.00498	0.00397	3.54	0.0388	0.00049	0.00154	0.00176	0.00396	0.00917	0.0123
Adult Female										
AUC Kidney (mg/L*hr)	0.00221	*0.00227*	4.30	0.0215	0.000284	0.00048	0.000612	0.00159	0.00449	0.00547
AUC Ovaries (mg/L*hr)	0.00262	0.00270	4.30	0.0255	*0.000337*	0.000569	0.000726	0.00189	0.00533	0.00649
Absorbed Dose (mg)	0.0339	0.0347	4.22	0.325	0.00422	*0.00726*	0.00934	0.0243	0.0675	0.0848
AUC Liver (mg/L*hr)	0.00224	0.00232	4.31	0.0218	0.000288	0.000486	0.000620	0.00162	*0.00456*	0.00557
AUC Venous Blood (mg/L*hr)	0.00272	0.00281	4.30	0.0265	0.000351	0.000592	0.000755	0.00196	0.00555	0.00675
Child Male										
AUC Kidney (mg/L*hr)	0.00248	0.00208	2.46	0.0168	0.000195	0.000559	0.000664	0.00185	0.00507	0.00617
AUC Testes (mg/L*hr)	0.00307	0.00257	2.46	0.0208	*0.000241*	0.000692	0.000821	0.00229	0.00627	0.00763
Absorbed Dose (mg)	0.0161	0.0133	2.46	0.109	0.00133	0.0036	0.00433	*0.0121*	0.0333	0.0389
AUC Liver (mg/L*hr)	0.00249	0.00208	2.46	0.0169	0.000196	0.000562	0.000667	0.00186	0.00510	0.00619
AUC Venous Blood (mg/L*hr)	0.00310	0.00259	2.46	0.0211	0.000243	0.000699	0.000830	0.00232	0.00633	0.00771

TABLE 3-9

48-Hour PBPK Modeled Absorbed Doses for TCA for the Adult Male, Adult Female, and Male Child

Demographic Group	Average	Standard Deviation	Skewness	Max	Min	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
Adult Male										
AUC Kidney mg/L*hr)	0.0201	0.0165	3.86	0.166	0.00216	0.00585	0.00729	0.0160	0.0375	0.0488
AUC Testes (mg/L*hr)	0.0317	0.0260	3.86	0.263	0.00341	0.00923	0.0115	0.0252	0.0592	0.0770
Absorbed Dose (mg)	0.0737	0.0576	3.26	0.541	0.00673	0.0231	0.0257	0.0578	0.135	0.186
AUC Liver (mg/L*hr)	0.0205	0.0167	3.85	0.169	0.00219	0.00597	0.00746	0.0163	0.0382	0.0497
AUC Venous Blood (mg/L*hr)	0.0305	0.0250	3.86	0.253	0.00328	0.00888	0.0111	0.0242	0.0570	0.0740
Adult Female										
AUC Kidney (mg/L*hr)	0.0118	0.0123	4.43	0.117	0.00151	0.00251	0.00330	0.00848	0.0237	0.0293
AUC Ovaries (mg/L*hr)	0.0176	0.0183	4.43	0.174	0.00224	0.00373	0.00489	0.0126	0.0352	0.0435
Absorbed Dose (mg)	0.0360	0.0369	4.22	0.346	0.00449	0.00772	0.00992	0.0258	0.0718	0.0901
AUC Liver (mg/L*hr)	0.0120	0.0126	4.45	0.119	0.00153	0.00255	0.00335	0.00861	0.0242	0.0298
AUC Venous Blood (mg/L*hr)	0.0177	0.0185	4.43	0.175	0.00226	0.00376	0.00494	0.0127	0.0356	0.0439
Child Male										
AUC Kidney (mg/L*hr)	0.0154	0.0131	2.47	0.106	0.0011	0.00344	0.00405	0.0114	0.0308	0.0413
AUC Testes (mg/L*hr)	0.0243	0.0206	2.47	0.166	0.00174	0.00543	0.00638	0.0180	0.0485	0.0652
Absorbed Dose (mg)	0.0171	0.0141	2.46	0.115	0.00142	0.00382	0.00459	0.0129	0.0354	0.0414
AUC Liver (mg/L*hr)	0.0155	0.0131	2.47	0.106	0.00111	0.00347	0.00408	0.0115	0.0310	0.0416
AUC Venous Blood (mg/L*hr)	0.0234	0.0198	2.47	0.160	0.00167	0.00522	0.00614	0.0173	0.0466	0.0627

default assumption that Haber's law (the toxic response is proportionate to the metric, "concentration times duration") holds for the toxicities and risk associated with these toxicants. For example, the AUC for BDCM in kidney of the adult male, under these conditions, expressed an average value of 0.00230 mg/L*hr, with values at the 5th and 95th percentile of the distribution of 6.72E-6 and 0.00643, respectively. In comparison, the AUC in the kidney of the adult female demonstrated an average value of 0.00269, and values of 5.36E-5 and 0.00723 mg/L*hr, respectively, at the 5th and 95th percentiles of the distribution. Finally, values for BDCM AUC in the kidney of the male child demonstrated an average value of 0.00132, and values at the 5th and 95th percentiles of the distribution of 4.85E-5 and 0.00440mg/L*hr, respectively. Because these values represent risk-relevant values within each tissue or organ, and because the PBPK model has already accounted for body mass, the values presented in Tables 3-6 through 3-9 are directly comparable without further adjustment. The variance in these values resulted from variance in water use patterns, travel between indoor locations with and without embedded water use appliances, in-home ventilation, and specific anatomic, biochemical and physiologic properties of the adult male, adult female and male child. Variance presented in these tables does not reflect variance of embedded model values (i.e., point estimates used for metabolic rates, tissue partition coefficients) which are well known to vary among individuals due to the biochemical individuality characteristic of outbred species. While their variance may appear quite high to those accustomed to reviewing PBPK model simulations from well-characterized chemical exposures, these simulations are intended to integrate the variance of water use patterns and other in-home variables in estimating internal (tissue-specific) doses, here presented as AUC values. Thus, while it may at first seem that differences in tissue

doses observed e.g., between the adult male and the male child may have their basis in age-related Pharmacokinetic differences, these results also are based on age-dependent differences in water use patterns, and time spent in various locations within and without the home during water use activities.

3.2.4. Sensitivity Analysis. The values of the parameters defining the modeling problem ultimately determine the predicted exposures and doses. The uncertainty in the estimated parameter values varies depending upon the parameter. For example, many estimated parameter values, such as water flow rate, water volume, house and room volumes, etc. are known within a reasonable and definable range. Other parameter estimates, such as those for skin permeability coefficients and various behavioral parameters may have uncertainties of an order of magnitude or higher.

Both sensitivity and uncertainty analyses were considered for evaluation. However, due to the difficulty of separating uncertainty and variability in many of the behavioral parameters, it was concluded that it would be more meaningful to conduct a screening-level sensitivity analysis to identify the parameters having the most significant impact (U.S. EPA, 1997c). Therefore, neither Monte Carlo simulation nor uncertainty analyses were conducted; however sensitivity analysis characterized the importance of each parameter, allowing a qualitative judgment of the importance of a parameter's uncertainty. The sensitivity analysis was conducted by first establishing a base-case scenario, consisting of a base-case set of activities and model parameters. To evaluate the sensitivity of a particular parameter, the value of that parameter was varied by 10% from its base-case value. The impact of this change was then evaluated by comparing the relative change in the chosen dose metrics. It was recognized that due to the sheer number of model parameters and the large uncertainty in some of the parameter

values, the results of the analysis would provide guidance in selecting the set of important parameters, but a more refined study would be necessary. In addition, the sensitivity of the various parameters was expected to be similar for each of the three modeled subjects, so the analysis was limited to the adult male. Some results were presented for the adult female and the child to demonstrate this similarity. In addition, the sensitivity analysis was limited to a subset of two DBPs, $CHCl_3$ and DCA. The analysis evaluated the two modeling components separately: (1) the exposure and uptake model components, and (2) the physiological model components. (See Section 5.0 of Appendix 1 for complete details.)

3.2.4.1. TEM Sensitivity Analysis Results — The TEM sensitivity analysis identified a number of important results (Section 5.4.1. of Appendix 1). From the analysis, it was clear that the conclusions are not consistent across chemicals. Parameters were ranked by their absolute value of relative sensitivity. Table 3-10 summarizes these results. For volatile chemicals, as represented by $CHCl_3$, the parameters influencing the air concentrations had the most significant impact. These parameters included the overall mass transfer coefficients, air exchange rates, zone volumes, water flowrates, and duration of water uses. The air exchange rates and zone volumes were inversely related to the absorbed dose because of they lower airborne concentrations. The overall mass transfer coefficient was the most sensitive parameter for $CHCl_3$, consistent with the inhalation route having the largest dose, causing approximately an 8% change in the total absorbed dose for a 10% change in the overall mass transfer coefficient. Although the mass transfer coefficients were examined as a group, it was clear that larger inhalation exposure events, such as showering, would be more sensitive to this parameter. For the volatile chemical, $CHCl_3$, the model was

TABLE 3-10

Average Relative Sensitivity Analysis of Total Absorbed Dose for Water Use, Environmental and Chemical Parameters for $CHCl_3$ and DCA, Ranked by Absolute Value

Parameter*	$CHCl_3$ Relative Sensitivity, % (Rank)			Parameter*	DCA Relative Sensitivity, % (Rank)		
	Male (15-45)	Female (15-45)	Child (6 years)		Male (15-45)	Female (15-45)	Child (6 years)
Overall Mass Transfer Coefficient (K_{OLA})	80.17 (1)	80.37 (1)	73.48 (1)	Consumption Volume, L/day	99.96 (1)	99.94 (1)	99.96 (1)
Air Exchange Rate (hr-1) and Interzonal Air Flows (m^3/hr)	-57.56 (2)	-70.70 (2)	-59.77 (2)	Shower Mean Duration, min	0.0135 (2)	0.0197 (2)	5.54E-4 (12)
Shower Flowrate, gal/min	34.08 (3)	31.91 (3)	4.65 (8)	Henry's Law Constant	0.0129 (3)	0.0188 (3)	0.00385 (5)
Shower Mean Duration, min	33.03 (4)	26.04 (4)	2.91 (13)	Overall Mass Transfer Coefficient (KOLA)	0.00299 (4)	0.00383 (6)	0.00650 (3)
House and Zone Volumes (m^3)	-26.63 (5)	-12.07 (5)	-23.38 (3)	Air Exchange Rate (hr-1) and Interzonal Air Flows (m^3/hr)	-0.00177 (5)	-0.00874 (4)	-0.00548 (4)
Kitchen Faucet Flowrate, gal/min	8.19 (6)	4.90 (8)	7.71 (6)	Shower Flowrate, gal/min	0.00165 (6)	0.00208 (8)	2.01E-4 (13)
Kitchen Faucet mean Duration, min	6.63 (7)	2.98 (10)	5.76 (7)	House and Zone Volumes (m^3)	-0.00137 (7)	0.00485 (5)	-0.00133 (7)

TABLE 3-10 cont.

Parameter*	$CHCl_3$ Relative Sensitivity, % (Rank)			Parameter*	DCA Relative Sensitivity, % (Rank)		
	Male (15-45)	Female (15-45)	Child (6 years)		Male (15-45)	Female (15-45)	Child (6 years)
Bathroom Faucet Mean Duration, min	5.84 (9)	7.78 (7)	2.76 (14)	Bathroom Faucet Mean Duration, min	0.00103 (9)	0.00214 (7)	7.01E-4 (10)
Consumption Volume, L/day	5.51 (10)	3.27 (9)	4.40 (9)	Kitchen Faucet Flowrate, gal/min	6.79E-4 (10)	6.67E-4 (10)	8.01E-4 (9)
Clothes Washer Mean Duration, min	3.23 (11)	2.56 (12)	3.11 (12)	Bathroom Faucet Flowrate, gal/min	1.64E-4 (11)	4.62E-4 (11)	0.000191 (14)
Henry's Law Constant	2.64 (12)	2.83 (11)	1.98 (15)	Clothes Washer Mean Duration, min	1.06E-4 (12)	1.41E-4 (13)	1.30E-4 (16)
Dishwasher Volume, gal	1.39 (13)	1.24 (13)	1.18 (17)	Dishwasher Mean Duration, min	9.36E-5 (13)	1.84E-4 (12)	1.30E-4 (15)
Clothes Washer Volume, gal	1.33 (14)	1.06 (14)	1.30 (16)	Bath Mean Duration, min	8.81E-5 (14)	3.77E-5 (14)	0.0108 (2)
Bath Flowrate, gal/min	0.90 (15)	0.276 (16)	17.20 (5)	Bath Flowrate, gal/min	7.57E-5 (15)	2.94E-4 (15)	0.00211 (6)
Bath Mean Duration, min	0.86 (16)	0.28 (15)	19.55 (4)	Dishwasher Volume, gal	4.75E-9 (16)	8.50E-9 (16)	6.03E-09 (17)
Bath Volume, gal	0.27 (17)	0.08 (18)	4.27 (10)	Bath Volume, gal	4.71E-10 (17)	1.86E-10 (18)	1.18E-08 (16)
Dishwasher Mean Duration, min	0.10 (18)	0.12 (17)	0.11 (18)	Clothes Washer Volume, gal	1.76E-10 (18)	2.33E-10 (17)	2.18E-10 (18)
Toilet Volume, gal/flush	0.00 (19)	0.00 (19)	0.00 (19)	Toilet Volume, gal/flush	0.00 (19)	0.00 (19)	0.00 (19)

relatively insensitive to the actual volume of non-flowing type water appliances (e.g., bath volume, dishwasher volume, clothes washer volume, toilet volume, etc.) with less than a 0.2% change in dose for a 10% change in the volume parameter. In addition, the model was relatively insensitive to Henry's law constant (H), yielding a relative change of less than 0.3% for a 10% change in H.

For low volatility chemicals, as represented by DCA, consumption and dermal contact played the most significant roles. Consumption was by far the most sensitive parameter, changing the total absorbed dose approximately 10% for a 10% change in the consumption volume. The dermal influence, though much less significant, was evident in the shower duration for the adults and in the bath duration for the child. Although the inhalation route's contribution to total absorbed dose was small relative to the other routes, it was interesting to note that, with the exception of Henry's law constant, the sensitivity of the inhalation parameters were in the same sequential order as for $CHCl_3$. The increased relative influence of Henry's law constant as compared to the mass transfer coefficient is due to the dynamics of the equilibrium relationship as defined by Henry's law. The concentration in the air is limited to the equilibrium condition, as defined by Henry's law, which is approached in the vicinity of the water appliance during water uses of duration longer than a few minutes, thereby attenuating the mass transfer rate. For this reason, Henry's law constant is the most sensitive parameter for the inhalation route.

Although $CHCl_3$ is a volatile chemical and DCA is a low volatility chemical, and as such they are generally representative of chemicals with similar chemical properties, many other factors affect the exposure and uptake of a chemical. Factors such as skin permeability are not highly correlated with volatility, and therefore the fractional dermal

uptake can be very different for chemicals with similar volatility. Therefore, the conclusions reached based on the sensitivity analysis for these two chemicals would have to consider the effect of the other chemical properties which impact uptake.

3.2.4.2. ERDEM Sensitivity Analysis Results — The ERDEM sensitivity analysis identified a number of highly sensitive parameters, but also identified numerous insensitive parameters. Table 3-11 presents a summary of the most sensitive model parameters for each dose metric for $CHCl_3$ and DCA. In some cases, the change in the dose metric variables, due to the perturbation of an input variable, was less than the relative error in the integration process. For these cases, the results were not reported. The relative sensitivities for liver AUC and testes AUC dose metrics were evaluated for $CHCl_3$ and DCA. For $CHCl_3$, the AUC estimates for the liver differed by a factor of around 10 from the estimates for the testes. But, for DCA, the values of AUC were very similar for liver versus testes. The volumes of the body, fat, and the slowly perfused tissue showed a high relative sensitivity in the liver but not in the testes. Liver metabolism was sensitive in the liver, but not in the testes.

The peak concentration of liver and testes dose metrics were also evaluated for $CHCl_3$. The input parameters exhibiting high relative sensitivity were: volume of the body, alveolar ventilation rate, cardiac output, the blood flows to the liver and slowly perfused tissue, and the partition coefficients for the static lung/air and static lung/blood.

The peak concentration of liver and testes dose metrics were also evaluated for $CHCl_3$. The input parameters exhibiting high relative sensitivity were: volume of the body, alveolar ventilation rate, cardiac output, the blood flows to the liver and slowly perfused tissue, and the partition coefficients for the static lung/air and static lung/blood. However, the volumes of the dermis, fat, rapidly perfused tissue, and slowly perfused

TABLE 3-11

Summary of the Most Sensitive Model Parameters for Each Dose Metric

Dose Metrics	Most Sensitive Model Parameters (Relative Sensitivity)	
	$CHCl_3$	DCA
Absorbed Dose at 24 hours (mg)	Alveolar Ventilation Rate (89.83%)	Blood Flow in Kidney (4.88%)
Amount Metabolized in Liver at 24 hours (mg)	Alveolar Ventilation Rate (52.98%)	N/A
AUC in Liver at 24 hours (mg*h/L)	Liver Metabolism Vmax (-107.34%)	Body Mass (-89.07%)
AUC in Testes at 24 hours (mg*h/L)	Blood:Testes Partition Coefficient (100.21%)	Blood:Testes Partition Coefficient (100.56%)
Concentration in Liver (mg/L)	Liver Metabolism Vmax (-108.98%)	Rate of Absorption into Portal Blood from Stomach (75.16%)
Concentration in Testes (mg/L)	Testes:Blood Partition Coefficient (99.50%)	Blood:Testes Partition Coefficient (99.41%)

tissue, and the partition coefficient of rapidly perfused tissue/blood were sensitive in the liver but not in the testes. The partition coefficient of testes/blood was sensitive in the testes only. In a similar manner to the results shown for $CHCl_3$, the relative sensitivities were examined for each dose metric for DCA. The dose metric – absorbed dose – had negligible relative sensitivity for all 34 input parameters for DCA, while for $CHCl_3$ the absorbed dose was most sensitive to alveolar ventilation rate (relative sensitivity of 89.38%).

3.2.4.3. Parameters Not Evaluated — Several model parameters were not explicitly examined as a part of this study, including the following:

- Location behavior of exposed individuals relative to sources of DBP exposures
- Impact of other occupants (family size, behavior of other occupants, etc.)
- Impact of mechanical systems (e.g., the heating/air conditioning system, other fans, etc.)
- Impact of changing physical conditions in the house (e.g., opening and closing of doors and windows)
- Impact of weather
- Water temperature
- Model appropriateness (mass balance model, uptake models, behavioral models, etc.)

Although these parameters were not explicitly studied, the impacts of several of the parameters were indirectly addressed. The impact of changing physical conditions and weather were addressed indirectly by looking at the effect of increasing the whole house air exchange rate and inter-zonal airflows. In general, changes causing increased ventilation would lower peak concentrations at the source. However, while opening an interior door would decrease the peak concentration at the source, it

increases the concentrations at other locations in the home, thereby potentially providing additional exposure to the occupants in those locations. Similarly, the use of a mechanical system would encourage mixing in the house, causing lower exposures near the source but potentially higher exposures at other locations. The impact of water temperature and other chemical properties were also indirectly examined by looking at the effect of changing the overall mass transfer coefficient. Water temperature impacts chemical diffusivity in water, and for chemicals whose volatilization is limited by liquid phase mass transfer, an increased water temperature will increase the overall mass transfer coefficient. The liquid and gas phase diffusivities will have a similar effect subject to the phase that provides the greatest resistance to mass transfer.

The impact of behavioral characteristics of the occupants clearly has the potential for causing the greatest variation. Wilkes et al. (1992) showed that, for TCE, someone taking a second shower immediately following another person's shower would be exposed to much greater air concentrations, and receive a higher absorbed dose. For the scenario examined by Wilkes et al., the second shower was estimated to provide approximately a 50% higher dose than the first shower of identical length and conditions due to the elevated air concentrations. Wilkes et al. (1996) showed, for TCE, a high degree of correlation between behavior and predicted dose, with the most important predictors being shower duration, bath duration, time spent in the bathroom, and total household water use. Wilkes et al. (1992) also compared the estimated exposures of single occupant households to two occupant households. The two person households showed a mean increase in the potential inhalation dose of 38% for the male population group and 11% for the female population group.

4. COMBINING THE CRPF METHOD WITH EXPOSURE ESTIMATES TO CONDUCT A DBP CUMULATIVE RISK ASSESSMENT

This report proposes that the CRPF method (described in Section 2.0 and Appendix 2) is a feasible approach for conducting cumulative risk assessments for DBPs. Data from exposure assessment and PBPK models can be used to estimate contaminant exposures and the resulting doses to internal tissues over time. The exposure data may be combined with relevant dose-response data and models to estimate risk posed by a contaminant mixture through multiple exposure routes over varying exposure time periods. This section envisions how the exposure estimates (described in Section 3 and in Appendix 1) may be combined with dose-response information under the CRPF approach, describing those steps necessary to perform such an assessment.

4.1. STRATEGY FOR CONDUCTING THE CRPF-BASED ASSESSMENT

Because animal dose-response data are typically available for only a single exposure route (usually oral), practical implementation of the CRPF approach for multiple exposure routes requires route extrapolations. Few inhalation or dermal toxicity data are available for the DBPs. Thus, although the CRPF analysis may be conducted using separate exposures for each route, it is more logical to develop the approach so it can be implemented using dose-response information on the oral route only. (PBPK models may also be useful in constructing physiologically-based extrapolations across different exposure routes.) The text that follows in this section focuses on the use of internal doses based on human exposures to all three routes. Working with the 13 DBPs for which example exposure and dose estimates have been developed (Appendix

1), it is envisioned that the following steps may be followed to conduct the CRPF-based assessment.

Group DBPs into Subclasses by Common MOA

1) Collect, evaluate and select the highest quality data for each of the 13 DBPs, including data on MOA and dose-response toxicology data.

2) Using the exposure assessment and PBPK modeling results and the MOA data, determine the best measure of a biologically effective dose. The PBPK modeling will provide improved understanding of the relationship between toxicity and doses in the target tissue. The analyst has several options for dose analysis:

   - Analysis of contaminants as exposures. (Not discussed further in this section. A CRPF analysis using separate exposures for each route requires dose-response information for each route. Thus, this option is not practical given the current state of the DBP toxicity data base.)
   - Analysis of contaminants as a total absorbed dose (e.g., blood concentrations).
   - Analysis of contaminants as tissue or organ doses.

3) Identify subclasses of the 13 DBPs, grouping them by similar toxic MOA for each endpoint of interest (e.g., cancer, developmental effects, reproductive effects).

4) Determine the appropriate dose metric based on MOA and available dose-response data. (Analyses may be based upon dose metrics such as area under the curve for absorbed and tissue doses or the maximum concentration.)

Conduct Dose Response Modeling of Toxicology Data

1) Beginning with data from an oral toxicology study, adjust the administered animal doses to internal animal doses using bioavailability factors.

2) Adjust the internal animal doses to internal human equivalent doses using allometric scaling or PBPK modeling.

3) Using these internal human equivalent doses, develop dose-response curves for the 13 DBPs individually.

4) Re-evaluate subclass groupings based on the requirement of the RPF method that the members of the subclass are to have similarly shaped dose-response curves within the exposure region of interest.

Develop RPF Estimates for Each Subclass and Combine Using the CRPF Approach

1) For each subclass, choose an index chemical and estimate RPFs for each member of the subclass relative to the index chemical.

2) Using the multiple route internal doses for the 13 DBPs, multiply each component dose by its RPF to obtain the Component ICED. Sum the Component ICEDs to generate an index chemical equivalent dose for each subclass (i.e., a Subclass ICED).

3) Use the dose-response curve for the index chemical to estimate risk for its subclass.

4) Based on response addition, sum the subclass risks to estimate the total multiple route mixtures risk for the DBPs.

5) Develop a full risk characterization for the analysis, including an analysis of uncertainty.

4.2. GROUP DBPS INTO SUBCLASSES BY COMMON MOA

The 15 DBPs evaluated in this report are fairly well studied, providing varying degrees of understanding of MOA, but the data are not sufficient to establish a consensus on MOA among researchers for most of these DBPs. For purposes of illustration, however, Table 4-1 offers one division into subclasses that can be loosely

TABLE 4-1

Example: DBPs Grouped into Subclasses by Common MOA*

Genotoxic Carcinogens	Non-Genotoxic Carcinogens
Bromodichloromethane (glutathione transferase activation, adduct formation is a distinct possibility) Bromoform (mechanism unknown, potentially oxidative damage, glutathione transferase activation) Chlorodibromomethane (mechanism unknown)	Chloroform (gross tissue damage and regeneration, "necrotic" foci) Dichloroacetic Acid (no observed necrotic foci) Trichloroacetic Acid (no observed necrotic foci)
Developmental Toxicants - Primary Effect is Cardiovascular,	**Developmental Toxicants - Primary Effect is for Whole Organism**
Monochloroacetic Acid (heart) Dichloroacetic Acid (heart) Trichloroacetic Acid (heart) Monobromoacetic Acid (heart) Trichloroacetonitrile (heart)	Dibromoacetic Acid (delayed parturition) Bromochloroacetic Acid (reduced pup viability) Dichloroacetonitrile (reduced pup viability) Bromodichloromethane (full litter resorption) Bromoform (full litter resorption) Chloroform (reduced pup weight)
Reproductive Toxicants - Primary Effect in Testis and Sperm	
Dichloroacetic Acid (testicular effects) Dibromoacetic Acid (testicular effects) Bromochloroacetic Acid (sperm effects) Bromodichloromethane (sperm effects)	

*Information summarized based on data presented in Klinefelter et al. (2001) and U.S. EPA (2000a).

supported by the toxicology data (see Klinefelter et al., 2001; U.S. EPA, 2000a). The carcinogens are divided into those that are thought to be genotoxic and non-genotoxic. The developmental/reproductive toxicants are divided into groups for which the primary effect is either cardiovascular defects, effects on the fetus or litter, or male reproductive effects. The scope of this report is not to debate the example classifications shown in Table 4-1, but to show that such an analysis can be performed, thus, allowing for the development of RPF estimates of risk for each of these five subclasses.

4.2.1. Developmental and Reproductive Effects from Exposure to DBPs. The HAAs, HANs, THMs and other DBPs have been shown to adversely affect reproduction and development in animals (Klinefelter et al., 2001). Studies of reproductive and developmental toxicity effects of DBPs have demonstrated alterations in sperm morphology, motility and count; decreased levels of fertility; spontaneous resorptions; decreased fetal body weight; and visceral, cardiovascular and craniofacial malformations (U.S. EPA, 2000a). The groups in Table 4-1 were formed from evaluations of these data sets, suggesting three general categories of effects that are the most sensitive endpoints in common for these chemicals:

1) Cardiovascular Effects (e.g., interventricular septal defects, defects between ascending aorta and right ventricle, and levocardia)
2) Effects on Fetus/Litter (e.g., decreased fetal body weight and crown-rump length, full litter resorption)
3) Male Reproductive Effects (e.g., sperm alterations, testicular effects).

Data on the actual toxicological mechanisms causing these effects are generally not available, so the groups in Table 4-1 were formed to reflect the primary effect observed in animal studies for each DBP.

4.2.2. Carcinogenicity from Exposure to DBPs. The divisions in Table 4-1 are based on mechanistic evidence in the toxicological literature of whether each DBP is genotoxic or non-genotoxic. For the THMs, kidney tumors were seen in male rats exposed to $CHCl_3$, whose MOA is thought to be cytolethality (cell death) and cellular regeneration, that is, $CHCl_3$ is thought to be non-genotoxic. The MOA for the other three THMs are less clear. BDCM is structurally similar to other known animal carcinogens, is mutagenic, and produced tumors at multiple sites in multiple species. DBCM 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 [see EPA's Integrated Risk Information System (IRIS) for this information (U.S. EPA, 2002c)]. Although there may be a cytolethality component to the MOA for these three THMs, evidence exists showing these three brominated THMs are genotoxic (Landi et al., 1999). It is noteworthy that, although the decisions in Table 4-1 were made in accord with these data on glutathione transferase and cytolethality, other opinions on MOA exist. For example, Fawell (2000) provides a discussion of MOA for the THMs, concluding that all four THMs are non-genotoxic.

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 [see IRIS for this information (U.S. EPA, 2002c)]. DCA and TCA promote the outgrowth of tumors with distinct genetic effects, thus their MOA may not be the same, but both appear to be tumor promoters. Evidence of genotoxicity is observed at concentrations greatly in excess of those anticipated to occur in humans. Thus, although DCA and TCA may

each have a dose-dependent genotoxic and a non-genotoxic MOA, the most relevant MOA for human exposures is non-genotoxic.

4.3. CONDUCT DOSE RESPONSE MODELING OF TOXICITY DATA

The multiple route exposure doses developed in Appendix 1 are combined to estimate internal doses for the human. In general, an internal dose is that amount of DBP, expressed as mg/kg body weight, which travels from the external environment (air, water) to the internal environment in the animal species under investigation. The total absorbed dose does not reflect concentration of DBPs in any given tissue, but represents the total amount of DBPs entering the body. To use the estimates of human total absorbed dose or tissue doses in a risk assessment based on animal toxicology data, the external animal dose must undergo two conversions: 1) the dose which the animal encounters in the external environment (air, water) must be converted to an internal dose, and 2) the animal's internal dose must be adjusted to an internal human *equivalent dose (HED) to account for animal:human differences in response. Figure* 4-1 illustrates these two conversions and shows that the dose response model is then built using the internal HED and the animal response data. This step assumes that the uptake in affected tissues is the same across species and that the animal response adequately characterizes the human response. Estimates can then be made using this dose-response function of single DBP human health risks, toxicity values (e.g., an ED_{10}) or slope factors for use in calculating RPFs, and index chemical human health risks (to be summed across subclasses to developing risk estimates by the CRPF approach).

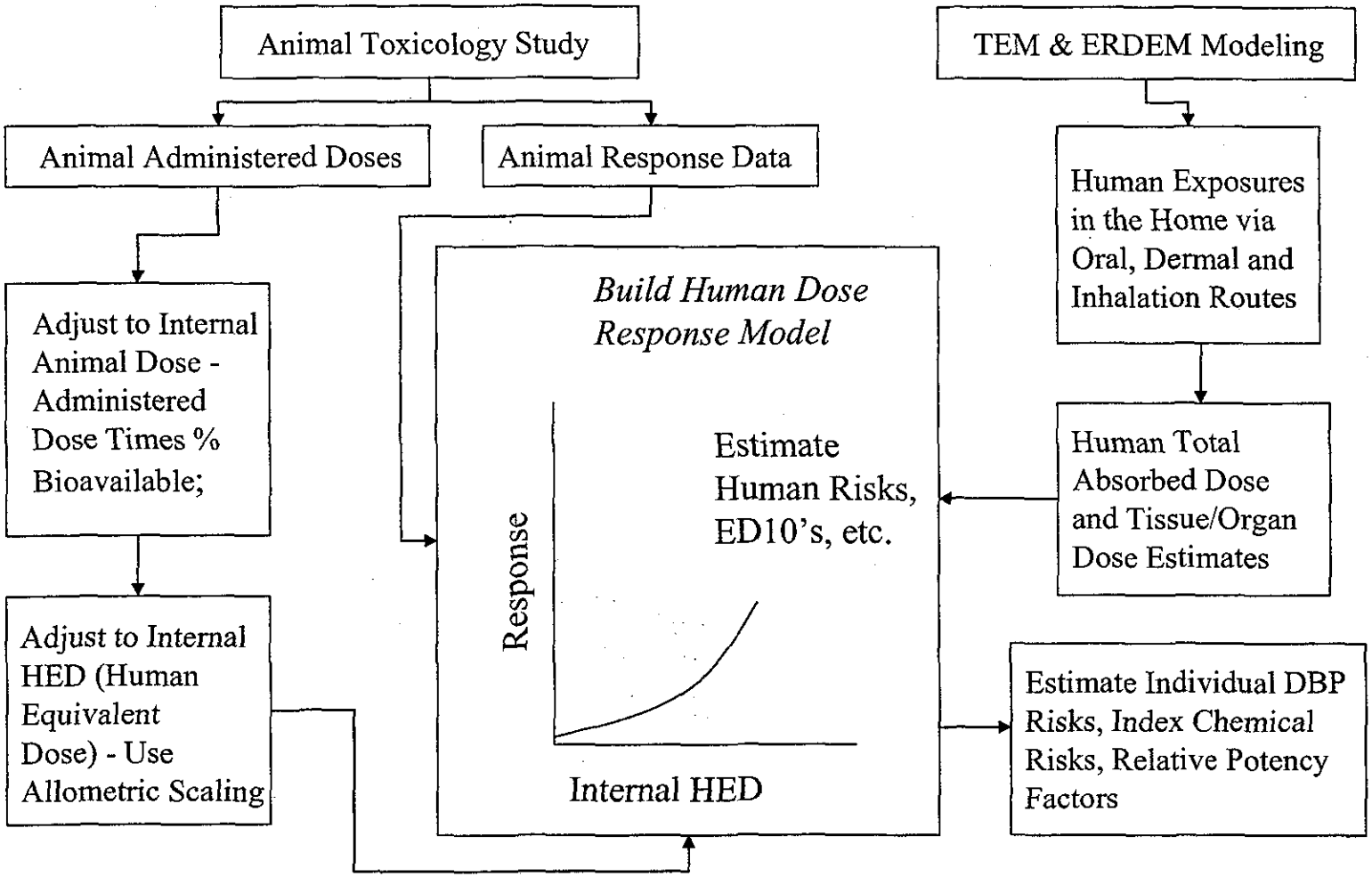

FIGURE 4-1

Dose-Response Development, Human Risk Estimates and RPF Calculations for Each Single DBP

The first conversion, from administered animal dose to an internal dose, is accomplished using an estimate of oral bioavailability (assuming a 100% oral bioavailability when data on this factor are lacking). When data on oral bioavailability are available for the chemical of interest under the relevant study conditions, then the measured oral bioavailability should be used to adjust the internal animal dose based on the administered dose. DBP toxicity results are rarely available from animal studies conducted via the inhalation and dermal routes. When these data become available, however, increased effort will be required to determine the internal dose based on the encountered dose, as was done for the human. This requires information on route-specific absorption of encountered concentrations of toxicants in the species. These are developed through applying assumptions and employing a PBPK model. The PBPK model was applied to the human (Appendix 1) to simulate an internal dose following oral, dermal and inhalation exposures to contaminants in air and water from delivery of the contaminants via disinfected drinking water, and oral, dermal and inhalation exposures to these contaminants in water or volatilized from water into air.

One method to perform the second conversion to an internal HED is to using body weight scaling to calculate equivalent doses across species. Equation (4-1), below, is based on allometric scaling laws that relate a biologic measure of physiology to body weight raised to a power (U.S. EPA, 1980, 1996b):

$$d_h = d_a \left[W_a / W_h \right]^{1/4} \qquad (4\text{-}1)$$

where:

d_h = internal human equivalent dose (mg/kg/day)

d_a = internal animal dose (mg/kg/day)

w_h = adult human body weight (e.g., 70 kg for a male adult human)

w_a = animal body weight (e.g., 0.35 kg for a male adult rat)

A second approach to scaling animal to human doses is to use PBPK models when data for humans and animals are available. The use of PBPK models can provide a credible scientific forum to do conversions based on target tissue dose extrapolation between animals and humans. Such an extrapolation can account for physiological differences which are not necessarily identified in the allometric method. Hence, reconstruction of the dose-response relationship for humans can be done using PBPK methods that will relate toxicity to target tissue concentrations.

For each DBP, and for each toxic event (response), dose-response functions are fitted to the internal HED to facilitate a comparison with the human internal doses derived from the multiple route exposure assessment. The oral dose-response function observed in research animals is appropriate for comparison with the internal dose derived in humans from the multiple route exposure estimates, based on several factors: 1) the toxic endpoints of concern are systemic, they are not manifest as portal of entry (route-specific) effects, 2) the systemic levels of toxicants are determined independent of route of exposure, and 3) there are no data describing the responses observed in research animals as a function of *tissue-specific* dose (i.e., concentration of toxicant in the testes or ovary) upon which a sound estimate of human risk can be made.

Once the dose response functions are modeled for each DBP, then the subclass designations should be revisited to ensure the dose-response curves are similarly shaped within a subclass. This is a requirement of the RPF method (U.S. EPA, 2000b) that allows use of the index chemical dose-response function to estimate risk for the subclass. Statistical methods are under development to test for similarity of dose response curves (e.g., Chen et al., 2001, 2002; U.S. EPA, 2001); at a minimum, graphical displays of dose-response functions for the DBPs within a subclass should be compared within the exposure region of interest.

This procedure for applying the CRPF approach will be illustrated throughout the remaining text in this Section 4 for the cancer endpoint only and utilizing the two subclasses that are hypothesized for cancer in Table 4-1. The basic schematic that will be followed for this illustration is shown in Figure 4-2.

Table 4-2 shows some dose response modeling results and RPF calculations that will be used to illustrate the steps in a CRPF analysis of the genotoxic and non-genotoxic subclasses shown in Table 4-1. With the exception of DCA, TCA, and chloroform, oral upper bound slope estimates for the cancer endpoint were taken directly from IRIS (U.S. EPA, 2002c) for BDCM, DBCM, and $CHBr_3$. 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 data sets and taking the Maximum Likelihood Estimate (MLE) value.

As noted in Table 4-2, "under the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996, 1999), chloroform is likely to be carcinogenic to humans

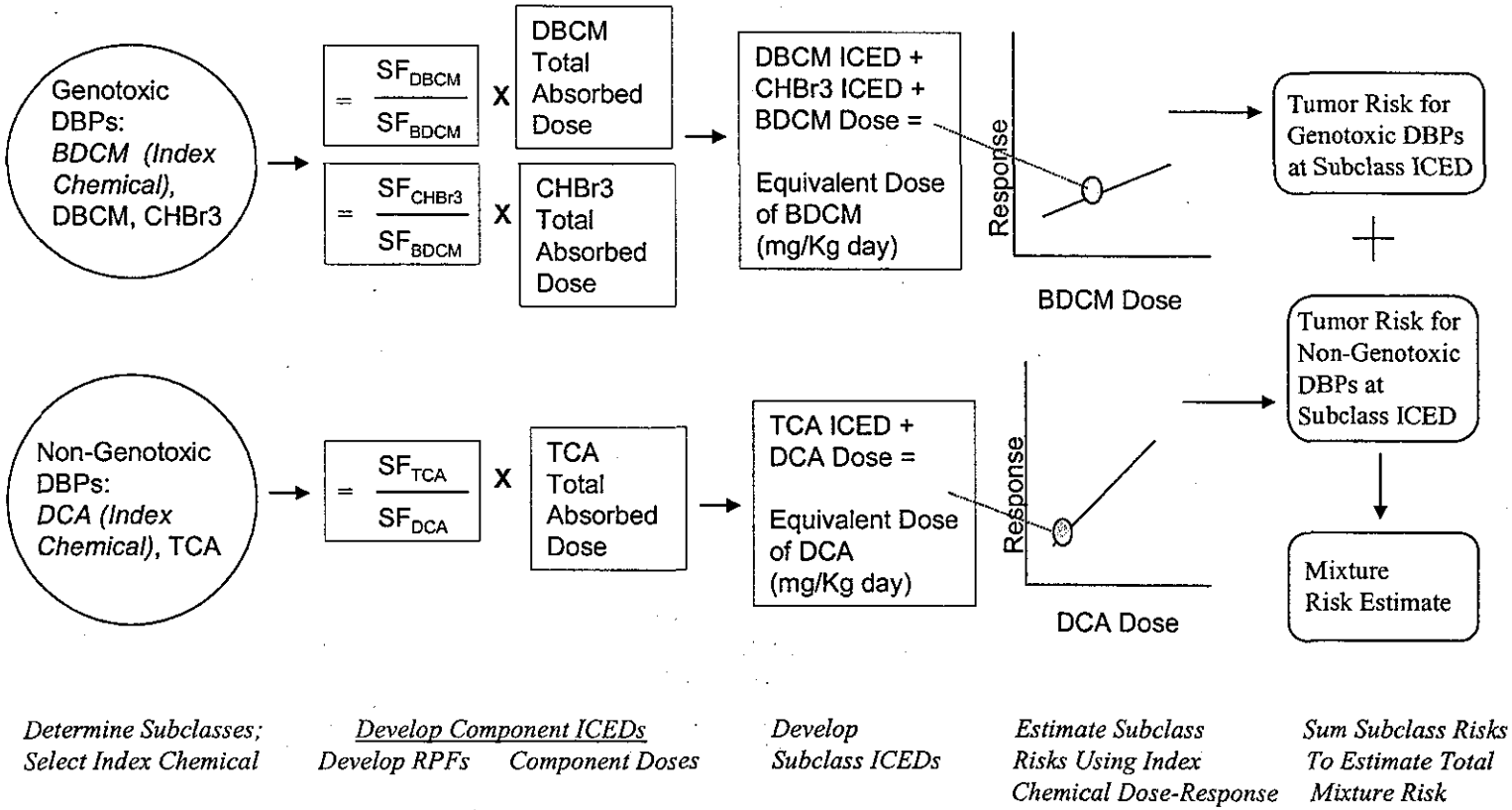

FIGURE 4-2

Schematic of CRPF Approach for Illustration of DBP Mixture Cancer Risk

TABLE 4-2

Incremental Cancer Risk per mg/kg-day

DBP	Slope Factor (SF) $(mg/kg\text{-}d)^{-1}$		RPF Calculations		Cancer Weight of Evidence IRIS, U.S. EPA, 2002c B2 = Probable Human Carcinogen C = Possible Human Carcinogen
	MLE	95%	Group	RPF (SF i /SF1)	
BDCM[a]	5.7×10^{-3}	6.2×10^{-2}	Genotoxic (Index Chemical)	1	B2. Based on inadequate human data and sufficient evidence of carcinogenicity in two animal species (mice and rats) as shown by increased incidence of kidney tumors and tumors of the large intestine in male and female rats, kidney tumors in male mice, and liver tumors in female mice.
DBCM[a]	7.2×10^{-4}	8.4×10^{-2}	Genotoxic	1.35	C. Based on inadequate human data and limited evidence of carcinogenicity in animals; namely, positive carcinogenic evidence in B6C3Fl mice (males and females), together with positive mutagenicity data, and structural similarity to other trihalomethanes, which are known animal carcinogens.
$CHBr_3$[a]	3.4×10^{-4}	7.9×10^{-3}	Genotoxic	0.13	B2. Based on inadequate human data and sufficient evidence of carcinogenicity in animals, namely an increased incidence of tumors after oral administration of bromoform in rats and intraperitoneal administration in mice. Bromoform is genotoxic in several assay systems. Also, bromoform is structurally related to other trihalomethanes (e.g., chloroform, bromodichloromethane, dibromochloromethane) which have been verified as either probable or possible carcinogens.

TABLE 4-2 cont.

DBP	Slope Factor (SF) $(mg/kg\text{-}d)^{-1}$		RPF Calculations		Cancer Weight of Evidence IRIS, U.S. EPA, 2002c B2 = Probable Human Carcinogen C = Possible Human Carcinogen
	MLE	95%	Group	RPF (SF i /SF1)	
DCA[b]	1.4×10^{-3}	1.0×10^{-1}	Non-Genotoxic (Index Chemical)	1	B2. Based on a lack of human carcinogenicity data and increased incidence of hepatocellular adenomas and carcinomas in male and female mice. Hyperplastic liver nodules, which are expected to progress into hepatocellular adenomas and carcinomas, were increased in both rats and mice.
TCA[b]	4.9×10^{-2}	8.4×10^{-2}	Non-Genotoxic	0.84	C. The classification is based on a lack of human data and limited evidence of an increased incidence of liver neoplasms in both sexes of one strain of mice. No evidence of carcinogenicity was found in rats. Results from genotoxicity studies are mixed; trichloroacetic acid does not appear to be a point mutagen.
$CHCl_3$ [a]	RfD = 1.0×10^{-2}	RfD = 1.0×10^{-2}	Non-Genotoxic	-	B2. Under the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996, 1999), chloroform is likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues (U.S. EPA, 1998a,b). Chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration.

[a]Slope factors are from IRIS, (U.S. EPA, 2002c). MLE slope factors are from the same dose-response model as the 95% upper bound slope factors.

[b]Slope factors are derived from data presented in Bull and Kopfler (1991). They are included here to illustrate the CRPF approach only and are not representative of EPA peer-reviewed, endorsed values.

by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues (U.S. EPA, 1998a,b). Chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration." Thus, this illustration assumes that exposures below chloroform's Reference Dose (RfD) of 0.01 mg/kg/day do not contribute to carcinogenicity.

For DCA and TCA, quantitative cancer estimates are not available on IRIS, but qualitative assessments there list B2 and C cancer classifications, respectively. For purposes of this illustration only, the upper bound and mean (MLE) slope factors for DCA and TCA were derived from risk levels given in Bull and Kopfler (1991). As was done for chloroform, DCA was reviewed by an expert panel regarding its mechanism of action. The panel concluded there was 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 RfD methodology as was applied in the case of chloroform, leaving open the question of low dose mechanism. Thus, DCA was kept as part of this quantitative illustration.

The two dose conversions discussed above in this section are accounted for in the Table 4-2 information. There is an implicit assumption here that each of these DBPs is 100% bioavailable to the experimental animal, so the administered animal dose is assumed to be equivalent to the absorbed animal dose. This assumption is a significant source of uncertainty that is only made here to simplify the illustration. The second conversion from internal animal dose to internal human equivalent dose is done for these chemicals using allometric scaling.

4.4. DEVELOP RPF ESTIMATES FOR EACH SUBCLASS AND COMBINE USING THE CRPF APPROACH

Once the dose conversions, individual DBP dose-response modeling and subclass designations are completed, the RPF methodology found in Agency guidance can be applied (U.S. EPA, 2000b). For each subclass, an index chemical is chosen. (Table 4-2 indicates that BDCM and DCA are the index chemicals for the genotoxic subclass and non-genotoxic subclasses, respectively.) The index chemical is generally a well-studied chemical with a well defined dose-response curve for the effect of interest and whose toxicologic similarity to the other chemicals in the subclass can be substantiated. RPFs are then calculated for each member of the subclass relative to the index chemical using the dose-response functions generated for the individual DBPs. (Table 4-2 shows the RPFs for each DBP, where the calculation was conducted using a ratio of slope factors.) Then, within each subclass, the multiple route internal exposure estimate for each DBP is multiplied by its RPF to calculate a Component ICED for each member of the subclass; these estimates are summed to yield a total Subclass ICED. The dose-response curve for the index chemical is used to estimate risk for that subclass at the Subclass ICED.

The subclasses were developed based on the assumption that the MOA for each subclass was truly different from the other subclasses. Thus, by design, it can be assumed that the toxic action of each subclass will be toxicologically independent of the other subclasses (i.e., the toxic action caused by one subclass would not affect the toxicity caused by the other subclasses). This assumption of independence of action is the basis for using response addition to calculate risk from exposure to a mixture. Under this assumption, the total risk of an overall effect, such as the risk of

developmental toxicity, can be calculated by summing the risks across the subclasses. As an example, for the hypothetical groupings presented in Table 4-1, developmental effect risks would be summed across the three subclasses to yield an overall risk of developmental effects. The end result is a multiple route, DBP mixtures risk estimate.

Table 4-3 provides an illustration of the cancer risk calculations that could be made for a 70 kg adult male by combining the dose-response information in Table 4-2 with the TEM total absorbed dose estimates shown in Table 3-4. The 50th percentile doses (mg/day) from Table 3-4 are converted to mg/kg/day doses (dividing by 70 kg) and then multiplied by the RPF for each DBP to obtain Component ICEDs. The sum of the Component ICEDs form the Subclass ICEDs. The product of each Subclass ICED and the MLE slope factor for the subclass index chemical provides an estimate of the average cancer risk for that subclass. The subclass risks are then added to obtain the final total average cancer risk for the whole mixture.

It is noteworthy that a strength of the CRPF approach is that it can be applied more broadly and expanded beyond this simple illustration using only six well-studied DBPs. In this hypothetical example, the toxicity of each chemical was well characterized. However, this approach can accommodate other DBPs for which fewer toxicity data exist. For example, other genotoxic carcinogens exhibiting similar MOA to BDCM may be present in the mixture. Although *in vivo* data may not be available, RPFs can be derived using other measures of potency (e.g., *in vitro* genotoxicity data), providing these data are relevant to the endpoint of interest and also exist for the index chemical. Clearly, exposure estimates would also need to be developed for the CRPF approach to be implemented.

TABLE 4-3

Illustration of CRPF Approach for Average Cancer Risk Calculations
(Includes assumption of 100% bioavailability)

DBP	95% Upper Bound Slope Factor (SF)	RPF (SF_i/SF_1)[a]	Total Absorbed Dose for 70 kg Male		Component ICED mg/kg/day	Subclass ICED mg/kg/day	Subclass Risk
			50% mg/day	50% mg/kg/day			MLE Slope Factor times Subclass ICED
Genotoxic Subclass							
BDCM[b]	6.20E-02	1.00	8.43E-02	1.20E-03	1.20E-03	2.32E-03	1.32E-05
DBCM	8.40E-02	1.35	5.49E-02	7.84E-04	1.06E-03		
$CHBr_3$	7.90E-03	0.13	3.00E-02	4.29E-04	5.46E-05		
Non-Genotoxic Subclass							
DCA[c]	1.00E-01	1.00	3.14E-02	4.49E-04	4.49E-04	8.49E-04	1.19E-06
TCA	8.40E-02	0.84	3.34E-02	4.77E-04	4.01E-04		
$CHCl_3$	RfD=0.01	--	3.02E-01	4.31E-03	--		
						Total Mixture Average Cancer Risk	1.44E-05

[a]SF_1 is slope factor for index chemical; SF_i is slope factor for i^{th} chemical in the subclass.

[b]Genotoxic Subclass Index Chemical, Maximum Likelihood Estimate (MLE) of Cancer Slope Factor (SF) = 5.7E-3

[c]Non-Genotoxic Subclass Index Chemical, MLE SF = 1.4E-3

The final step of such an effort is to fully characterize the uncertainties that exist as a product of the analysis. This risk characterization should include uncertainties in the CRPF process, including discussions regarding subclass development, choice of index chemical, and the strength of the exposure assessment. In this illustration of the CRPF approach for estimating DBP cancer risk, there are a number of uncertainties. Several key uncertainties are listed below.

- Based upon expected differences in toxicodynamic MOA, the carcinogenic DBPs considered were categorized into 2 broad groups: genotoxic carcinogens and non-genotoxic carcinogens. The genotoxic carcinogens are assumed to share a common MOA and the non-genotoxic carcinogens also are assumed to share a common MOA (for CA and TCA this may, in fact, be unlikely). The genotoxic and non-genotoxic modes of action are assumed to be independent. The outcomes (i.e., cancer) are assumed to be statistically independent. The common outcome being modeled through the CRPF approach in the human is cancer that results from DBP multiroute exposures. The target organ is not specified.
- Calculated slope factors for the individual chemicals are assumed to be an appropriate basis for relative potency factors. In this example, upper bound (95th percentile) confidence limits of the maximum likelihood estimate were employed. While the slope factors as presented on IRIS (U.S. EPA, 2002c) and by Bull and Kopfler (1991) were used in this example, other estimates of slope such as the MLE, which represents the best estimate of dose response, may be more appropriate measures on

which to base an evaluation of relative potency. Additionally, the slope factors are based on test animal responses and the original study doses were transformed to human equivalent doses for purposes of calculating the slope factors.

- The slope factors used to estimate relative potency factors were derived from studies that had broad dose intervals. The use of slope factors derived from these studies to estimate RPFs assumes that the chemicals' MOA does not change over the range of study doses. Some RPFs are based on ratios of ED_{10} to avoid this potential problem.
- For calculating doses in the bioassay data, the individual DBPs were assumed to be 100% bioavailable. Multiroute human exposures to DBPs were estimated as total absorbed doses. The study doses were assumed to be equivalent to the estimated total absorbed dose in the human. A more detailed approach that estimates absorbed doses in the rodent bioassays would reduce the uncertainty associated with the assumption. RPFs could also be based on animal absorbed doses; this would eliminate some pharmacokinetic uncertainty in the estimation of the RPFs.
- This example is based on total absorbed dose without further consideration of pharmacokinetic differences between chemicals, target tissue dosimetry, and is based on the assumption that target tissue dosimetry at these doses is similar in rodents and humans.
- The RPFs were developed from rodent studies and are applied to humans. This assumes that the MOA for individual chemicals are the similar for humans and rodents. This also assumes that the between-

chemical differences in pharmacokinetics are similar between humans and rodents.

- These RPFs were developed from single chemical bioassays. The RPF approach does not account for pharmacokinetic interactions (e.g., competition for metabolizing enzymes or inhibition of elimination mechanisms). These interactions may significantly influence tissue dosimetry of the individual chemicals when the exposure occurs to the mixture. As a result, the assessment of relative potency and risk may not be consistent between model predictions and observations of toxicity when rodents are exposed to the whole mixture.

5. FEASIBILITY OF CUMULATIVE RISK ASSESSMENT FOR COMPLEX DBP MIXTURES

Exposure modeling techniques and risk assessment methods are available to formulate CRA estimates for specified groups of DBPs. This analysis illustrates that multiple route exposure estimates can be developed that account for human activity patterns affecting contact time with identified DBPs in tap water by developing internal dose estimates for selected DBPs. Although important data gaps still exist (e.g., chemical properties of some DBPs such as bromate, MOA data for appropriately assigning DBPs into subclasses), additional data on these chemicals continue to be developed by many researchers. Application of this approach may provide a more scientific basis for evaluating risks posed by different mixtures of DBPs than comparisons developed based on concentrations of individual DBPs and single route risk analyses. With sufficient data, applications of this approach should provide a more useful comparison to epidemiologic studies than analyses based on concentrations of individual DBPs and single routes of exposure. Cumulative risk estimates developed using these approaches can be compared across different types of treatments of the same source water or across geographic areas. These estimates of risk should be compared on a relative basis, rather than an absolute basis. For example, a Hazard Index or other component based mixtures risk assessment approach may be applied (see U.S. EPA, 2000b) using cumulative dose estimates. For more difficult problems, such as predicting actual risks from exposure to chlorinated drinking water (e.g., number of cases of cancer for a population served by a particular system), additional research will be required before credible CRAs can be implemented. To improve upon the current effort, the following information still needs to be developed:

1) A careful treatment is needed to determine MOA for the major DBPs of concern for health risk assessment. At a minimum, MOA should be determined for cancer, developmental effects and reproductive effects.

2) Dose response models need to be developed for the major DBPs of concern for all relevant endpoints. Although some initial work has been done in the 1990's (U.S. EPA, 2000a), this research should be updated to include the current literature base. In addition, issues to be carefully considered in the development of new dose response models include consideration of vehicle effects, non-linear responses at low doses, different MOA at low and high doses, background response rates, and litter effects.

3) The exposure and PBPK model predictions used in this analysis need to be further evaluated against independent data sets.

4) Improved quantitative skin permeability rates need to be developed. A large range of uncertainty exists in the dermal estimates that make it difficult to compare the dermal route to the inhalation and ingestion routes. Similarly, much uncertainty associated with inhalation exposures could be reduced through better estimation of volatilization.

5) A factor that limited the exposure modeling results to 13 of the 15 chemicals was lack of data on chemical properties, e.g., Henry's law constant, Kow, boiling point, vapor pressure, liquid and gas phase diffusivities (see Section 3 for a chemical-specific detailed list). This is a important data gap, particularly because bromate was not included in the exposure modeling estimates. (Bromate, a suspected carcinogen, is of

concern for high bromide source waters where ozonation is the primary disinfectant for the treatment system.)

6) Some physiological parameters are still needed for improved PBPK modeling. The sensitivity analysis (based on $CHCl_3$ and DCA) indicated that certain parameters could produce relatively large changes in the exposure estimates. These included alveolar ventilation rates, blood flow in the kidney, volume in the liver, liver metabolism Vmax, volume in the body, the partition coefficient for testes/blood, and stomach to portal blood rate.

7) Future exposure modeling efforts should ensure that a complete uncertainty analysis be conducted and that the sensitivity analyses include all modeled chemicals and demographic groups in the study.

8) Research needs to be conducted to determine whether populations sensitive to particular DBPs or DBP classes exist. Sensitivity may arise through different activity patterns among people (e.g., long vs. short shower durations), toxicokinetic differences among individuals, and toxicodynamic differences between individuals.

9) Approximately 50% of DBPs in the finished drinking water consists of unidentified material. EPA has conducted research to identify these DBPs (Richardson, 1998), to estimate the potential toxicity of these chemicals (Moudgal et al., 2000; Woo et al., 2002), and to estimate the additional health risk from exposure to this unknown fraction of DBPs (Teuschler et al., 2001; U.S. EPA, 2000a). Research needs to be

conducted to enhance the CRPF approach to account for the potential toxicity of the unknown fraction.

While comprehensive lists of needed research are useful, they generally provide little insight as to which of the research needs are of the highest priority. The current understanding of the risks that DBPs pose through multiple exposure routes would be improved ultimately through the successful conduct of any research listed here. To determine which areas of research would be most useful in refining risk estimates, quantitative human health risk estimates for DBPs need to be developed, including detailed analyses of uncertainly and variability. The research needs could be evaluated based on the expected improvement in the confidence in estimated DBP risks. This evaluation could serve as a ranking approach for DBP research needs.

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APPENDIX 1

DEVELOPING INDIVIDUAL HUMAN EXPOSURE ESTIMATES FOR INDIVIDUALS DBPs

Developing Individual Human Exposure Estimates for Individual DBPs

Developing Exposure Estimates

Final Report

September 2002

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Notice

This is the final report of a three-task effort to model exposures to disinfection byproducts for a typical three-person US family. The research presented herein was compiled under the following tasks: Task 1, Identifying an Appropriate Mathematical Exposure Model and Developing Model Parameters; Task 2, Developing Individual Human Exposure Estimates; and Task 3, Report on Sensitivity and Uncertainty Analysis.

The study conducted and described in this report is meant to demonstrate route specific exposure and uptake of 15 relatively common disinfection byproducts. For many of the chemicals evaluated in this report, there are significant gaps in the understanding of the specific chemical parameters impacting exposure and uptake, such as the overall mass transfer coefficients, skin permeability rates and partition coefficients. In some cases the validity of these parameter estimates are not well understood. This document presents a combination of approaches based on best available data and methods, primarily from peer-reviewed publications. Any new data or advances in methods should be considered when using the results of this analysis.

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1.0 Introduction

Disinfection of drinking water is widely recognized for its significant role in reducing illness caused by waterborne pathogens which are responsible for numerous diseases. Although disinfection is necessary for the elimination of these pathogenic organisms, it can also lead to the generation of a variety of chemicals, known as disinfection byproducts (DBPs), which are formed as a result of reactions of the disinfectant with organic matter in the water. In the U.S., where the primary form of disinfection is chlorination, public drinking water contains low levels of many DBPs and is a potential source of exposure to these compounds. The potential for exposure is significant by ingestion, but has also been shown to be significant through inhalation and through contact with the skin. The importance of each route varies with chemical characteristics, use patterns, physiological characteristics, and a variety of other factors (Wilkes et al., 1996; Olin, 1999). For example, exposure to a volatile chemical, such as chloroform, occurs most significantly during large household water uses, such as showering, bathing, and clothes washing activities. Although all three primary routes can be significant, typically inhalation dominates the exposure for these volatile compounds. For the less volatile compounds, ingestion and dermal contact play more significant roles in exposure and uptake.

In the early 1970s, advances in gas chromatography and mass spectrometry led to improvements in the detection of various DBPs in drinking water. In 1974, Rook (1974) and Bellar et al. (1974) showed that trihalomethanes (THMs) result from the chlorination process. Subsequently, a significant amount of research identified THM formation pathways as complicated reactions involving aqueous halogen species and natural aquatic humic substances, particularly humic and fulvic acids (Glaze et al., 1979; Peters et al. 1980; Urano et al., 1983). In addition, more recent research has identified the formation of haloacetic acids (HAAs), haloacetonitriles (HANs), and a variety of other DBPs and verified their existence in water supplies (Krasner et al., 1989, Westrick et al., 1984, Miller et al., 1990, Richardson, 1998).

Based on data collected under the information collection rule, U.S. EPA reported that mean concentrations of dichloroacetic acid in the distribution system ranged from 0.4 to 36 µg/L, and mean concentrations of trichloroacetic acid ranged from 0.2 to 28µg/L (U.S. EPA, 2001). In areas where naturally-occurring bromine ion is present in surface water, significant amounts of bromo- and chlorobromo acetic acids can form (Ireland et al., 1988). In addition to HAA, several haloacetonitriles (HAN) (dichloroacetonitrile, trichloroacetonitrile, dibromoacetonitrile, bromochloroacetonitrile) can form in chlorinated drinking water. In addition to THM, HAA, and HAN, two haloketones (1,1-dichloropropanone and 1,1,1-trichloropropanone), chloropicrin, and trichloroacetaldehyde monohydrate (chloral hydrate) have all received some attention as potential DBPs. Alternative forms of disinfection can also produce DBPs. For example, ozonation has been shown to lead to the formation of aldehydes and ketones (Miltner *et al.*, 1992). A study involving the ozonation of humic substances revealed the formation of mutagenic compounds, primarly glyoxal and glyoxylic acids (Matsuda *et al.*, 1992).

In 1979, the U.S. EPA issued the National Interim Primary Drinking Water Regulations, which established a maximum contaminant level (MCL) of 100 µg/L for total trihalomethanes (TTHM) in drinking water. In 1986, Congress passed amendments to the Safe Drinking Water Act (SDWA), an action that required the U.S. EPA to establish regulations for a wide range of drinking water contaminants. In 1988, the U.S. EPA published the Drinking Water Priority List (DWPL), and revised the list in 1991. The DWPL includes THMs, as well as several of the other DBPs described above. In 1998, U. S. EPA issued National Primary Drinking Water Regulations: Disinfectants and Disinfection Byproducts; Final Rule, which lowered the MCL for TTHMs to 80 µg/L. In addition, maximum contaminant level goals (MCLGs) were set for each of the four THMs, with the MCLG for chloroform,

bromodichloromethane, and bromoform set at zero, and the MCLG for dibromochloromethane set at 60 µg/L.

MCLs were also set for other disinfection by-products. For the haloacetic acids (HAAs), an MCL 60 µg/L was set for the sum of five HAAs (monochloroacetic acid, dichloroacetic acid, trichloroacetic acid, monobromoacetic acid, and dibromoacetic acid; referred to as HAA5). MCLGs were set for two HAAs, dichloroacetic acid at zero, and trichloroacetic acid at 300 µg/L. For bromate, the MCL was set at 10 µg/L and the MCLG was set at zero.

Exposure to DBPs originating in the drinking water is a very complex problem, influenced by a multitude of factors, including chemical properties of the contaminant, physical characteristics of the indoor environment, behavior of the individual relative to the contaminant, and behavioral and physiological characteristics of the exposed population. Previous modeling studies have demonstrated the considerable impact human behavior has on an individual's exposure to waterborne contaminants (Wilkes et al., 1996; Wilkes, 1999), demonstrating that differences in behavior can produce exposures varying across more than an order of magnitude. Mathematical exposure and uptake models represent a realistic, cost-effective means for estimating human exposure. Mathematical models within a probabilistic framework allow a close examination of the factors that lead to exposures and provide a basis for addressing higher risk populations. However, in the case of exposure to waterborne contaminants, previous modeling studies (Wilkes et al., 1996; Wilkes, 1999) have shown that a strictly probabilistic framework would fail to capture the effect of an individual's activities on his or her exposure. The ideal model would therefore combine a probabilistic representation of human behavior related to water use and exposure with a deterministic calculation of the concentrations in the contact media leading to the exposure (i.e. in the water and air). Such modeling frameworks also offer the ability to evaluate the impacts of parameter uncertainty and variability, such that results may be incorporated into meaningful and useful sets of outcomes.

1.1 Project Objectives

The goal of this project is to implement a comprehensive exposure model to estimate population-based exposures and doses to various DBPs. This project is limited to considering the factors and processes affecting exposure and uptake to waterborne contaminants from the point where the contaminants enter the considered household at a specific water appliance through the uptake by the exposed individual. As such, this project does not consider the nature of the raw water supply, the treatment processes, the transport of the water to the household, or any of the chemical and physical processes that occur during the treatment and transport of the water supply. In addition, this project does not consider factors that occur in the household prior to use of the water, such as chemical reactions that occur in the hot water heater.

The DBPs of concern in this project are listed in Table 1. The populations of concern in this project are the following: (a) women of reproductive age (ages 15-45); (b) men of similar age (ages 15-45); and (c) children (age 6). To begin the process of estimating the exposure of these populations to the given DBPs, we chose the Total Exposure Model (TEM) as our modeling tool and identified, collected, and summarized all the model parameters necessary to set up the modeling study. This report presents and discusses these various model parameters needed for running TEM, specifically those related to chemical volatilization, human activity patterns, ingestion, building characteristics, and chemical concentration in the water supply. Furthermore, to assess the population doses associated with the resultant exposures, the

PBPK model ERDEM will be adjoined with TEM. This report also presents and discusses the model parameters necessary for ERDEM.

Table 1. List of Chemicals for Exposure Assessment

DBP Subclass	Chemical Name	CAS Number
Trihalomethanes	Chloroform	67-66-3
(THMs)	Bromodichloromethane (BDCM)	75-27-4
	Dibromochloromethane (DBCM)	124-48-1
	Bromoform	75-25-2
Haloacetic Acids	Chloroacetic acid (CAA)	79-11-8
(HAAs)	Dichloroacetic acid (DCA)	79-43-6
	Trichloroacetic acid (TCA)	76-03-9
	Bromoacetic acid (MBA)	79-08-3
	Dibromoacetic acid (DBA)	631-64-1
	Bromochloroacetic acid (BCA)	5589-96-8
Haloacetonitriles	Dichloroacetonitrile (DCAN)	3018-12-0
(HANs)	Trichloroacetonitrile (TCAN)	545-06-2
	Bromochloroacetonitrile (BCAN)	83463-62-1
	Dibromoacetonitrile (DBAN)	3252-43-5
Miscellaneous	Bromate	15541-45-4

2.0 Model Selection

The exposure and dose model chosen for this study is the Total Exposure Model (TEM), developed by Wilkes Technologies. The PBPK model chosen for this study is the Exposure Related Dose Estimating Model (ERDEM, formerly DEEM) developed by Anteon Corporation in collaboration with the Human Exposure Research Branch of the National Environmental Research Laboratory of the U.S. EPA in Las Vegas, Nevada.

2.1 Exposure and Dose Model

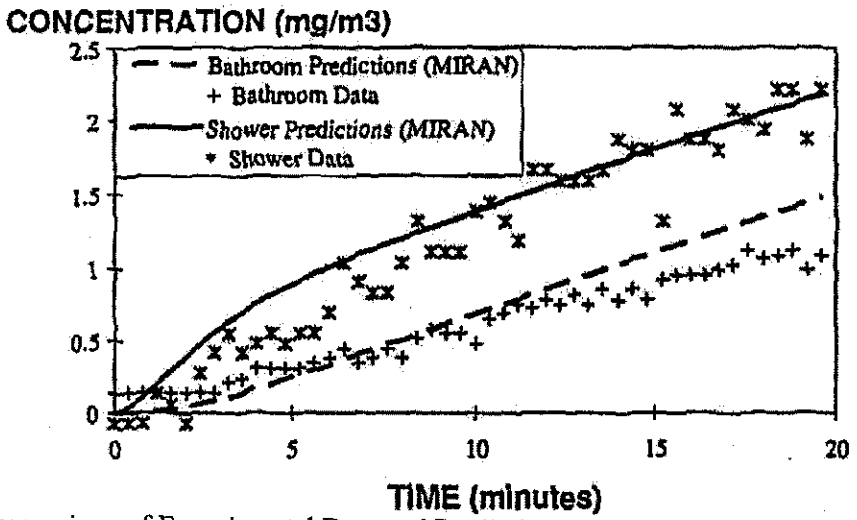
TEM is an indoor-air-quality human exposure model that combines probabilistic and deterministic principles in a single framework. This framework combines probabilistic sampling of parameters that have natural variability, such as water use behavior and other behavior affecting exposure, with deterministic representation of the physical and chemical processes, resulting in a prediction of the air and water concentrations at the interface with the exposed individuals. The deterministic framework uses the activities generated by the probabilistic algorithms to predict the release of contaminants, the fate and transport of the contaminants within the building, and finally the resulting exposures. In the case of volatilization of DBPs during water use, the deterministic framework incorporates realistic models for predicting the transfer from the liquid phase to the gas phase during household water uses. Additionally, route specific uptake models are used to estimate the transfer of the chemical to the exposed individual.

TEM was chosen because it provides the following capabilities:

1. Sources and chemicals: TEM will deterministically represent the emission of DBPs during household water uses. The emission models are based on fundamental theory (i.e., two-film volatilization theory) and include source-specific representation (i.e., the model has explicit representations of the various water appliances and fixtures, such as the clothes washer, toilet, and shower). The models shall account for both the emissions into the air as well as the resulting concentrations in the water for "pool-type" water uses, such as bathtubs. The model is capable of addressing chemicals with a wide range of volatilities.
2. Building, transport and removal: The model will deterministically represent transport and removal of chemical contaminants resulting from the use of household water. The transport component will represent multiple zones, such that each room in a house with a water-using appliance or fixture can be individually represented. This capability is vital, since research has demonstrated the importance of behavior and location relative to the water-use for volatile compounds (Wilkes et al., 1996).
3. Human activities and water uses: The model will sample activity patterns from the human activity pattern databases, such as the National Human Activity Pattern Survey (NHAPS). The model will simulate water uses appropriate to the sampled individual, and the selected activity pattern, based on analysis of actual water use behavior and deterministically incorporate the emissions resulting from these uses to predict the resulting air and water concentrations.
4. Exposure: The model will merge the probabilistic behavior with the deterministic predictions of contaminant concentrations in contact with the exposed individual to estimate the exposure.

TEM is a PC based model written in C++ by Dr. Charles Wilkes, utilizing a combination of probabilistic and deterministic techniques, and has been applied in a number of exposure assessment research projects. The original model, entitled Model for the Analysis of Volatiles and Residential Indoor air Quality (MAVRIQ), was developed as part of a research project at Carnegie Mellon University (Wilkes, 1994),

where the showering emission and finite difference algorithms were validated against analytical solutions and field data. The results of the calculations and the analytical solution were virtually identical. For the field validation, the air flows in the model were set using tracer gas data, and the resulting model predictions for airborne TCE concentrations were compared to the field measured data. The predictions of the model compared very favorably to the field measurements as shown in the following figure (Wilkes, 1994).



Comparison of Experimental Data and Predictions by MAVRIQ for the Vanport TCE Data. (Reproduced from Wilkes PhD Thesis, Wilkes, 1994).

The TEM model has been further developed under a contract with the US Air Force and the US Environmental Protection Agency. This model can be executed on a personal computer (PC) under the Microsoft Windows 95 or later operating system, and is capable of simulating a wide variety of exposure scenarios. The model performs finite-difference calculations to predict air emissions and air concentrations for each location in the modeled household. The model parameters can be either pre-defined or sampled from distributions characterizing the parameters. Physical parameters, such as room volumes, house configuration, number of family members, and water flow rates will be sampled from databases or characteristic distributions.

The source model will involve applications of fundamental mass transfer kinetics and two-phase mass balances to estimate the volatilization of DBPs during various residential water uses. The rate of volatilization from water to adjacent air is typically modeled based on the two-film volatilization theory (Lewis and Whitman, 1924). See Equation 1 (Section 3.1).

The human behavior model allows the use of two approaches for modeling human activities. The first approach allows the activity pattern for the individual to be pre-defined, allowing a complete description of a particular case of interest. When using this approach, all activities and water uses will be explicitly described for the time period of interest using a computer-generated, graphical input screen that facilitates parameter input through the use of drop-down menus and other tools. The IAQ model then makes use of this information to calculate concentration versus time profiles. It then combines concentration predictions with the location behavior to estimate inhalation exposure.

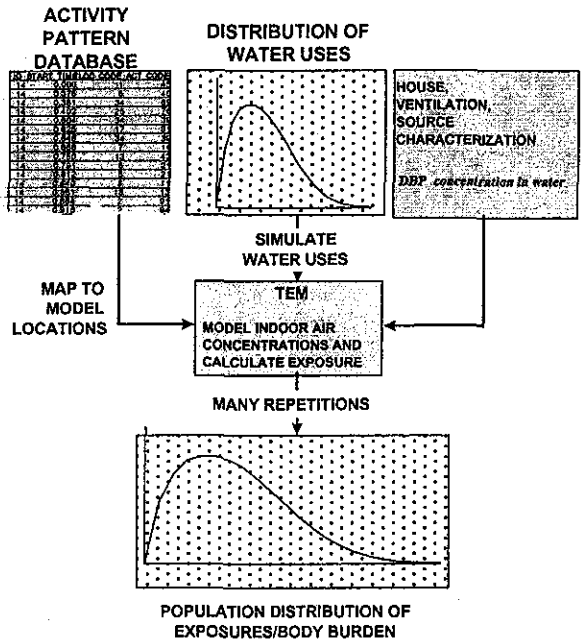


Figure 1. Estimation of Population Exposures to Compounds Originating in the Water Supply

The second approach functions stochastically and deterministically, and develops a distribution of likely exposures for a population group. This is accomplished by sampling model parameters and executing the model for many repetitions. This Monte-Carlo technique includes sampling of activity databases such as the National Human Activity Patterns Survey (NHAPS) and the California Air Resources Board database of human activity patterns (California Air Resources Board, 1991). The Monte-Carlo technique also includes known or estimated distributions for other behavioral parameters such as water-use characteristics, as illustrated in Figure 1. The model simulates water uses appropriate to the sampled activity pattern based on the characteristics of the population group. The model will estimate the distribution of exposures to a population by repeatedly sampling from the specified databases and parameter distributions, executing the model, and estimating the resultant exposure. The model will also be capable of evaluating the co-exposure effects (interaction of multiple individuals) to evaluate the impact of an individual's behavior on other family members.

TEM has been applied to several modeling studies examining the exposure and dose to waterborne contaminants as a result of household water use. Wilkes et al. (1992) examined a typical exposure for a three person family to trichloroethylene (TCE) from normal water uses. An analysis of behavioral factors leading to inhalation exposure quantified the importance of time spent in the bathroom and in showering and bathing activities (Wilkes et al., 1996). A study comparing the exposure to DBPs to that of TCE as a result of constructing a municipal treatment facility analyzed whether the remediation lowered the carcinogenic risk to the community (Wilkes and Giardino, 1999; Giardino and Wilkes, 1999). As part of an International Life Sciences Institute (ILSI/RSI) Working group entitled "Working Group on Estimation of Dermal and Inhalation Exposures to Contaminants in Drinking Water", a modeling study demonstrating the application of TEM to produce population-based estimates of exposure and uptake to 3 contaminants (chloroform, methyl parathion, and chromium) was conducted and is presented as a case study (Wilkes, 1999). Many of these same strategies will be utilized in this project as discussed below.

2.2 Pharmacokinetic Model for Estimation of Relevant Dose

The physiologically based pharmacokinetic (PBPK) model ERDEM (Exposure Related Dose Estimating Model) was chosen to model the determination of a relevant dose to certain organs of the human body. See Figure 2. This model, formerly known as DEEM (Dose Estimating Exposure Model), has been in development for many years by Jerry Blancato of the U.S. EPA, and by Jerry Elig and Fred Power of Anteon Corporation. Results have been reported at five meetings of the Society of Toxicology and at the year 2000 International Society of Exposure Analysis meeting . It uses the time proven ACSL (Advanced Continuous Simulation Language) for which the health application rights were acquired by AEgis Technology Group.

2.2.1 Physiologically Based Pharmacokinetic Modeling

The physiologically based PBPK model consists of a group of compartments representing different parts of the body. These are tied together with blood flow, membranes, chemical interactions, and exposure routes into the body. The models may be flow limited or diffusion limited. The volumes and blood flows are required for each compartment or sub-section for a compartment. The breathing rates, the gastro-intestinal absorption rates, and the skin permeation coefficients, in part, determine the absorbed dose of chemical into the body. Partition coefficients for tissue to blood, tissue to air, and blood to air, determine how much of the chemical remains and how much passes to the next state. Metabolic constants determine the amount of chemical that is converted to metabolites. The greatest difficulty is determining values for the various parameters needed for a species and chemical. Just having values for volumes and blood flows for a set of compartments or sub-compartments is not enough. Each type of chemical that is modeled may require the use of a different set of compartments. Some compartments may be combined, or others may be broken up into multiple sub compartments. The chemically dependent parameters are determined from many sources, or are estimated using various techniques, such as QSARs (Quantitative Structure-Activity Relationships). The choices are made based on the state of the science for the chemicals, their metabolism pathways, and the type of chemical.

A PBPK model can be used to extrapolate from low dose to high dose, to compare exposures for one exposure route to another. The exposure scenarios can be varied from a single exposure to multiple exposures and can even take exposure time history input. Some models handle multiple exposures to chemicals and their metabolites.

This application of PBPK modeling, for DBPs in the water, is to determine the dose metric variability arising from the variation of the exposure due to the different activities of subjects in their indoor environment.

2.2.2 The Exposure Related Dose Estimating Model (ERDEM)

The Exposure related Dose Estimating Model, a PBPK model, is designed to model the exposure of a species to multiple chemicals, determine the dose of the exposure chemicals and their metabolites to each compartment or sub-compartment of the chemical species. ERDEM models up to eight different exposure inputs. Multiple chemicals may be included in each exposure scenario and up to nine different scenarios may be defined. Time histories may be input for inhalation, dermal and rate ingestion input. The parent exposure chemicals may have multiple metabolites and these metabolites may have metabolites, etc. All metabolites and parent chemicals may circulate. ERDEM consists of the compartments: Arterial Blood, Brain, Carcass, Derma, Fat, Intestine, Kidney, Liver, Ovaries, Rapidly Perfused Tissue, Slowly Perfused Tissue, Spleen, Static Lung, Stomach, Testes, and Venous Blood. The Static Lung models breathing using a partition coefficient blood-air exchange. See Figure 2 for the ERDEM system flow chart.

The Breathing Lung utilizes the following compartments: Alveoli, Lower Dead Space, Lung Tissue, Pulmonary Capillaries, and Upper Dead Space. The full gastro-intestinal model consists of the Wall and Lumen for the Stomach, Duodenum, Lower Small Intestine, and Colon with Lymph Pool and Portal Blood compartments included. Bile flow is treated as an output from the Liver to the Duodenum Lumen. Chylomicron flow is modeled between the Lymph Pool and selected compartments.

Each of the compartments Brain, Carcass, Fat, Kidney, Liver, Lung Tissue, Ovaries, Rapidly and Slowly Perfused Tissues, Spleen, Static Lung, and Testes have two forms of elimination, an equilibrium binding process, and multiple metabolites. The Gastro-Intestinal Walls of the Stomach, Duodenum, Lower Small Intestine, and Colon have metabolism but no added elimination or binding. The Arterial Blood, Pulmonary Capillaries, Portal Blood, and Venous Blood have binding.

2.2.3 The ERDEM Front End

The inputs to such a PBPK model are very complicated and many of the necessary inputs can be easily missed. A graphical-user-interface (GUI) front end has been written (currently as Beta 3.3) to aid the user in data preparation and file management. Each set of data for a model is called a Model Data Set (MDS). Each type of input is specified in a window. After inputting all of the necessary parameter values the user runs an export, which converts the data to the command file format required by the ACSL (Advanced Continuous Simulation Language) model engine. One of the main menu items is entitled "Model" where details are entered to set up of the model, including choosing the subsystem models, specifying compartment volumes, and specifying the scaling and the reference body volume. An Activity menu is provided where the user specifies one or more activities - differentiated by changing Cardiac output for each activity. The Alveolar Ventilation Rate is specified for each activity, and the blood flow to each compartment is input for each activity. The chemical menu is used for input of the exposure chemicals, and their metabolites. The metabolism pathways are defined for each chemical. The Chemical Compartments menu provides for input of chemically specific information for each compartment active for a specific chemical. This includes the partition coefficients, elimination and binding constants, and Stomach/Intestine absorption rates. The metabolism constants are input for each metabolism defined in the Chemical menu for each compartment that has been specified as having metabolism. The Exposure menu provides the options for choosing the exposure routes, the chemicals active for which exposure routes, the exposure scenarios, and the exposure concentration for each exposure route, chemical and scenario specified.

2.2.4 Exposure Time History Input

ERDEM has the ability to handle exposure time histories by using the Table function in ACSL. The exposure time histories generated by the TEM model have been formatted as ASCII files for input to special ERDEM subroutines for preprocessing. When a user generates time histories they need to follow a particular format including limitations on the number of time steps in an exposure period and the minimum step between data points. For special cases subroutines can be written to convert the time histories to a format suitable for input to ERDEM. The Dermal, Open Chamber Inhalation, and Rate Ingestion Oral exposures have been implemented. Currently, the user can define input time histories for up to five different exposure chemicals.

These time histories can be generated for multiple variations of the TEM exposure model inputs to provide a measure of the uncertainty in model results due to exposure variation. Then sensitivity and Monte Carlo analyses can be performed on the input PBPK model parameters using the mean exposures from TEM and thus estimate the uncertainties in the relevant dose due to the PBPK input model parameters.

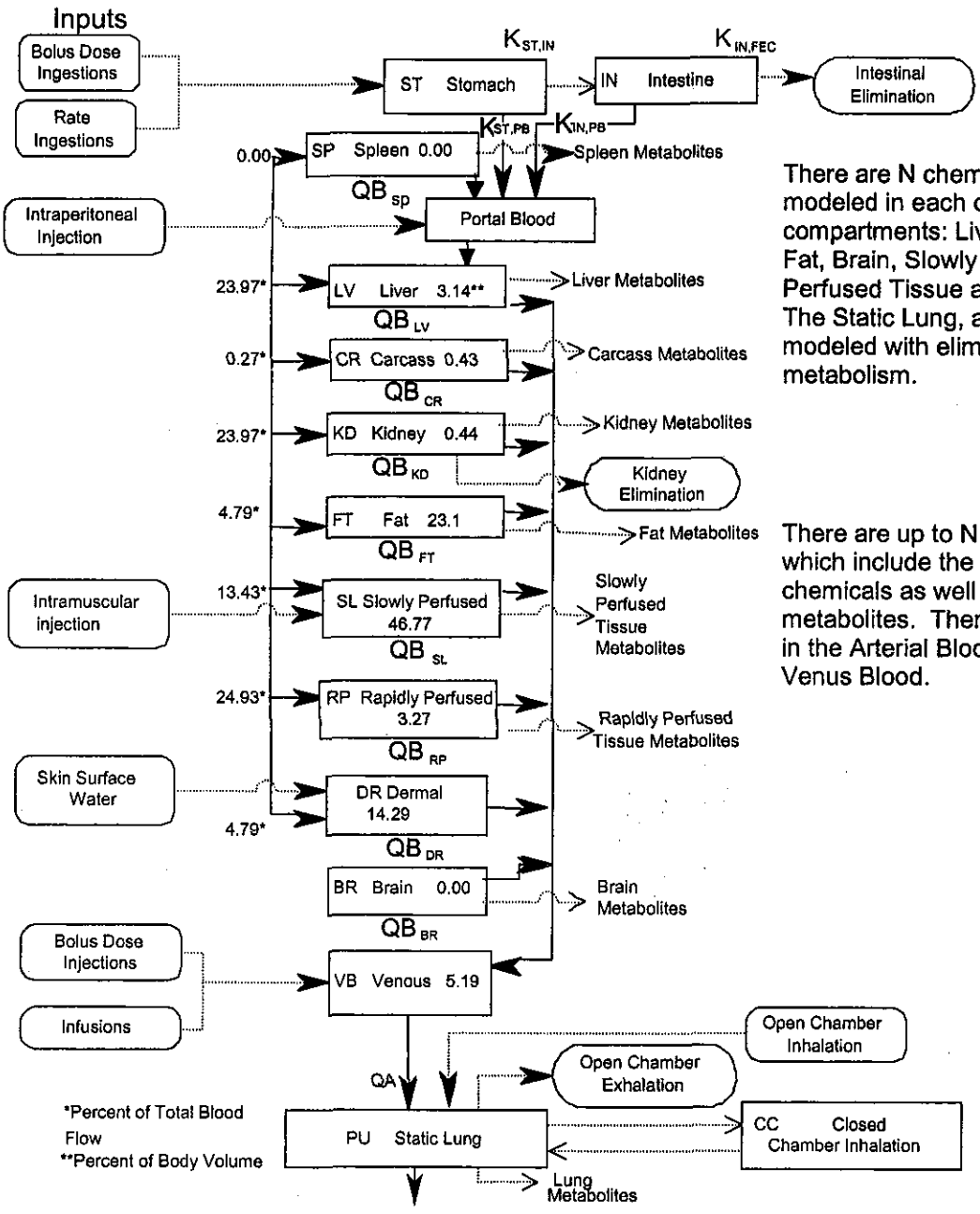


Figure 2. ERDEM System Flow Chart – With Static Lung/Stomach/Intestine Inputs

3.0 Model Parameters

For each identified parameter, the values have either been collected from published literature or estimated. An attempt has been made to identify parameter values from multiple sources to assist in the execution of the sensitivity and uncertainty analysis. The collected values are evaluated and a judgment made to select the most appropriate value(s) for use in the model execution.

The TEM model input parameters include the following:

- Parameters needed for implementation of volatilization model
- Human behavior characteristics that drive the activity model, including location and water use behaviors
- Ingestion characteristics
- Building characteristics
- Chemical concentrations in water supply

The ERDEM model input parameters include the following:

- Compartment volumes by demographic group
- Compartment blood flows by activity for each demographic group
- Definition of the exposure scenarios for each exposure route for each chemical
- The compartment-to-blood partition coefficients for each chemical
- The skin permeation coefficients for each chemical
- The rate constants for the gastro-intestinal model to be used for each chemical
- The lung-to-blood and blood-to-air partition coefficients for the lung model for each chemical
- The metabolism pathways for each parent chemical
- The metabolism rate constants, or the V-Max and the Michaelis Menten constants for each metabolism to be modeled
- The elimination rate constants for the urine, feces, and any other required compartments, by chemical
- The binding input parameters for those chemicals as needed

3.1 Volatilization Model Parameters

Each of the water-using appliances or fixtures, when operated, represents an opportunity for emission of waterborne chemicals. The emission behavior during a given water use is a function of a variety of chemical and physical factors, including water temperature, surface area, concentration, chemical diffusivities, and Henry's Law constant.

To facilitate prediction of water and air concentrations, the emission behavior is idealized using two types of models: the plug flow model (PFM) and the completely mixed flow model (CMFM). The derivations of these models are presented elsewhere (Little and Chiu, 1999).

The plug flow model is derived assuming a constant uniform flow and a volume and surface area that remains essentially constant. The PFM is appropriate for use in representing emissions during continuous flowing water uses such as faucets and showers. Emissions for sources idealized as plug flow are represented by the following equation:

$$S = K_V\left(C_l - \left(\frac{C_g}{H}\right)\right) \quad (1)$$

$$K_V = Q_L(1 - \exp(Z)) \quad (2)$$

$$Z = -\frac{K_{OL}A}{Q_L} \quad (3)$$

$$\frac{1}{K_{OL}A} = \frac{1}{K_L A} + \frac{1}{HK_G A} \quad (4)$$

where: S = *source emission rate (mass/time)*

K_V = *volatilization coefficient (volume/time)*

C_l = *contaminant concentration in the water supply prior to volatilization (mass/volume)*

C_g = *concentration in the air surrounding the water stream (mass/volume)*

H = *dimensionless Henry's Law constant*

Q_L = *volumetric flow rate of the water (volume/time)*

K_{OL} = *overall mass transfer coefficient (L/time)*

A = *interface area between water and air (L^2)*

K_L = *liquid phase mass transfer coefficient (L/time)*

K_G = *gas phase mass transfer coefficient (L/time)*

The rate of volatilization is maximized if C_g/H is negligible relative to C_l. Conversely, if C_g/H approaches C_l, a state of chemical equilibrium may be achieved with a corresponding suppression of volatilization. This equilibrium condition may occur for sources that include a headspace with poor air exchange (e.g., dishwashers) or that involve chemicals with low Henry's law constants. The concentration of a contaminant in the liquid phase may be effectively spatially uniform (e.g., in well-mixed systems such as washing machines), or may vary with space (e.g., the flowing water film or droplets associated with showers). The interfacial area, A, is typically difficult, if not impossible, to determine for residential water uses. This is particularly true when significant amounts of splashing occur (e.g., in kitchen wash basin), disintegrated films or droplets occur (e.g., showers and dishwashers), and/or when entrained air bubbles are present (e.g., during the filling of bathtubs). Thus, interfacial area and overall mass transfer coefficients are typically combined ($K_{OL}A$).

The completely mixed flow model assumes a well-mixed volume of water with a constant surface area, and is appropriate for use in representing emissions from standing water-type water uses. An example of

a CMFM type source is a filled bathtub. Emissions for sources idealized as CMFM are represented by the following equation:

$$S=K_{OL}A\left(C_l-\left(\frac{C_g}{H}\right)\right) \tag{5}$$

The volatilization coefficient represents the rate of transfer across the liquid/gas interface where the water is in contact with the air, while Henry's Law constant is used to quantify the concentration gradient relative to equilibrium.

3.1.1 Method for Estimating Overall Mass Transfer Coefficient

The volatilization coefficient, a function of the overall mass-transfer coefficient (K_{OL}), is primarily a function of the water temperature, surface area, and the chemical's diffusion coefficients in water and air. Using a power relationship between liquid-phase and gas-phase diffusivities and the liquid-phase and gas-phase mass transfer coefficients ($K_L \propto D_L^p$ and $K_G \propto D_G^q$), Little (1992) derived the following equation for predicting the overall mass-transfer coefficient for a desired chemical based on the measured coefficient for a reference chemical:

$$\frac{1}{(K_{OL}A)_i}=\frac{1}{(K_LA)_r}\left(\frac{D_{Lr}}{D_{Li}}\right)^p+\frac{1}{(K_GA)_r}\frac{1}{H_i}\left(\frac{D_{Gr}}{D_{Gi}}\right)^q \tag{6}$$

where: D_L = Liquid-phase diffusivity (L^2/T)
D_G = Gas-phase diffusivity (L^2/T)
i = Chemical for which the overall mass-transfer coefficient is being estimated
r = Reference chemical
p, q = power constants

Using this relationship and the observations of previous researchers that the ratio of K_G/K_L is approximately constant for a given mass-transfer system (Little, 1992, Corsi and Howard, 1998), Corsi and Howard rearranged Equation 6 to obtain the following equation:

$$\frac{(K_{OL}A)_i}{(K_{OL}A)_r}=\left(\frac{D_{Li}}{D_{Lr}}\right)^p\left(\frac{D_{Gi}}{D_{Gr}}\right)^q\left(\frac{H_i}{H_r}\right)\left\{\frac{1+\left(\frac{K_{Gr}}{K_{Lr}}\right)H_r}{\left(\frac{D_{Li}}{D_{Lr}}\right)^p+\left(\frac{D_{Gi}}{D_{Gr}}\right)^q\left(\frac{K_{Gr}}{K_{Lr}}\right)H_i}\right\} \tag{7}$$

The above equation provides a means for estimation of $K_{OL}A$ for a chemical based on measurements for another chemical based on the diffusivities, Henry's Law constants, and the ratio of K_G/K_L for the given system. Corsi and Howard (1998) conducted a series of laboratory experiments to determine the values of $K_{OL}A$ and K_G/K_L. The experiments were conducted for 5 reference chemicals (acetone, ethyl acetate,

toluene, ethylbenzene, and cyclohexane) and for 5 water-use types (sinks, showers, bathtubs, wash machines, and dishwashers) covering a significant range of Henry's law constants and diffusivities.

Using the measured values, Corsi and Howard present a method for estimating the product of the overall mass transfer coefficient and the interfacial surface area ($K_{OL}A$). Evaluation of liquid phase concentration is complicated for acids since only fully-protonated molecules can volatilize from water. For haloacetic acids, the pK values are significantly lower than the typical range of pH for drinking water, and therefore it is unlikely that significant quantities of HAA are generally available for volatilization.

3.1.2 Literature Review of Chemical Properties

The chemicals of interest for this study are the Trihalomethanes (THMs), Haloacetic Acids (HAAs), Haloacetonitriles (HANs), and Bromate, as listed in Table 1, above, and in Table 2, below. The properties of interest are Henry's law constant, liquid phase diffusivity, gas phase diffusivity, octanol/water partition coefficient, and molecular weight. Boiling point and volatility are additional properties of value for the study.

3.1.2.1 Literature Search

The literature was searched to identify reliable values of the desired chemical properties. Values were obtained from chemical handbooks and dictionaries or online data banks. The results of the search are summarized in Table 2. References to the relevant journal articles have been provided where available.

Table 2. Physical Properties of Chemicals of Interest

Chemical	Henry's Law Constant				Diffusivity in Water			Diffusivity in Air			Octanol/H_2O Partition Coef.		Molecular Weight	Boiling Point		Vapor Pressure		
	Dimensionless H	Temp. (°C)	$\frac{\Delta H}{RT}$ (°K)	Reference	D_w (cm^2/s)	Temp. (°C)	Reference	D_A (cm^2/s)	Temp. (°C)	Reference	Log K_{ow}	Reference		T_b (°C)	Reference	P_{vp} (mmHg)	Temp. (°C)	Reference
TRIHALOMETHANES (THMs)																		
Chloroform (CAS: 67-66-3) $CHCl_3$	0.150 0.150 (a) *0.151 (a)* 0.163 (a)	25 24 25 25	 4500	1 2 *5a* 5b	1.0×10^{-5}		1	0.1040	25	1	1.96 1.97	1 2	119.38	61.17	3	160 (v.den. 4.12)	20	4
Bromodichloromethane (CAS: 75-27-4) $CHBrCl_2$	0.0656 0.0866 (a) 0.065 0.095 0.085 0.102	 25 25 25 25 25	 4700	1 2 5d 5d 5d 5e	1.06×10^{-5}		1	0.0298		1	1.88 2.00	1 2	163.83	90 90	3	50	20	6g
Dibromochloromethane (Chlorodibromomethane) (CAS: 124-48-1) $CHBr_2Cl$	0.037 0.034 0.056	25 25 25	 4700	5d 5d 5e	1.05×10^{-5}		1	0.0196		1	2.09 2.16 2.24	1 2 5	208.28	120 119-120	3 4	76	20	4
Bromoform (CAS: 75-25-2) $CHBr_3$	0.0219 0.0219 (a) 0.0255 (a) 0.0240 (a)	25 25 25 25	 5200	1 2 5a 5b	1.03×10^{-5}		1	0.0149		1	2.30 2.40	1 2	252.73	149.1 150-151	3 4	5.6 (v.den. 8.7)	25	4
HALOACETIC ACIDS (HAAs)																		
Chloroacetic Acid (MCA) (CAS: 79-11-8) $C_2H_3ClO_2$	2.66×10^{-6} (a) 3.71×10^{-7} (a)	25 25	 9700	1 5c	1.21×10^{-5}		1	0.0733		1	0.22	2	94.50	189.3 189	3 4	1	43	4
Dichloroacetic Acid (DCA) (CAS: 79-43-6) $C_2H_2Cl_2O_2$	3.41×10^{-7} (a)	25	8000	5c							0.92 0.92	1 2	128.95	194 194	3 4	0.1787	25	6c
Trichloroacetic Acid (TCA) (CAS: 76-03-9) $C_2HCl_3O_2$	5.52×10^{-7} (a)	25	8700	5c							1.33 1.33	1 2	163.39	196.5 196	3 4	1 0.06	51 25	4 6d
Bromoacetic Acid (MBA) (CAS: 79-08-3) $C_2H_3BrO_2$	2.72×10^{-7} (a)	25	9300	5c							0.41	6a	138.95	208	3	0.1185	25	6d
Dibromoacetic Acid (DBA) (Dibromoethanoic Acid) (CAS: 631-64-1) $C_2H_2Br_2O_2$	1.78×10^{-7} (a)	25	8900	5c							0.70	67b	217.84	195 (@250 mmHg) 130 (@16 mmHg)	3			
Bromochloroacetic Acid (BCA) (CAS: 5589-96-8) $C_2H_2BrClO_2$											0.61	6b	173.39	215	3			

Table 2. Physical Properties of Chemicals of Interest

Chemical	Henry's Law Constant				Diffusivity in Water			Diffusivity in Air			Octanol/H_2O Partition Coef.		Molecular Weight	Boiling Point		Vapor Pressure		
	Dimensionless H	Temp. (°C)	$\frac{\Delta H}{RT}$ (°K)	Reference	D_w (cm^2/s)	Temp. (°C)	Reference	D_A (cm^2/s)	Temp. (°C)	Reference	Log K_{ow}	Reference		T_b (°C)	Reference	P_{vp} (mmHg)	Temp. (°C)	Reference
HALOACETONITRILES (HANs):																		
Dichloroacetonitrile (DCAN) (CAS: 3018-12-0) C_2HCl_2N	1.55×10^{-4} (a, b)	25		6b							0.29	6b	109.94	112.5 110-112	3 4	2.82	25	6e
Trichloroacetonitrile (TCAN) (CAS: 545-06-2) C_2Cl_3N	5.48×10^{-5} (a, b)	25		6b							2.09	6a	144.39	85.7 83-84	3 4	58 74.12	20 25	5 6f
Bromochloroacetonitrile (BCAN) (CAS: 83463-62-1) $C_2HBrClN$													154.39					
Dibromoacetonitrile (DBAN) (CAS: 3252-43-5) C_2HBr_2N	1.66×10^{-5} (a, b)	25		6b							0.42 0.47	4 6b	198.84	169 169-170	3 4	0.301	25	6e
MISCELLANEOUS:																		
Bromate (CAS: 15541-45-4) BrO_3											0.63	7	79.90					

NOTES:

(a) Henry's law constant is reported in the literature with concentration and partial pressure units. The value reported in the table was converted to dimensionless H.

(b) Estimated

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3.1.2.2 Missing information
The literature search identified many of the needed chemical properties, however the following properties, displayed in Table 3, are unavailable:

Table 3. Data Gaps for Chemical Properties

Chemical	Data Gaps for Chemical Properties
Bromochloroacetic Acid (BCA)	Henry's law constant, vapor pressure, liquid and gas phase diffusivities
Dichloroacetic Acid (DCA)	Liquid and gas phase diffusivities
Trichloroacetic Acid (TCA)	Liquid and gas phase diffusivities
Bromoacetic Acid (MBA)	Liquid and gas phase diffusivities
Dibromoacetic Acid (DBA)	Vapor pressure, liquid and gas phase diffusivities
Bromochloroacetonitrile (BCAN)	Henry's law constant, K_{ow}, boiling point, vapor pressure, liquid and gas phase diffusivities
Bromodichloromethane	Henry's law constant for the desired temperatures
Dichloroacetonitrile (DCAN)	Liquid and gas phase diffusivities
Trichloroacetonitrile (TCAN)	Liquid and gas phase diffusivities
Dibromoacetonitrile (DBAN)	Liquid and gas phase diffusivities
Bromate	Henry's law constant, K_{ow}, boiling point, vapor pressure, liquid and gas phase diffusivities

3.1.3 Estimating Chemical Properties

Prediction methods are used to supplement the literature review for chemical properties that were not found in the literature. Values for the liquid and gas phase diffusivitiy, the dimensionless Henry's Law Constant, and the overall mass transfer coefficient are predicted and discussed in the following subsections.

3.1.3.1 Estimating Liquid and Gas Phase Diffusivity and Henry's Law Constant
The liquid phase diffusivity is predicted using the Hayduk and Laudie method (Lyman et al., 1990, pp 17-20). This method is reasonably accurate for a wide range of compounds and has been validated using compiled measured data. The method uses the molal volume as predicted by the LaBas method and the viscosity of water to predict the liquid phase diffusivity as a function of temperature. Similarly, the gas phase diffusivity is predicted using the Wilke and Lee method (Lyman et al., 1990). This method was found to have an absolute average error of 4.3% when compared to measured values for approximately 150 compounds. This method uses the molecular weight, boiling point, the molal volume, and properties of air to predict the chemical's diffusivity in air. The estimated values for liquid and gas phase diffusivities are given in Table 4.

Henry's Law Constant can be found in current literature for most chemicals, but often not at the temperature of interest. Therefore, a method to adjust H to the designated temperature is

necessary. The following equation is used to adjust Henry's law constant for temperature dependence.

$$H = H^{\theta} x \exp\left(\frac{-\Delta H}{R}\left(\frac{1}{T} - \frac{1}{T^{\theta}}\right)\right) \quad (8)$$

Where:
H = Henry's law constant at desired temperature
H^{θ} = Henry's law constant at standard conditions
ΔH = enthalpy of solution
R = gas constant = 0.082057 $\frac{\text{L-atm}}{\text{°K mol}}$
T = temperature (°K)
θ = denotes standard condition (298.15°K)

The values for Henry's law constant adjusted for temperature are presented in Table 4.

3.1.3.2. Estimating Overall Mass Transfer Coefficients

Modeling emissions of disinfection byproducts during water usage requires knowledge of the overall mass transfer coefficient ($K_{OL}A$) as a function of the appliance, the water temperature, the water flowrate, and the chemical. The $K_{OL}A$ for each of the 15 DBPs and each type of water use are estimated applying the methods discussed in Section 3.1.1. This estimation method requires using measured data as a means for estimating parameters for the case of interest. Although the uncertainties of estimates arrived at by methods described in Section 3.1.1 and Equation 7 have not be robustly quantified, it is clear that this method is greatly influenced factors such as the chemical behavior and the physical conditions of the water use. For this reason, the measured data upon which the estimates are based should similar to the conditions being represented.

In selecting the predictor chemicals, an effort was made to select to measured data gathered under similar conditions as those being modeled. The measured data are taken from the set of chemicals studied by Corsi and Howard (1998). Corsi and Howard conducted laboratory experiments and estimated the overall mass transfer coefficients for common household water appliances for the following five chemicals: Acetone, Ethylacetate, Toluene, Ethylbenzene, and Cyclohexane. Using Equation 7, these chemicals are used as predictor chemicals for the chemicals modeled in this study. Since the mass transfer behavior of a given chemical is related to its liquid and gas diffusivities and Henry's Law Constant, the predictor chemical was chosen such that these values were most similar to the desired chemical. The predictor chemicals used in this estimation for each of the 15 DBPs are presented in Table 5. For each water use, the measured data from the most similar set of physical condition were used. In some cases, the desired condition was outside of the range encompassed by the measured data. For example, The estimated values of the $K_{OL}A$ for each of the 15 DBPs, derived from this predictor process, are given in Table 6. The values presented in Table 6 are estimated assuming a water temperature and hydrodynamic conditions similar to those under which the experiments were conducted (e.g. dropsize distribution, water flowrate, air turbulence, etc.). Temperature is another important factor, affecting mass transfer and uptake kinetics. There is a great deal of uncertainty in the understanding of temperature and temperature effects, and this is an area where future research is warranted.

Table 4. Estimated Values for Liquid Phase Diffusivity, Gas Phase Diffusivity, and Dimensionless Henry's Law Constant

Temp	Chloroform			BDCM			DBCM			Bromoform			MCA			DCA			TCA		
°C	D_l/(1E-6)	D_g	H[b]	D_l/(1E-6)	D_g	H	D_l/(1E-6)	D_g	H	D_l/(1E-6)	D_g	H	D_l/(1E-6)	D_g	H	D_l/(1E-6)	D_g	H	D_l/(1E-6)	D_g	H
6	8.200	0.0894	0.1086	8.077	0.0849	0.0586	7.9588	0.0814	0.0245	7.8452	0.0787	0.0134	8.3612	0.0869	1.4E-07	7.3871	0.0773	1.5E-07	6.6689	0.0706	2.3E-07
17	8.443	0.09	0.1105	8.316	0.0854	0.0618	8.1943	0.082	0.0259	8.0773	0.0792	0.0142	8.6086	0.0874	1.6E-07	7.6057	0.0778	1.7E-07	6.8662	0.0711	2.5E-07
18	8.699	0.0906	0.1123	8.5685	0.086	0.0651	8.4431	0.0825	0.0274	8.3226	0.0797	0.0151	8.87	0.088	1.7E-07	7.8366	0.0784	1.8E-07	7.0747	0.0716	2.8E-07
19	8.951	0.0912	0.1142	8.8162	0.0866	0.0686	8.6872	0.0831	0.0289	8.5632	0.0802	0.016	9.1264	0.0886	1.9E-07	8.0632	0.0789	2E-07	7.2792	0.072	3.1E-07
20	9.206	0.0917	0.1161	9.0674	0.0871	0.0722	8.9347	0.0836	0.0305	8.8072	0.0808	0.017	9.3865	0.0892	2.2E-07	8.293	0.0794	2.2E-07	7.4866	0.0725	3.4E-07
21	9.465	0.0923	0.1236	9.3226	0.0877	0.076	9.1862	0.0841	0.0322	9.055	0.0813	0.018	9.6506	0.0898	2.4E-07	8.5263	0.0799	2.4E-07	7.6973	0.073	3.8E-07
22	9.726	0.0929	0.131	9.5802	0.0882	0.0799	9.44	0.0847	0.0339	9.3052	0.0818	0.0191	9.9173	0.0904	2.7E-07	8.7619	0.0804	2.6E-07	7.91	0.0735	4.1E-07
23	9.992	0.0935	0.1384	9.8418	0.0888	0.0841	9.6978	0.0852	0.0358	9.5593	0.0823	0.0203	10.188	0.091	3E-07	9.0012	0.081	2.9E-07	8.126	0.074	4.6E-07
24	10.260	0.0941	0.1459	10.106	0.0894	0.0884	9.9579	0.0858	0.0377	9.8157	0.0829	0.0214	10.461	0.0915	3.3E-07	9.2426	0.0815	3.1E-07	8.3439	0.0744	5E-07
25	10.532	0.0947	0.1533	10.374	0.09	0.0929	10.222	0.0863	0.0397	10.076	0.0834	0.0227	10.739	0.0921	3.7E-07	9.4879	0.082	3.4E-07	8.5654	0.0749	5.5E-07
26	10.807	0.0953	0.1617	10.645	0.0905	0.0976	10.489	0.0869	0.0418	10.339	0.0839	0.024	11.019	0.0927	4.1E-07	9.7356	0.0825	3.7E-07	8.789	0.0754	6.1E-07
27	11.085	0.0959	0.1701	10.919	0.0911	0.1025	10.759	0.0874	0.044	10.606	0.0845	0.0254	11.303	0.0933	4.6E-07	9.9863	0.0831	4E-07	9.0153	0.0759	6.7E-07
28	11.368	0.0965	0.1785	11.197	0.0917	0.1076	11.034	0.088	0.0463	10.876	0.085	0.0269	11.591	0.0939	5.1E-07	10.241	0.0836	4.4E-07	9.2452	0.0764	7.3E-07
29	11.653	0.0971	0.1869	11.478	0.0922	0.1129	11.31	0.0885	0.0487	11.149	0.0856	0.0284	11.882	0.0945	5.6E-07	10.498	0.0841	4.8E-07	9.4771	0.0769	8E-07
30	11.942	0.0977	0.1953	11.763	0.0928	0.1185	11.59	0.0891	0.0512	11.425	0.0861	0.03	12.176	0.0951	6.2E-07	10.758	0.0847	5.2E-07	9.7119	0.0773	8.8E-07
31	12.233	0.0983	0.2037	12.05	0.0934	0.1243	11.873	0.0897	0.0538	11.704	0.0866	0.0317	12.474	0.0957	6.9E-07	11.021	0.0852	5.7E-07	9.949	0.0778	9.6E-07
32	12.527	0.0989	0.2122	12.339	0.094	0.1303	12.159	0.0902	0.0565	11.985	0.0872	0.0335	12.774	0.0963	7.7E-07	11.285	0.0857	6.2E-07	10.188	0.0783	1.1E-06
33	12.825	0.0995	0.2207	12.633	0.0946	0.1366	12.448	0.0908	0.0594	12.27	0.0877	0.0353	13.077	0.0969	8.5E-07	11.554	0.0863	6.7E-07	10.43	0.0788	1.2E-06
34	13.126	0.1002	0.2291	12.929	0.0951	0.1431	12.74	0.0913	0.0624	12.558	0.0883	0.0373	13.384	0.0975	9.4E-07	11.825	0.0868	7.3E-07	10.675	0.0793	1.3E-06
35	13.431	0.1008	0.2376	13.229	0.0957	0.1499	13.035	0.0919	0.0654	12.849	0.0888	0.0393	13.694	0.0981	1E-06	12.099	0.0874	7.9E-07	10.923	0.0798	1.4E-06
36	13.739	0.1014	0.2475	13.533	0.0963	0.157	13.335	0.0925	0.0687	13.145	0.0894	0.0415	14.009	0.0987	1.1E-06	12.377	0.0879	8.5E-07	11.174	0.0803	1.5E-06
37	14.050	0.102	0.2575	13.839	0.0969	0.1643	13.637	0.093	0.072	13.442	0.0899	0.0437	14.326	0.0994	1.3E-06	12.657	0.0884	9.2E-07	11.426	0.0808	1.6E-06
38	14.362	0.1026	0.2674	14.147	0.0975	0.172	13.94	0.0936	0.0756	13.741	0.0905	0.0461	14.644	0.1	1.4E-06	12.938	0.089	1E-06	11.68	0.0813	1.8E-06
39	14.680	0.1032	0.2773	14.46	0.0981	0.1799	14.248	0.0942	0.0792	14.045	0.091	0.0485	14.968	0.1006	1.5E-06	13.225	0.0895	1.1E-06	11.939	0.0818	2E-06
40	15.001	0.1039	0.2872	14.776	0.0987	0.1882	14.559	0.0947	0.083	14.352	0.0916	0.0511	15.296	0.1012	1.7E-06	13.514	0.0901	1.2E-06	12.2	0.0823	2.1E-06
41	15.324	0.1045	0.2981	15.094	0.0993	0.1968	14.873	0.0953	0.087	14.661	0.0921	0.0538	15.625	0.1018	1.8E-06	13.805	0.0906	1.3E-06	12.463	0.0828	2.3E-06
42	15.649	0.1051	0.3093	15.415	0.0999	0.2057	15.189	0.0959	0.0911	14.972	0.0927	0.0566	15.957	0.1024	2E-06	14.098	0.0912	1.4E-06	12.727	0.0833	2.5E-06
43	15.976	0.1057	0.3209	15.736	0.1005	0.2149	15.506	0.0965	0.0954	15.285	0.0932	0.0595	16.29	0.1031	2.2E-06	14.392	0.0917	1.5E-06	12.993	0.0838	2.7E-06
44	16.310	0.1063	0.3328	16.065	0.1011	0.2245	15.83	0.097	0.0999	15.604	0.0938	0.0625	16.63	0.1037	2.5E-06	14.693	0.0923	1.6E-06	13.264	0.0843	3E-06
45	16.644	0.107	0.3451	16.394	0.1017	0.2345	16.154	0.0976	0.1045	15.924	0.0944	0.0657	16.971	0.1043	2.7E-06	14.994	0.0928	1.7E-06	13.536	0.0848	3.2E-06
46	16.981	0.1076	0.3577	16.727	0.1023	0.2449	16.482	0.0982	0.1093	16.247	0.0949	0.0691	17.315	0.1049	3E-06	15.298	0.0934	1.9E-06	13.811	0.0853	3.5E-06
47	17.322	0.1082	0.3707	17.062	0.1029	0.2556	16.812	0.0988	0.1143	16.572	0.0955	0.0726	17.662	0.1055	3.2E-06	15.604	0.094	2E-06	14.087	0.0858	3.8E-06
48	17.668	0.1089	0.3841	17.403	0.1035	0.2667	17.148	0.0994	0.1195	16.903	0.0961	0.0762	18.015	0.1062	3.5E-06	15.916	0.0945	2.2E-06	14.369	0.0863	4.1E-06
49	18.012	0.1095	0.3979	17.742	0.1041	0.2782	17.482	0.0999	0.1249	17.233	0.0966	0.08	18.366	0.1068	3.9E-06	16.226	0.0951	2.3E-06	14.649	0.0869	4.5E-06
50	18.362	0.1101	0.4121	18.086	0.1047	0.2902	17.822	0.1005	0.1306	17.567	0.0972	0.084	18.723	0.1074	4.2E-06	16.541	0.0956	2.5E-06	14.933	0.0874	4.9E-06

Table 4 (continued). Estimated Values for Liquid Phase Diffusivity, Gas Phase Diffusivity, and Dimensionless Henry's Law Constant

Temp	MBA			DBA			BCA			DCAN			TCAN			BCAN			Dibromoacetonitrile		
°C	D_l/(1E-6)	D_g	H	D_l/(1E-6)	D_g	H	D_l/(1E-6)	D_g	H [a]	D_l/(1E-6)	D_g	H [a]	D_l/(1E-6)	D_g	H [a]	D_l/(1E-6)	D_g	H	D_l/(1E-6)	D_g	H
16	8.2316	0.0821	1.1E-07	7.2039	0.0732	7.2E-08	7.294	0.0742		7.9109	0.0855		7.0603	0.0784		7.0603			7.691	0.0779	
17	8.4751	0.0827	1.2E-07	7.417	0.0737	8E-08	7.5098	0.0747		8.145	0.0861		7.2692	0.0789		7.2692			7.919	0.0784	
18	8.7325	0.0832	1.3E-07	7.6423	0.0742	8.9E-08	7.7378	0.0752		8.3923	0.0867		7.4899	0.0794		7.4899			8.159	0.0789	
19	8.985	0.0838	1.5E-07	7.8633	0.0747	9.8E-08	7.9615	0.0757		8.635	0.0872		7.7065	0.0799		7.7065			8.395	0.0795	
20	9.241	0.0844	1.6E-07	8.0873	0.0752	1.1E-07	8.1884	0.0762		8.881	0.0878		7.9261	0.0805		7.9261			8.635	0.08	
21	9.5011	0.0849	1.8E-07	8.3149	0.0757	1.2E-07	8.4188	0.0767		9.1309	0.0884		8.1491	0.081		8.1491			8.878	0.0805	
22	9.7636	0.0855	2E-07	8.5446	0.0762	1.3E-07	8.6514	0.0772		9.3832	0.0889		8.3743	0.0815		8.3743			9.123	0.081	
23	10.03	0.086	2.2E-07	8.7779	0.0767	1.5E-07	8.8877	0.0777		9.6394	0.0895		8.6029	0.082		8.6029			9.372	0.0816	
24	10.299	0.0866	2.5E-07	9.0134	0.0772	1.6E-07	9.126	0.0782		9.8979	0.0901		8.8337	0.0825		8.8337			9.623	0.0821	
25	10.573	0.0871	2.7E-07	9.2526	0.0777	1.8E-07	9.3683	0.0787	1.31E-06	10.161	0.0907	1.55E-04	9.0682	0.0831	5.48E-05	9.0682		5.32E-04	9.879	0.0826	1.66E-05
26	10.849	0.0877	3E-07	9.4942	0.0782	2E-07	9.6128	0.0792		10.426	0.0913		9.3049	0.0836		9.3049			10.137	0.0831	
27	11.128	0.0883	3.3E-07	9.7386	0.0787	2.2E-07	9.8604	0.0798		10.694	0.0918		9.5445	0.0841		9.5445			10.398	0.0837	
28	11.412	0.0888	3.7E-07	9.987	0.0792	2.4E-07	10.112	0.0803		10.967	0.0924		9.7879	0.0846		9.7879			10.663	0.0842	
29	11.698	0.0894	4.1E-07	10.238	0.0797	2.6E-07	10.365	0.0808		11.242	0.093		10.033	0.0852		10.033			10.930	0.0847	
30	11.988	0.09	4.5E-07	10.491	0.0802	2.9E-07	10.622	0.0813		11.521	0.0936		10.282	0.0857		10.282			11.201	0.0853	
31	12.28	0.0905	4.9E-07	10.747	0.0807	3.1E-07	10.882	0.0818		11.802	0.0942		10.533	0.0862		10.533			11.475	0.0858	
32	12.576	0.0911	5.4E-07	11.006	0.0812	3.4E-07	11.143	0.0823		12.086	0.0947		10.786	0.0868		10.786			11.750	0.0863	
33	12.875	0.0917	6E-07	11.267	0.0817	3.8E-07	11.408	0.0828		12.373	0.0953		11.043	0.0873		11.043			12.030	0.0869	
34	13.177	0.0923	6.6E-07	11.532	0.0822	4.1E-07	11.676	0.0834		12.664	0.0959		11.302	0.0879		11.302			12.312	0.0874	
35	13.482	0.0928	7.3E-07	11.799	0.0827	4.5E-07	11.947	0.0839		12.957	0.0965		11.564	0.0884		11.564			12.598	0.088	
36	13.792	0.0934	8E-07	12.07	0.0832	5E-07	12.221	0.0844		13.255	0.0971		11.83	0.0889		11.83			12.887	0.0885	
37	14.104	0.094	8.8E-07	12.343	0.0837	5.4E-07	12.498	0.0849		13.555	0.0977		12.097	0.0895		12.097			13.179	0.0891	
38	14.417	0.0946	9.6E-07	12.617	0.0843	5.9E-07	12.775	0.0855		13.856	0.0983		12.366	0.09		12.366			13.471	0.0896	
39	14.736	0.0951	1.1E-06	12.897	0.0848	6.5E-07	13.058	0.086		14.162	0.0989		12.64	0.0906		12.64			13.769	0.0902	
40	15.059	0.0957	1.2E-06	13.179	0.0853	7.1E-07	13.343	0.0865		14.472	0.0995		12.916	0.0911		12.916			14.070	0.0907	
41	15.383	0.0963	1.3E-06	13.463	0.0858	7.7E-07	13.631	0.087		14.784	0.1001		13.194	0.0917		13.194			14.374	0.0913	
42	15.71	0.0969	1.4E-06	13.748	0.0863	8.4E-07	13.92	0.0876		15.098	0.1007		13.474	0.0922		13.474			14.679	0.0918	
43	16.038	0.0975	1.5E-06	14.035	0.0869	9.2E-07	14.211	0.0881		15.413	0.1013		13.756	0.0928		13.756			14.985	0.0924	
44	16.373	0.0981	1.7E-06	14.329	0.0874	1E-06	14.508	0.0886		15.735	0.1019		14.043	0.0933		14.043			15.298	0.0929	
45	16.708	0.0987	1.8E-06	14.622	0.0879	1.1E-06	14.805	0.0892		16.057	0.1025		14.331	0.0939		14.331			15.612	0.0935	
46	17.047	0.0993	2E-06	14.919	0.0884	1.2E-06	15.105	0.0897		16.383	0.1031		14.621	0.0944		14.621			15.928	0.094	
47	17.388	0.0999	2.2E-06	15.217	0.089	1.3E-06	15.408	0.0902		16.711	0.1037		14.914	0.095		14.914			16.247	0.0946	
48	17.736	0.1004	2.4E-06	15.521	0.0895	1.4E-06	15.715	0.0908		17.045	0.1043		15.212	0.0955		15.212			16.572	0.0952	
49	18.081	0.101	2.6E-06	15.824	0.09	1.5E-06	16.022	0.0913		17.377	0.1049		15.509	0.0961		15.509			16.895	0.0957	
50	18.432	0.1016	2.8E-06	16.131	0.0906	1.7E-06	16.333	0.0919		17.714	0.1056		15.81	0.0966		15.81			17.223	0.0963	

a. Value predicted at 25 °C. Because of extremely low value, this value will be used as H for all temperatures

b. Henry's law constants in this table are based on combination of literature reported values and estimates derived from procedures presented in Section 3.1.3.1.

Table 5. Predictor Chemicals for DBPs used to Estimate Mass Transfer Coefficients

Disinfection Byproduct	Predictor Chemical
Chloroform	Toluene
Bromodichloromethane (BDCM)	Toluene
Dibromochloromethane (DBCM)	Toluene
Bromoform	Toluene
Chloroacetic acid (MCA)	Toluene
Dichloroacetic acid (DCA)	Toluene
Trichloroacetic acid (TCA)	Ethylbenzene
Bromoacetic acid (MBA)	Cyclohexane
Dibromoacetic acid (DBA)	Toluene
Bromochloroacetic acid (BCA)	Toluene
Dichloroacetonitrile (DCAN)	EA
Trichloroacetonitrile (TCAN)	Toluene
Bromochloroacetonitrile (BCAN)	Toluene
Dibromoacetonitrile (DBAN)	Toluene
Bromate	

The predictor chemical was chosen based on the minimum sum of the normalized difference between the predictor and desired chemical's liquid diffusivity, gas diffusivity, and Henry's law constants at 20 °C and 40 °C. A sample calculation for identifying the predictor chemical for chloroform is as follows:

Relevant Chemical Properties for Chloroform

Desired Chemical:	Chloroform
Liquid Diffusivity (cm^2/sec):	9.21E-06 (20 °C); 1.5E-05 (40 °C)
Gas Diffusivity (cm^2/sec):	0.09175 (20 °C); 0.10386 (40 °C)
Henry's Law Constant:	0.1161(20 °C); 0.2872 (40 °C)

Relevant Predictor Chemical Properties

Property	Predictor Chemical				
	Acetone	Ethylacetate	Toluene	Ethylbenzene	Cyclohexane
Liquid Diffusivity @ 20 °C (cm^2/sec):	1.05E-05	8.36E-06	7.96E-06	7.19E-06	7.96E-06
Liquid Diffusivity @ 40 °C (cm^2/sec):	1.71E-05	1.36E-05	1.30E-05	1.17E-05	1.30E-05
Gas Diffusivity @ 20 °C (cm^2/sec):	0.110	0.0880	0.0831	0.0753	0.0853
Gas Diffusivity @ 40 °C (cm^2/sec):	0.124	0.0997	0.0942	0.0853	0.0966
Henry's Law Const @ 20 °C:	0.0011	0.00445	0.215	0.252	6.18
Henry's Law Const @ 40 °C:	0.00298	0.0132	0.456	0.642	11.62

The normalized difference between the chemical properties for each predictor chemical and chloroform is calculated as follows:

$$ND_{i,j} = \frac{(Predictor\ Chemical\ Property_i - Chloroform\ Chemical\ Property_i)}{Chloroform\ Chemical\ Property_i} * 100\%$$

Where:

$ND_{i,j}$ = Normalized difference between the predictor chemical property i and the chloroform property i.

i = chemical property

j = predictor chemical

EXAMPLE CALCULATION (For Acetone, Liquid Diffusivity at 20 $^{\circ}$ C):

$$ND_{Liquid\ Diffusivity,\ Acetone} = \frac{Liquid\ Diffusivity_{Acetone} - Liquid\ Diffusivity_{Chloroform}}{Liquid\ Diffusivity_{Chloroform}} * 100$$

$$ND_{Liquid\ Diffusivity,\ Acetone} = \frac{1.05E-05 - 9.21E-06}{9.21E-06} * 100 = 14\%$$

Summary of Normalized Difference for Between Chloroform and Each Predictor Chemical

Property	Average Normalized Difference				
	Acetone	**Ethylacetate**	**Toluene**	**Ethylbenzene**	**Cyclohexane**
Liquid Diffusivity	14%	9%	13%	22%	14%
Gas Diffusivity	19%	4%	9%	18%	7%
Henry's Law Constant	99%	96%	72%	120%	> 200%

Based the Average Absolute Difference, Toluene is chosen as the predictor chemical for Chloroform.

Table 6: Estimated Values for Overall Mass Transfer Coefficient ($K_{OL}A$)

Appliance	Temp °C	Estimated $K_{OL}A$ (m^3/hr)														
		Chloro-form	BDCM	DBCM	Bromo-form	MCA	DCA	TCA	MBA	DBA	BCA	DCAN	TCAN	BCAN	DBAN	Brom-ate
Shower	40	0.432	0.428	0.415	0.402	4.49E-04	4.37E-04	4.53E-04	4.41E-04	4.28E-04	4.39E-04	0.00381	0.00143		7.24E-04	
Bath: Fill	35	0.245	0.228	0.186	0.153	1.05E-05	7.42E-06	1.22E-05	1.33E-05	4.12E-06	1.20E-05	0.00290	5.18E-04		1.57E-04	
Bathing	35	0.0780	0.0735	0.0625	0.0531	4.64E-06	3.27E-06	5.39E-06	3.56E-06	1.81E-06	5.28E-06	7.71E-04	2.28E-04		6.90E-05	
Clothes Washer: Fill	35	0.317	0.265	0.174	0.124	5.24E-06	3.69E-06	6.08E-06	3.54E-06	2.05E-06	5.97E-06	7.73E-04	2.59E-04		7.81E-05	
Wash	35	0.113	0.0637	0.0293	0.0177	5.21E-07	3.67E-07	6.05E-07	2.69E-07	2.04E-07	5.94E-07	8.95E-05	2.58E-05		7.78E-06	
Rinse	35	0.403	0.265	0.122	0.0735	2.16E-06	1.52E-06	2.51E-06	1.14E-06	8.46E-07	2.46E-06	2.51E-04	1.07E-04		3.23E-05	
Toilets	25	0.00468	0.00368	0.00312	0.00265	2.32E-07	1.63E-07	2.69E-07	1.78E-07	9.06E-08	2.64E-07	3.26E-05	1.14E-05		3.45E-06	
Faucets: Kitchen	35	0.128	0.116	0.0913	0.0731	5.07E-06	3.58E-06	5.89E-06	4.26E-06	1.99E-06	5.78E-06	9.28E-04	2.50E-04		7.58E-05	
Bathroom	35	0.128	0.116	0.0913	0.0731	5.07E-06	3.58E-06	5.89E-06	4.26E-06	1.99E-06	5.78E-06	9.28E-04	2.50E-04		7.58E-05	
Laundry Room	30	0.117	0.104	0.0792	0.0613	3.01E-06	2.32E-06	3.68E-06	2.58E-06	1.23E-06	5.67E-06	9.08E-04	2.44E-04		7.41E-05	

Note: Dishwashers are modeled as equilibrium sources and therefore do not require a $K_{OL}A$ for modeling.
Temperature of water for the various water appliances are selected based on judgement.

3.2 Behavioral Characteristics

Activity patterns and water use behavior have been shown to have a significant impact on predicted exposure (Wilkes et. al., 1996). TEM represents the influence of behavior by using activity pattern databases and analysis of other behaviors that influence contaminant release and subsequent human exposure. The activity pattern database is queried to obtain a subset of records having the desired demographic characteristics. This subset is randomly sampled to obtain an activity pattern record, and this record is used to specify locations within the household and opportunities for conducting activities that may result in exposure. The actual water uses are simulated based on parameters defined from analysis of other water-use studies. This results in occupant driven water uses, which ultimately lead to exposure to the waterborne contaminants.

As discussed in Section 1.1, the chosen population for this exposure estimation modeling study is a three-person family in which both parents are within their reproductive years. The family consists of one male between the ages of 15 and 45, one female between the ages of 15 and 45, and one child of approximately six years old. Because there are few records in the database reflecting six year-olds, the child is characterized by sampling the database for children between the ages of one and nine. Although it is recognized that there is significant difference in behavior between a toddler and a nine year old, it was necessary to represent the child as a range of ages to allow a reasonable sample size in the database. It is not entirely clear what the impact of this assumption is on the ultimate exposure to DBPs. Younger children likely spend a greater fraction of their day at home, and for higher volatility chemicals this may increase their exposure. For less volatile chemicals, the impact of inhalation exposure is minimal, and the resultant exposure is highly dependent upon the child's water-use behavior.

3.2.1 Activity Patterns

In order to most accurately represent individuals' exposure to waterborne contaminants, it is necessary to understand the frequency of each type of water use (e.g. how often they shower), and the duration of the events (e.g. minutes occupant spends in shower). In this study, the frequency and duration are described for each of the six water-use activities most important to exposure, including showering, bathing, and using the clothes washer, dishwasher, toilet, and faucet. For some of these events, the frequencies and/or durations are described as distributions from which individual usages will be sampled, in other cases (e.g. dishwasher duration), the parameters are specified as the best available estimate.

The water-use behavior parameters needed for TEM have been developed from the data presented in the National Human Activity Patterns Survey (NHAPS), the Residential End Use Water Study (REUWS), Residential Energy Consumption Survey (RECS), in appliance manufacturer data, and supplemented, as necessary, by best judgement. These databases are described below.

3.2.1.1. Available Activity Pattern Databases

NHAPS

The NHAPS database contains the results from a two-year nationwide activity pattern survey commissioned by the U.S. EPA National Exposure Research Laboratory. During the period from October 1992 through September 1994, 9,386 persons residing in the 48 contiguous United States were chosen using a telephone random-digit dial method and interviewed over the phone (Tsang and Klepeis, 1996). First, respondents were asked to recall their activities and locations for the previous 24 hours. The locations and activities were recorded as codes chosen from a list of 83 possible locations and 91 possible activities. This diary section had minimal information

regarding water use. The only activity choice that specifically pertained to water-use was "bathing." All of the other activities are more generally defined such as "food clean-up", "plant care", "personal care".

Then the respondents were asked a series of multiple-choice questions. Every respondent was asked for specific demographic information, including date of birth, gender, race, geographical region, level of education, etc., and they were asked a multitude of questions, asking for demographic information as well as information about various activities, most relating to possible exposure to contaminants in the air and water, such as "How long did you spend in the shower?" or "Was a dishwasher used yesterday when you were home?" Not everyone was asked the same questions as there were two versions of the questionnaire. NHAPS did not acquire information on toilet use, and acquired only limited information on faucet use.

REUWS

The REUWS database contains water use data obtained from 1,188 volunteer households throughout North America (Mayer et al., 1998). The REUWS study was funded by the American Water Works Association Research Foundation (AWWARF). During the period from May 1996 through March 1998, approximately 100 single-family detached homes in each of 12 different municipalities (located in California, Colorado, Oregon, Washington, Florida, Arizona, and Ontario) were outfitted with a data-logging device (Meter Master 100 EL, manufactured by Brainard Co., Burlington, NJ) attached to their household water meter (on only magnetic driven water meters). The data logger recorded the water flows at 10-second intervals for a total of four weeks (two in warm weather and two in cool weather) at each household. Following the study, the data was retrieved and analyzed by a flow trace analysis software program, called Trace Wizard, developed by Aquacraft, Inc., Boulder, CO, which disaggregated the total flows into individual end uses (i.e. toilet, shower, faucet, dishwasher, clothes washer, etc) (Mayer et.al. 1998). In addition to identifying the type of water use (e.g. shower, faucet, toilet), Trace Wizard identified the event durations, volumes, peakflows, and mode measurements for each water-using event.

The REUWS database includes demographic information on each household based on a mail-in survey. This information includes employment status (unemployed, part-time, full-time), education level of the primary wage earner (less than high school, high school graduate, some college, Bachelor's, Master's, Doctoral), and household income. It does not give information on age or gender.

RECS

The Residential Energy Consumption Survey (RECS), conducted nationwide in 1997, contains energy usage characteristics of 5,900 residential housing units. The information was acquired through on-site personal interviews with residents; telephone interviews with rental agents of units where energy use is included in the rent; and mail questionnaires to energy suppliers to the units. The database contains information on physical characteristics of the housing units, demographic information of the residents, heating and cooling appliances used, fuel types, and energy consumption.

3.2.1.2. Modeling Activity Patterns

NHAPS represents the most comprehensive survey of activities of U.S. residents available. However, water use behavior data associated with the survey data is sparse and incomplete. The 24-hour record of locations and activities contains general locations (e.g. kitchen, bathroom, etc.) and activities (e.g. personal care, cooking , cleaning, etc.). However, the 24-hour activity record

does not specify actual water use events such as dishwasher use, clothes washer use, and showering. To model the activity patterns, TEM samples a 24-hour record from NHAPS and, using a transition matrix, places the occupant in the modeled house such that his/her location is consistent with the recorded activity and location in the NHAPS database. Information on water use behavior gathered from other sources is then used to simulate appropriate water use activities.

Water use occurrences are simulated as a Poisson process using frequency data obtained from analyses of NHAPS, REUWS, and RECS. The water-use activity duration is also simulated based on, typically, a lognormal distribution, also resulting from analyses of NHAPS, REUWS, and RECS. For more information on how the activities are mapped to model locations and how the water use simulation is implemented, see Wilkes, 1999.

3.2.2 Water Use Behaviors for Groups of Interest

Release of airborne contaminants occurs as a result of typical household water uses. In addition, dermal contact occurs during some household water uses like showers and baths. For this reason, it is imperative to represent these water uses as accurately as is reasonable within the daily activity patterns of the model occupants. From a population exposure point of view, the water use activities that have a significant impact are use of showers, baths, clothes washers, dishwashers, toilets, and faucets. For each of these water uses, the published literature and other data sources such as survey data have been reviewed, analyzed, and summarized in the following sections.

After analysis, it was concluded that NHAPS provides reliable data on frequency of occasional water-use events (e.g. showering and bathing), but is believed to provide poor estimates of the event durations because the values were based on recall (Wilkes et. al., 2002a). The respondents tended to estimate event durations around 5 minute intervals, and the values were not consistent with published literature (Wilkes et al. 2002a). In contrast, because REUWS is derived from direct water meter measurements, REUWS provides reasonable data on the durations and volumes of some water-use events, particularly showers, clothes washers, and toilets. However, since REUWS is based on the entire household water use, personal frequencies of water use events for individual persons cannot be reliably discerned. In regard to clothes washer frequencies, RECS provides the best data for our purposes.

3.2.2.1. Showers

The model uses shower frequency, duration, water flowrate and temperature to represent occupant showering behavior and subsequent contaminant release and occupant exposure. A Poisson process is used to simulate shower occurrence, and a lognormal distribution is sampled to simulate the duration. Analysis has shown that showering characteristics vary among demographic groups. A number of shower studies have been done throughout the United States to determine typical shower frequency, durations, and volumes. These studies include a study of 162 U.S. households by Brown and Caldwell (1984), a study was conducted of 25 homes in Tampa, Florida (Konen and Anderson, 1993), and a study of 25 homes in Oakland, California (Aher et al., 1991). In general, these studies revealed an average frequency of around 5 showers per week and a duration ranging from 6.3 to 10.4 minutes. The flowrates measured in the Tampa and Oakland studies ranged from 1.5 to 2.5 gpm.

In addition to the above studies, NHAPS and REUWS have been analyzed for showering characteristics, as discussed above. The analysis conducted by Wilkes et al. (2002a) concluded that NHAPS provided the most reasonable basis for specifying shower use frequency, and

REUWS provided the most reasonable basis for specifying shower duration characteristics. The results of the frequency analyses from both NHAPS and REUWS are presented in Table 7. The results of the duration, volume and flowrate analyses from REUWS are presented in Table 8. For a more detailed discussion of these data sources and analyses, refer to Wilkes et al., 2002a. The actual selected parameter values for showering frequency, duration and flowrate used in the modeling study discussed in this report are presented in Table 9.

Table 7. Shower Frequency Values from NHAPS and REUWS Analyses

Statistic	Population				
	Children 5-12 years (NHAPS)	Men 18-48 years (NHAPS)	Women 18-48 years (NHAPS)	All Households (NHAPS)	All Households (REUWS)
Shower Frequency per person-day	0.55	1.24	1.12	0.98	0.82

Table 8. Summary Statistics for Shower Duration, Volume and Flowrate from REUWS Analyses

Statistic for All Households (REUWS)	Geometric Mean	Geometric Standard Deviation	Arithmetic Mean
Shower Duration	6.8 minutes	0.493	7.65 minutes
Shower Volume (adults only)	15.80 gallons/shower	0.560	19.30 gallons/shower
Shower Flowrate	2.00 gallons/minute	0.455	2.40 gallons/minute

Table 9. Selected Model Parameters for Showers

Statistic	Value
Shower Frequency per person per day	
Children 6 years	0.55
Men 15-45 years	1.24
Women 15-45 years	1.12
Shower Duration	7.65 minutes
Shower Flowrate	2.40 gallons/minute

3.2.2.2. Baths

The model uses bath frequency, duration and water volume and temperature to represent occupant bathing behavior and subsequent contaminant release and occupant exposure. A Poisson process is used to simulate bath occurrence, and a lognormal distribution is sampled to simulate the duration. Relatively few studies have been conducted in the United States to determine typical bath frequencies, duration, and volumes. The Brown and Caldwell study in 1981-83 found that people who only bathe (do not shower) take about 2.9 baths per week. The NHAPS database is analyzed for bathing frequencies and duration. Although the bathing durations given in NHAPS tended to cluster around 5 minute intervals, and are based on recall, it is the best available data.

The REUWS database does not provide bathing durations, only the amount of time it took to fill the tub. The results of the NHAPS bathing frequencies and durations for the three subpopulations of interest are provided in Table 10. The results of the REUWS analysis to determine bath flowrate is presented in Table 11. The bathtub emission model uses a bathtub water volume, a fill duration, and a bath duration. Although no studies have analyzed the volume of water used in bathing, Brown and Caldwell (1984) estimated 50 gallons (189L) based on the physical size of a typical bathtub. The fill duration was set at 8 minutes, which is consistent with the amount of time required to fill a 50-gallon bathtub, based on a mean flowrate of 25 L/minute (6.6 gal/minute). This mean bath fill flowrate was derived by evaluating both field measurements and the REUWS data. The flowrate in two independent field measurements in household bathtubs were 8.9 and 9.3 gallons/minute (Wilkes, 2002b). The REUWS analysis resulted in a mean bath fill flowrate of 4.9 gallons/minute, with a standard deviation of 2.1 gallons/minute. The selected bath fill flowrate value of 6.6 gallons/minute is consistent with the REUWS study at approximately the 85th percentile. The actual parameter values used in the modeling study are presented in Table 12.

Table 10. Bath Frequency and Duration Values from NHAPS Analyses

Statistic (NHAPS)	Population			
	Men 18-48 years	Women 18-48 years	Children 5-12 years	All Households
Bath frequency per person per day	0.21	0.38	0.48	0.32
Bath Duration				
Geometric Mean (minutes)	17.15	17.75	18.60	17.60
Geometric Standard Deviation	0.694	0.718	0.511	0.633
Arithmetic Mean (minutes)	20.75	21.48	20.80	20.90

Table 11. Bath Volume and Flowrate Values from REUWS Analyses

Statistic for All Households (REUWS)	Geometric Mean	Geometric Standard Deviation	Arithmetic Mean
Bath Flowrate	4.40 gallons/minute	0.537	4.90 gallons/minute

Table 12. Selected Model Parameters for Bathing

Statistic	Men 15-45 years	Women 15-45 years	Children 6 years
Bathing Frequency per person per day	0.21	0.38	0.48
Bathing Duration	20.75 minutes	21.48 minutes	20.80 minutes
Bath Volume	50 gallons	50 gallons	50 gallons
Bath Fill Duration	8 minutes	8 minutes	8 minutes

3.2.2.3. Clothes washers

The model uses clothes washer frequency, the number of cycles and information about each cycle, including fill duration, agitation duration, water volume and water temperature to represent occupant use of clothes washers and subsequent contaminant release and occupant exposure. A Poisson process is used to simulate clothes washer use. Both the NHAPS and the RECS surveys asked respondents questions about their clothes washer use. The two questions asked in NHAPS were: "How often do you wash clothes in a machine?" and "How many separate loads of laundry were done when you were home?" The answers for the first question were recorded as: Almost every day, 3-5 times a week, 1-2 times a week, Less often, or Don't know. The answers for the second question were recorded as actual number of loads under 10, or "over 10". The problem with the first question was that the frequency range in the choices is too broad, and the question is unclear whether it refers to how many actual loads or how many days per week they did laundry regardless of how many sequential loads they did in one day. The major problem with the second question is that it required the individual to be at home during the event. In the RECS survey, the question relating to clothes washer use was more specific; however, the answer choices likewise offered a range. The RECS question was: "In an average week, how many loads of laundry are washed in your clothes washer?" The answer choices were: 1 load or less each week, 2 to 4 loads, 5 to 9 loads, 10 to 15 loads, More than 15 loads, or Don't know.

RECS was analyzed for clothes washer frequency behavior (Wilkes 2002a) because the questionnaire was less ambiguous than the one used for NHAPS. The results for three-person families are presented in Table 13. The analysis of three-person families excluded families with individuals over the age of 65 because we were attempting to represent families with children. The REUWS and experimental data are analyzed for clothes washer volume and durations of the various wash and rinse fills, and agitation cycles. The results of the analysis are presented in Table 14. Table 15 presents selected parameters to be used in modeling clothes washer use.

Table 13. Frequency of Clothes Washer Use for 3-Person Households: RECS

	3-Person Family	
Frequency	**%**	**N**
15+ loads/wk	3.00	370,834
10-15 loads/wk	15.10	1,847,105
5-9 loads/wk	50.50	6,189,132
2-4 loads/wk	28.60	3,501,403
1 load or less/wk	2.80	337,711
Total	100.00	12,246,185
Estimated Mean Frequency	**6.74 loads/wk**	

Table 14. Typical Clothes Washer Parameters: Based on REUWS and Experimental Data

Parameter			Comments[a]
Number of Cycles	2.2		Average Number of Fills (REUWS)
Cycle 1: Wash			
Volume	16.6	gallons	Mean Volume for First Fills (REUWS)
Time to fill	3.3	minutes	Mean Volume/Mean Mode Flow Rate of 5.01 gallons per minute (REUWS)
Time to Agitate	7.4	minutes	Based on REUWS time btwn 1st and 2nd fill (14.7 min)-typical drain/spin (4 min)-wash time (3.3 min)
Cycle 2: Rinse			
Volume	15.2	gallons	Mean Volume for Second Fills (REUWS)
Time to fill	3.5	minutes	Mean Volume/Mean Mode Flow Rate of 4.36 gallons per minute (REUWS)
Time to Agitate	4.0	minutes	Based on Experimental Data on Time to Agitate for a typical rinse cycle
Cycle 3: Rinse			
Volume	15.3	gallons	Mean Volume for Third Fills (REUWS)
Time to fill	3.4	minutes	Mean Volume/Mean Mode Flow Rate of 4.51 gallons per minute (REUWS)
Time to Agitate	4.0	minutes	Based on Experimental Data on Time to Agitate for a typical rinse cycle
Spin Rinse			
Volume	2.8	gallons	Mean Volume of Small Fills (REUWS) (includes events with 0 gal spritzes)
Duration	unknown		The duration of spin rinse varies significantly across machines and is difficult to quantify
Totals for Clothes Washer Events			
Volume	37.4	gallons	
Duration	25.2	minutes	Time until end of last fill
	29.2	minutes	Estimated time through last agitation (spin cycle follows)

Note: Cycle 2 is 100% likely to occur
Cycle 3 is 18.7% likely to occur
Cycle 4 is 0.8% likely to occur

a. Values based on REUWS data and experimental data (Wilkes et. al. 2002a and 2002b)

Table 15. Selected Model Parameters for Clothes Washer Use

Parameter	Value Used in Modeling
Temperature	35 °C
Wash	
Fill Duration	3.3 minutes
Agitation Duration	7.4 minutes
Volume	16.6 gallons
Rinse	
Fill Duration	4.2 minutes
Agitation Duration	9.8 minutes (5 min. added for spin rinse)
Volume	21.0 gallons
Frequency	0.99 events per day for 3 person household

Note: The model is currently set up to handle 2 complete cycles. The first event is the wash cycle, consisting of the wash fill and the wash agitation and drain, the second event is a combination of all the rinse activities, which are represented as 1.2 rinse cycles.

3.2.2.4. Dishwashers

The model uses dishwasher frequency, the number of cycles and information about each cycle, including cycle duration, water volume and water temperature to represent occupant use of dishwashers and subsequent contaminant release and occupant exposure. A Poisson process is used to simulate dishwasher use. There are very few studies on the water use characteristics of dishwasher use. In 1994, a US Department of Housing and Urban Development study (Brown and Caldwell, 1994) reported that people generally used the dishwasher 3.7 times per household per week, or 1.2 times per person per week. A 1983 Consumer Reports study (reported in Brown and Caldwell, 1994) found that dishwashers at the time were using from 8.5 to 12 gallons per load, and older dishwashers were using 14 gallons per load. Similar to the NHAPS clothes washer data, the NHAPS dishwasher data is likewise unreliable as the questions pertaining to dishwashers were ambiguous. The NHAPS questions relating to dishwashers were, "How often does (respondent) use the dishwasher?" This does not indicate how often the family used the dishwasher. However, the RECS respondents were asked, "Which category best describes how often your household actually uses the automatic dishwasher in an average week?" Their answer choices were as follows: Less than 4 times a week, 4 to 6 times a week, or At least once each day. The RECS data were analyzed for three person households, excluding all families with a member over 65 years old in order to best represent families with a child. The results are presented in Table 16.

Table 16. Frequency of Dishwasher Use for 3-person Households: RECS, 1997

Frequency	3-Person Family	
	%	N
Daily	17.70	1,459,081
4-6 times/wk	29.90	2,473,849
Less than 4 times/week	52.40	4,328,473
Total	100.00	8,261,403
Estimated Mean Frequency	**3.78 times/wk**	

The most reliable data on dishwasher cycle volumes and durations were obtained from the manufacturers. These data are presented in Tables 17 and 18.

Table 17. Manufacturer Supplied Dishwasher Information Summary

Condition	Total Volume, gal	Number of Fills	Average Volume per Fill, gal
Dishwasher Model:	**Whirlpool GU980SCG [a]**		
Rinse Only -- Heavy Soil	4.3	2	2.15
Rinse Only – Light Soil	2.2	2	1.1
Quick Wash - Heavy Soil	6.9	2	3.45
Quick Wash - Light Soil	4.8	2	2.4
China – Heavy Soil	8.6	3	2.87
China - Light Soil	6.5	3	2.17
Low Energy - Heavy Soil	8.6	3	2.87
Low Energy - Light Soil	6.5	3	2.17
Normal - Heavy Soil	10.8	3 or 4	3.60 - 2.7
Normal - Medium Soil*	8.6	3 or 4	2.87 - 2.15
Normal – Light Soil	6.9	3 or 4	2.30 - 1.725
Heavy - Heavy Soil	10.8	5	2.16
Heavy - Medium Soil	10.8	5	2.16
Heavy - Light Soil	8.6	5	1.72
Dishwasher Model:	**Whirlpool DU920PFG [a]**		
Rinse Only	2.2	2	1.1
Low Energy/China	6.5	3	2.17
Normal*	6.9	3	2.3
Heavy	8.6	5	1.72
Pots-N-Pans	8.6	5	1.72
Dishwasher Model:	**Whirlpool DU850DWG [a]**		
Rinse Only	2.9	2	1.45
Light Wash	5.8	4	1.45
Normal*	7.2	5	1.44
Pots-N-Pans	8.6	6	1.43
Dishwasher Model:	**GE Potscrubber [b]**		
Rinse and Hold	3	2	1.5
Short Wash	7	5	1.4
Water Saver Cycle	6.1	4	1.53
China/Crystal Cycle	7.3	5	1.46
Light Wash Cycle	7	5	1.4
Normal Wash Cycle*	8.5	6	1.42
Potscrubber Cycle	10.1	7	1.44

a. whirlpool@in-response.com 9/2000
b. answerctr@exchange.appl.ge.com 2001
* Normal cycles used for calculations in following table of selected model parameters.

Table 18. Selected Model Parameters for Dishwasher Use

Characteristic	Average *
Volume of Water	8.5 gallons
Number of Cycles (without drying)	2 Cycles
Volume of Water per Cycle	4.25 gallons
Duration per Cycle	30 minutes
Frequency	0.54 events per day for 3 person households

* Based on the average of the "normal" cycles of selected dishwashers

3.2.2.5. Toilets

The model uses the frequency of flushing to incorporate toilet use into the sampled activity pattern. Once a toilet flush has occurred the emission models also require the volume of water for the flush. For modeling purposes, it is assumed that a flush duration is instantaneous.

Several recent studies reported toilet flush frequency and volume. These studies focused on the performance of ultra-low toilets, contrasting their performance after retrofit with the performance of the low flow and older non-conserving toilets they replaced. The Tampa Florida study (Konen and Anderson, 1993) retrofitted the showers and toilets in 25 single-family homes with ultra-low flow devices and monitored their water usage for 30 days before and 30 days after retrofit. The Oakland California study (Aher et.al., 1991) retrofitted 25 single-family homes with ultra-low flow toilets and monitored their water usage for 21 days before and 21 days after retrofit. The Dept. of Housing and Urban Development study (Brown and Caldwell, 1984) monitored 196 households with 545 persons found that people flushed toilets approximately 4 times per day. The results from these studies are presented in Table 19.

Table 19. Summary of Reported Toilet Use Characteristics from Literature

Toilet Type	Reported Frequency (fpcd)[a]	Volume (gal/flush)	Population/ Sample Size	Reference	Special Study Conditions
Low-Flow (Avg. 3.6 gpf)	Mean = 3.8 Min =1.8 Max = 8.4	Mean =3.6 Min = 1.7 Max = 5.6	Tampa, Florida, 25 single family homes	Konen and Anderson, March 1993	Study comparison of low flow to ultra-low flow retrofit (average 2.9 persons/home)
Ultra-low Flow (rated 1.6 gpf)	Mean = 4.5 Min = 1.7 Max = 12.8	Mean = 1.6 Min = 1.1 Max =3.0	Tampa, Florida 25 single family homes	Konen and Anderson, March 1993	
Low-Flow (Avg. 4.0 gpf)	Mean = 3.2 or 12.8 fphd[b]	Mean = 4.0	Oakland, California, 25 single family homes	Aher et al., Oct. 1991	Study comparison of low flow to ultra-low flow retrofit (average. 4.4 persons/home)
Ultra-low Flow (rated 1.6 gpf)	Mean = 3.7 or 15.9 fphd	Mean = 1.8 Min = 1.34 Max = 2.44	Oakland, California, 25 single family homes	Aher et al., Oct. 1991	
Variety of toilets (33% low volume models or devices)	Mean = 4.0		CA, CO, D.C., VA, WA, 196 households, 545 persons, 356 toilets	Brown and Caldwell, U.S. HUD, June 1984	Study subjects recorded toilet flush counts.

a. fpcd: Flushes per capita day
b. fphd: Flushes per home per day

REUWS also provides toilet use data. The data were derived from an analysis of household water meter monitoring. Because the water meters record total water use for the household, it is impossible to attribute each flush to any given individual. Therefore, the average frequency of toilet use in REUWS was derived by analyzing the total frequency of use for each family divided by number of persons in the household. The data contained in REUWS has been analyzed for frequency of toilet use and water volume characteristics. For a complete description of the analysis of REUWS refer to Wilkes et al., 2002a.

The frequency of toilet use will be modeled as Poisson process with a mean frequency of 5.23 flushes per person per day. The volume per flush was found to best represented as a normal distribution with a mean of 3.5 gallons and a standard deviation of 1.2 gallons. The results of the REUWS analysis are presented in Table 20. The actual toilet use frequency and volume values used in the DBP modeling study are presented in Table 21.

Table 20. Statistics for Toilet Flushes from REUWS

	All Flushes			Single Flushes Only		
	Frequency (flushes/person/day)	Family Size	Sampling Days	Duration of Tank Fill (seconds)	Volume (gallons)	Mode Flow (gallons per minute)
Minimum	0.03	0.00	1.00	10.00	0.29	0.00
Maximum	42.73	9.00	16.00	2,720.00	9.77	14.10
Mean	5.23	2.76	10.65	71.43	3.48	3.89
Standard Deviation	3.15	1.37	1.63	29.77	1.18	1.31
Number of Records or Households [b]	2,145 [a]	2,158	2,158	245,328	245,331	245,331

a. *13 surveys indicated "0" for Q.31 or Q.30 regarding the number of people in selected age groups (households aggregated from* 295,660 records).

b. Number of households reflects the combined total of homes participating in the first sampling period (1,173) and second sampling period (985).

Table 21. Selected Parameters for Toilet Use

Statistics	Value
Frequency	6 flushes/person/day
Volume of water used per flush	3.5 gallons/flush

Note: *model assumes instant filling*

3.2.2.6. Faucets

Faucet use characteristics for bathrooms and kitchens were researched in a study of 25 homes in the City of Tampa (Konen and Anderson, 1993). The mean water flowrate was 2.4 gpm from the kitchen faucet and 3.4 gpm from the bathroom faucet, each with the faucets were fully open. Brown and Caldwell (June 1984) estimated that faucet use in the homes they studied was 9.0 gallons/person/day. The frequency of faucet use was not given. These data are presented in Table 22.

The faucet use characteristics reported in REUWS are analyzed and reported in Table 23. The REUWS database should be used with caution in respect to faucet use, since the techniques used to acquire the data in REUWS are unreliable, and it is expected that many uses labeled as faucets are misclassified and that many of the uses labeled as "leaks" and "unknown" could be faucets. For a complete discussion of the analysis, refer to Wilkes et. al., 2002a. The actual faucet use parameter values selected for use in the DBP modeling study are presented in Table 24. The frequency and duration values were adjusted from those in the REUWS analysis because the room locations and activity patterns sampled from NHAPS do not typically provide adequate opportunity for the frequency of faucet use reflected in the analysis of REUWS. Most probably resulting from the fact that people don't often report being in the locations of faucet use, they tend to under-report bathroom visits, and small water uses overall. In addition, there is no reasonable information on which household faucet is being used (eg. bathroom, laundry, kitchen). Therefore, to compensate for the discrepancies (i.e., interface with activity patterns), the faucet frequencies were adjusted downward, while the durations were increased. The frequency and mean duration used in the study, 15.5 events per day and 1.1 to 1.7 minutes mean duration, as reported in Table 24, was chosen through iterative modeling trials to best represent the actual total desired daily duration of faucet use. The combination chosen allowed the model to simulate reasonable faucet use by the occupants which resulted in total faucet use (duration of summed faucet uses) similar to the parameters reported in Table 23.

Table 22. Summary of Reported Faucet Frequency and Volume of Use Characteristics in Literature

Type of Appliance	Location	Frequency	Volume (gpm)	Population/ Sample Size	Reference
Conventional	Kitchen	Not given	Maximum flow [a] Mean =2.4 Min = 1.5 Max = 3.8	Tampa, Florida, 25 single family homes (avg. 2.9 persons/home)	Konen and Anderson, March 1993
Conventional	Bathroom	Not given	Maximum flow [a] Mean = 3.4 Min = 0.9 Max = 7.9	Tampa, Florida, 25 single family homes (avg. 2.9 persons/home)	Konen and Anderson, March 1993
Conventional	Not given	Not given	9.0 gal/pers/day [b]	Nationwide	Brown and Caldwell, June 1984

a. Measured flowrates with faucets in fully open position
b. Estimated value

Table 23. Summary Statistics for Faucet Use from REUWS

	Duration (minutes)	Volume (gallons)	Mode Flow (gpm)	Frequency of Use per day per person	Frequency of Faucet Use by household
Minimum	0.00	0.10	0.00	0.89	14.00
Maximum	90.00	37.60	10.70	227.25	5508.00
Mean	0.57	0.65	1.20	20.64	969.56
Standard Deviation	0.76	0.98	0.68	15.40	655.19
Number of Records	1,150,867	1,150,872	1,150,871	1,185 (households)	1,150,872

Table 24. Selected Parameters for Faucet Use

Statistic	Value
Faucet Use Duration	Range from 1.1 to 1.7 minutes
Flowrate	1.20 gallons per minute
Frequency of Faucet Use	15.5 events per day

3.3 Ingestion Characteristics

The most obvious route of human exposure to waterborne contaminants is via ingestion. Every day, people drink water directly and consume water indirectly in juices, sodas, soups, foods, coffee, tea, etc. In order to assess a person's ingestion exposure to chemicals found in the water system, it is important to appropriately represent and estimate the amount of water the person consumes, and from what sources. In order to understand the dynamics of exposure uptake and distribution in the body, we must first consider the dynamics of direct and indirect consumption from an exposure perspective. For direct consumption, we must develop a methodology for representing the number of drinks and volumes consumed, either assuming that the contaminant level remains constant from tap to glass to body, or consider that some contaminant volatilized during air contact. For indirect water consumption, such as via food or reconstituted drinks, we also need to consider the quantity consumed, and also evaluate whether the fraction of the contaminant remaining in the drink or food after volatilization and preparation is still significant or should the drink or food be ignored in the exposure calculation.

3.3.1 Available Data Sources

Currently, the U.S. EPA typically assumes that adults consume an upper-percentile quantity of 2 liters of tap water per day and infants (body mass of 10 kg. or less) consume 1 liter per day (USEPA, 1997a). These rates include the tap water consumed directly and the tap water consumed in other drinks like juices, coffee, etc. Prior to 1995, the primary survey used to estimate tap water intake in the U.S. was the USDA's 1977-1978 National Food Consumption Survey, Ershow and Cantor, 1989 in Exposure Factors Handbook (U.S. EPA, 1997a)). However, newer studies have been conducted that better reflect consumption behavior for modern times, reflecting our changed habits such as drinking more bottled or filtered water, and drinking more soda and other canned drinks. Furthermore, water intake is assumed to vary with levels of physical activity and outdoor temperatures and Americans are exercising more than ever.

There are two major recent surveys that prove useful when estimating the amount of water people ingest per day. One is NHAPS and the other is the Combined 1994-1996 Continuing Survey of Food Intake by Individuals (CSFII) (Jacobs et al., 2000) conducted by the U.S. Department of Agriculture (USDA). There are also a few other studies presented in the Exposure Factors Handbook (EFH Vol. 1, USEPA, August 1997).

3.3.1.1 Ingestion: Exposure Factors Handbook

The Exposure Factors Handbook, Volume 1, Chapter 3 (U.S. EPA, 1997a) presents the key and relevant drinking water intake studies prior to 1995. These surveys and studies include the following: 1981 *Tapwater Consumption in Canada* study by the Canada Department of Health and Welfare; 1977-78 *Nationwide Food Consumption Survey* by the US Department of Agriculture, analysis by Ershow and Cantor; 1978 *Drinking Water Consumption in Great Britain,* analysis by Hopkins and Ellis; 1987 *Bladder Cancer, Drinking Water Source, and Tapwater*

Consumption study by the National Cancer Institute, analysis by Cantor et al.; and the 1992-1994 *National Human Activity Patterns Survey* (NHAPS) analysis by Tsang and Klepeis. For a more complete discussion of these studies, see Wilkes et al., 2002a. The tapwater consumption data from these studies are summarized in Table 25, specifically for the subpopulations that most closely represent the three groups of interest identified in Section 1.1.

Table 25. Tapwater consumption characteristics

Population	Average Consumption (units)
Canadian Department of Health [a]: 970 individuals, 295 households	
Children, 3-5 Years	48 mL/kg
Children, 6-17 Years	26 mL/kg
Females, 18-34 Years	23 mL/kg
Females, 35-54 years	25 mL/kg
Males, 18-54 Years	19 mL/kg
Average Daily Consumption, (All) 90th Percentile	1.34 L/day 2.36 L/day
1978 Drinking Water Consumption in Great Britain [b]: N = 3,564 People	
Females, 5-11 Years	0.533 L/day
Females, 18-30 Years	0.991 L/day
Females, 31-54 Years	1.091 L/day
Males, 5-11 Years	0.550 L/day
Males, 18-30 Years	1.006 L/day
Males, 31-54 Years	1.201 L/day
1987 National Cancer Institute Study [c]: N = 8,000 White Adults	
Females, 21-84 Years	1.35 L/day
Males, 21-84 Years	1.4 L/day
Females and Males, 18-44 Years	1.3 L/day
1977 – 78 USDA Nationwide Food Consumption Survey (NFCS) [d]: N = 26,000	
Adults, 20 to 75 or older Years 90th Percentile	1.2 L/day 2.1 L/day
Adults, 15-19 Years [e]	999 mL/day (N = 2998)
Adults, 20-44 Years [e]	1,255 mL/day (N = 7171)
Children, 4-6 Years [e]	37.9 mL/kg-day (N = 1702)
Pregnant Women [f]	2,076 mL/day (N = 188)
Lactating Women [f]	2,242 mL/day (N = 77)
Non-Pregnant, Non-Lactating Women, 15-49 Years [f]	1,940 mL/day (N = 6201)

All references discussed and cited in Exposure Factors Handbook, U.S. EPA, 1997a

a. Canadian Ministry of National Health and Welfare, 1981
b. Hopkins and Ellis, 1980
c. Cantor et al., 1987
d. Ershow and Cantor, 1989
e. Ershow and Cantor, 1989
f. Ershow and Cantor, 1991

3.3.1.2 1994-1996 USDA's Continuing Survey of Food Intake by Individuals (CSFII)

The 1994-96 USDA's Continuing Survey of Food Intake by Individuals (CSFII) is the most recent and comprehensive consumption database available. CSFII was conducted over the three-year period between January 1994 and January 1997. More than 15,000 persons in the United States were interviewed on two non-consecutive days with questions about what drinks and foods

they consumed in the previous 24 hours. The U.S. EPA report, Estimated Per Capita Water Ingestion in the United States (Jacobs et al., 2000), presents estimates of per capita water ingestion based on the CSFII data for direct and indirect water intake.

The study uses the following definitions:

- Direct water: plain water consumed directly as a beverage.
- Indirect Water: water used to prepare foods and beverages at home or in a restaurant.
- Intrinsic Water: water contained in foods and beverages at the time of market purchase before home or restaurant preparation. Intrinsic water includes both the "biological water" of raw foods and any "commercial water" added during manufacturing or processing.

In the survey, respondents were asked:

- What is the main source of water used for cooking? (Community water, private well, spring, bottled, other?)
- What is the main source of water used for preparing beverages? (same)
- What is the main source of plain drinking water? (same)
- How many fluid ounces of plain drinking water did you drink yesterday?
- How much of this plain drinking water came from your home? (All, most, some, none)
- What was the main source of plain drinking water that did not come from your home? (Tap or drinking fountain, bottled, other, don't know)
- Recall everything they ate over the past 24 hours. Where was the food obtained?

3.3.2 Ingestion Behavior for the Three Populations: Results of Analysis

Of the available references providing water consumption data on the subpopulation groups of interest for our study, the CSFII survey was chosen as the most useful because of its current relevance and its comprehensive specification of water intake in its various forms. The intakes for the two days of the survey were averaged for each person, providing the estimated mean two-day average. Table 26 lists the distribution parameters (geometric mean and standard deviation) for direct and indirect tapwater consumption in the U.S. for women and men over 20 and children between one and ten from the CSFII study. Table 27 shows a comparison of the consumption percentiles for the data set and the fitted lognormal distributions for each of the demographic groups. The actual parameters selected for use in this DBP modeling study are presented in Table 28.

Table 26. Parameters of Fitted Lognormal Distribution for Water Ingestion in the United States

Population	Geometric Mean ml/day	Geometric Standard Deviation
Women, direct (20+ years)	394	2.52
Women, indirect (20+ years)	384	2.20
Men, direct (20+ years)	389	2.69
Men, indirect (20+ years)	418	2.33
Children, direct (1-10 years)	188	2.50
Children, indirect (1-10 years)	97	2.51
All ages, direct	321	2.79
All ages, indirect	290	2.53

Source: Fitted to data from Table A1 in Jacobs et.al. 2000.

Table 27. Comparison of Consumption for Raw Data and Fitted Distributions based on CSFII Data

Percentile	Men, 20+ years				Women, 20+ years				Children, 1-10 years				Total Population			
	Direct Consumption (ml/d)		Indirect Consumption (ml/d)		Direct Consumption (ml/d)		Indirect Consumption (ml/d)		Direct Consumption (ml/d)		Indirect Consumption (ml/d)		Direct Consumption (ml/d)		Indirect Consumption (ml/d)	
	Data [1]	Fitted Lognormal Distribution	Data [1]	Fitted Lognormal Distribution	Data [1]	Fitted Lognormal Distribution	Data [1]	Fitted Lognormal Distribution	Data [1]	Fitted Lognormal Distribution	Data [1]	Fitted Lognormal Distribution	Data [1]	Fitted Lognormal Distribution	Data [1]	Fitted Lognormal Distribution
1	---	39	---	58	---	46	---	61	---	22	---	11	---	30	---	33
5	---	77	---	104	---	86	---	105	---	42	---	21	---	60	---	63
10	---	110	---	142	---	121	---	140	---	58	---	30	---	87	---	88
50	352	390	412	419	349	394	365	385	174	189	84	97	290	322	262	290
90	1,450	1,380	1,210	1,235	1,395	1,285	1,080	1,057	696	611	352	316	1,270	1,193	1,008	952
95	1,891	1,980	1,597	1,682	1,865	1,799	1,394	1,410	919	854	457	441	1,769	1,734	1,334	1,336
99	3,773	3,897	3,094	3,000	3,062	3,386	2,367	2,421	1,415	1,601	734	828	3,240	3,499	2,373	2,523

1. Data taken from CSFII

Table 28. Selected Parameters for Tapwater Consumption Modeling Study

Statistic	Men (age 15-45 years)		Women (age 15-45 years)		Child (age 6 years)	
	Direct Consumption	Indirect Consumption	Direct Consumption	Indirect Consumption	Direct Consumption	Indirect Consumption
Volume						
Geometric Mean (Liters/day)	0.390	0.419	0.394	0.385	0.189	0.097
Geometric Standard Deviation	0.988	0.8449	0.9228	0.4894	0.9173	0.9187
Duration (time to consume water)						
Geometric Mean (minutes)	2.236	3.162	2.236	3.162	2.236	3.162
Geometric Standard Deviation	1.269	1.517	1.269	1.517	1.269	1.517
Arithmetic Mean (minutes)	5	10	5	10	5	10
Arithmetic Standard Deviation (min.)	10	30	10	30	10	30
Mean Frequency	8	8	8	8	8	8
Time of Day	5 am – 10 pm	5 am – 10 pm	5 am – 10 pm	5 am – 10 pm	5 am – 10 pm	5 am – 10 pm

3.3.2.1 Methodology for distributing water consumption is distributed throughout day.
No studies were identified that quantify the manner in which water consumption is distributed throughout the day. A reasonable, common sense approach is being adopted for implementing this distribution. The water consumption will be distributed into a specified number of consumption events represented by a Poisson process. The consumption volume is sampled from the appropriate lognormal distribution as identified in Section 3.3.2, with the total volume randomly placed among the consumption events.

3.4 Building Characteristics

Housing characteristics, including zonal volumes, interzonal airflows, and whole house air exchange rates, also have a significant impact on the estimated exposures. The important building parameters are volumes of the whole house, volumes of the individual water-use zones, whole house air exchange rates, and interzonal airflows.

TEM will model each subject residence as a collection of individual water-use zones in flow communication with a "Rest-of-House" (ROH) zone that aggregates the zones that are free of water-use sources. In order to execute TEM for typical conditions and building characteristics, information related to indoor volume and airflows is needed.

3.4.1 Representation of Household Volumes

The *Exposure Factors Handbook* (U.S. EPA 1997b) recommends using 369 m^3 as the central estimate of volume for American residences. If an underlying normal distribution is assumed, it would have a standard deviation of 258 m^3, giving 209 m^3 as the most reliable conservative estimate. These estimates are based on peer-reviewed data appraisals drawn from statistically representative surveys of American households through the Residential Energy Consumption Survey (RECS). RECS was first conducted in 1978 and was updated on a biennial basis until 1984, after which the survey was conducted periodically, every three or four years. In addition to data related to energy consumption, RECS solicits information on demographics, building characteristics, and other factors that relate to the needs of TEM. The distribution of indoor residential volume contained in the *Exposure Factors Handbook* was calculated based on the estimated floor area assuming 8-foot (2.44 m) ceiling height.

Estimates for total house volume contained in the *Exposure Factors Handbook* were derived primarily from RECS data collected in 1993 and published in 1995 (U.S. DOE, 1995). Results of the 1997 survey (U.S. DOE, 1999) only became available after the *Exposure Factors Handbook* was updated. Initial reviews of the 1997 RECS data indicate that total house volume estimates derived from the 1997 RECS data would be very similar to the earlier data. The RECS data was analyzed and the representativeness of several distributions was evaluated. Based on the fit, a lognormal distribution was chosen to represent the distribution of volumes, as shown in Figure 3. The probability density function for the chosen lognormal distribution is compared to a histogram of housing volumes in Figure 4. The volume of the median 3-bedroom American home from the 1997 RECS data is characterized by a total volume of 317 m^3 (Table 29, Figure 3). Such housing corresponds to a modest (~1400 ft^2) residence occupied by 3 or 4 people. In addition to expected general appliances, all such homes are equipped with a kitchen (which usually contains an automatic dishwasher), and nearly all have 2 baths plus a laundry, as well as a basement. The "average" house has a central forced-air system to support heating and cooling needs.

Selection of Total House Volume: Total house volume for 3-bedroom cases are selected from the statistical distribution derived from the 1997 RECS data (Table 29, below). The distribution of total volume for 3-bedroom homes is lognormal (Figure 3), and is characterized by a geometric mean volume of 317 m^3 (11,195 ft^3) and geometric standard deviation of 0.4218.

Table 29. Analysis of RECS for Total House Volume for 3-Person U.S. Households (RECS 1997).

Percentile	Area, ft^2	Area, m^2	Volume, ft^3	Volume, m^3 [a]
4.1	0 - 600	55.7	4800	135.9
22.3	601 - 999	92.8	7992	226.3
60.4	1000 - 1599	148.6	12792	362.3
79.7	1600 - 1999	185.7	15992	452.9
90.5	2000 - 2399	222.9	19192	543.5
96.6	2400 - 2999	278.6	23992	679.5

a. Volumes were calculated by assuming an 8 ft ceiling height

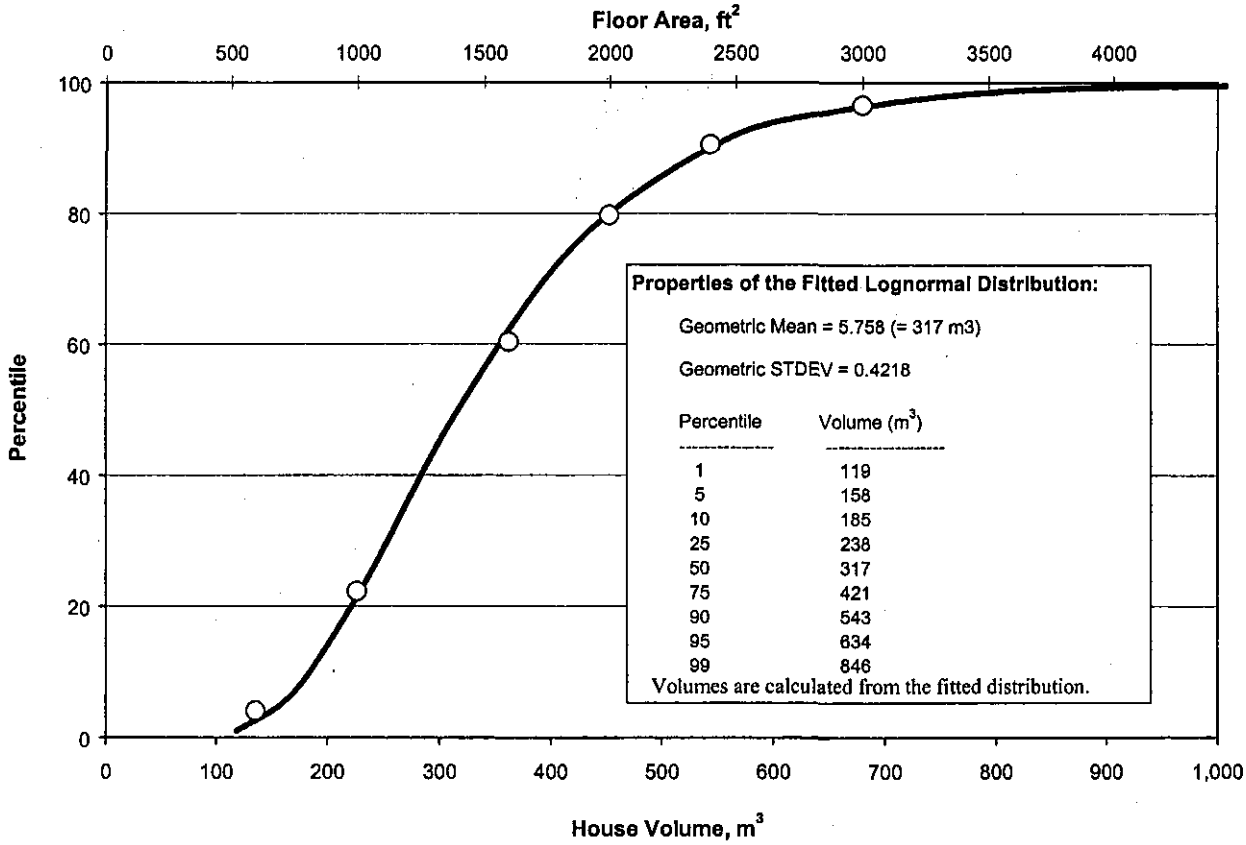


Figure 3. Cumulative Distribution Function of Volume for 3-Person Households.
Source: Analysis of RECS 1997 data

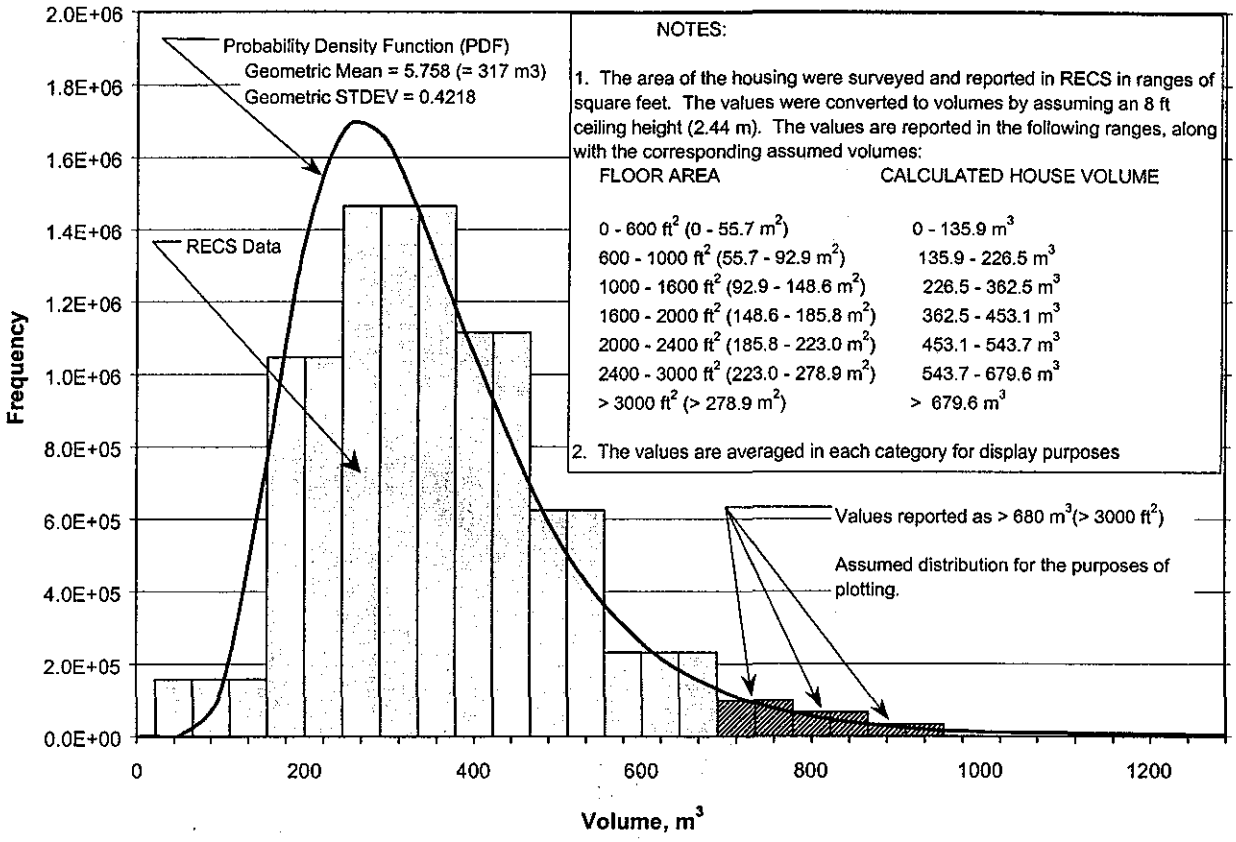


Figure 4. Comparison of RECS Data and the Fitted Probability Density Function of Volume for 3-Person Households.
Source: Analysis of RECS 1997 data

The RECS data does not identify volumes for individual water-use zones. Given that indoor spaces are designed to meet specific patterns of use, the *Architectural Graphics Standards* published through the American Institute of Architects (Hoke, 1988, 1994) provides a basis for assigning floor areas to specific zones. This resource summarizes the range of basic dimensions for key zones for various sized households. The range of kitchen dimensions is keyed to the number of people in the household. Table 30 summarizes this range for a household composed on 3-4 people (the predominant household size for 3-bedroom US homes). Bathroom dimensions, on the other hand, are largely independent of the number of people. Floor areas have been transformed to volume estimates assuming 8-foot (2.44 m) ceiling height.

Table 30. Dimensions of Water-Use Zones

Zone	Dimension	Low End	High End
Hall Bath	Area (m^2)	3.2	6.1
	Volume (m^3)	7.9	14.9
Master Bath	Area (m^2)	2.0	3.5
	Volume (m^3)	4.9	8.5
Kitchen	Area (m^2)	6.3	7.4
	Volume (m^3)	15.4	18.1
Laundry	Area (m^2)	5.5	10.4
	Volume (m^3)	13.5	25.4
Shower	Area (m^2)	1.2	1.8
	Volume (m^3)	2.9	4.5

Source: Hoke 1988, 1994

This range of zonal volumes is largely unverified in the professional literature, but the values in Table 30 have the intuitive appeal of being derived from an authoritative source that guides residential design. Residential laundry facilities, for the most part, are installed in a host space rather than taking up a separate room. In homes featuring a heated basement, the laundry should be positioned in that zone. In homes built to slab-on-grade and crawlspace designs, the laundry is usually assigned to the kitchen, and the kitchen-laundry zone should be sized to accept both uses.

> *Selection of Indoor Volumes for Water-Use Zones*: The range for zonal sizes are defined from the *Architectural Graphics Standards*. For each type of water-use zone, each range listed in Table 30 (above) will be used to define zone-specific uniform distributions. Values assigned to individual model cases will be randomly selected from these distributions within TEM.

3.4.2 Representation of Whole House Air Exchange Rates and Interzonal Airflows

The Exposure Factors Handbook (U.S. EPA 1997b) recommends using 0.45 ACH as the "typical" value for air exchange in American residences. The national distribution of residential air exchange is described in the *Exposure Factors Handbook* and summarized in Table 31. In the absence of comprehensive measurement surveys, the distribution in Table 31 was derived from analysis of perfluorocarbon tracer (PFT) data collected for a number of research programs since the early 1980s (Koontz and Rector 1995).

> *Selection of Air Exchange Rate*: The national distribution of residential air exchange rates are defined from the *Exposure Factors Handbook* (See Table 31). Values assigned to individual model cases will be randomly selected from this distribution within TEM.

Table 31. Summary Statistics for US Residential Air Exchange Rates.

	West Region	North Central Region	Northeast Region	South Region	All Regions
Arithmetic Mean (h^{-1})	0.66	0.57	0.71	0.61	0.63
Arithmetic Standard Deviation (h^{-1})	0.87	0.63	0.60	0.51	0.65
Geometric Mean (h^{-1})	0.47	0.39	0.54	0.46	0.46
Geometric Standard Deviation	2.11	2.36	2.14	2.28	2.25
10th Percentile (h^{-1})	0.20	0.16	0.23	0.16	0.18
50th Percentile (h^{-1})	0.43	0.35	0.49	0.49	0.45
90th Percentile (h^{-1})	1.25	1.49	1.33	1.21	1.26
Maximum (h^{-1})	23.32	4.52	5.49	3.44	23.32

Source: U.S. EPA, 1997b

Given the simplified scenarios envisioned for initial model runs, interzonal airflows can be assigned through the air exchange rate. That is, interzonal airflows would be sized by the air exchange terms. The next level of complexity could utilize the algorithms developed by Koontz and Rector (1995) from their analysis of the PFT data cited above. Under this scheme, the normalized interzonal airflow (Q_N, h^{-1}) for any zonal pair is defined as a function of the flow from zone 1 to zone 2 (Q_{12}), flow from zone 2 to zone 1 (Q_{21}), and total (V, m^3) such that:

$$Q_N = \frac{(Q_{12} + Q_{21})}{2} \cdot \frac{1}{V} \tag{9}$$

While the analysis showed differences in the correlation equations, the practical differences are negligible in that both estimators produce a normalized interzonal airflow term of 0.22 h-1 at an air exchange rate (I, h-1) of 0.45:

$$\text{Bedroom: } Q_N = 0.078 + 0.31I \tag{10}$$

$$\text{Kitchen: } Q_N = 0.046 + 0.39I \tag{11}$$

It is expected that bathrooms are used with the door closed. Relatively little direct data exists to define airflows. Experimental work by Giardino et al. (1996) provides useful values published in a peer-reviewed journal. For a 13 m^3 bath, these determinations found exiting airflow from the bath to the adjacent hallway to be 4.2 m^3 h^{-1} with the door closed and 15.1 m^3 h^{-1} with the door open. Similarly, entering airflows from the hallway to the bath were found to be 16.3 m^3 h^{-1} with the door closed and 47.9 m^3 h^{-1} with the door open. These flows were utilized in subsequent residential exposure modeling of radon volatilized from various water-use scenarios (Rector, Wilkes, and Giardino, 1996)

At higher levels of complexity, dynamic and engineering estimators can be applied to recognize the influences of weather and operation of the heating/cooling system. These strategies are discussed in a recent model strategies report (Rector et al., 2001).

A modeling study conducted by researchers at the National Institute of Standards and Technology (NIST) developed simplified approaches to modeling interzonal dispersal of indoor contaminants in homes served by central air-conditioning/heating systems (Persily, 1998). Under the NIST study, patterns of fan operation were defined by the following rules:

- Airflows were assumed to be 50 L s^{-1} (180 m^3 h^{-1}) at major supply registers and 25 L s^{-1} (90 m^3 h^{-1}) at minor supply registers when the central air handler was running. (These values are consistent with standard guidance in ASHRAE 1992).

- System on-time was assumed to be 60 percent (of the total timeframe) at design conditions. (i.e., the highest temperature reached 98-99 percent of the time during the cooling months, or the lowest outdoor temperature reached 98-99 percent of the time during the heating months).

The NIST study also addressed local exhaust fans operating in the kitchen and bathrooms under user control. Based on analysis of commercially-available equipment and engineering judgement, kitchen exhaust flows were assigned to be 170 m^3 h^{-1} (100 cfm), and bath exhaust flows in the NIST study were assigned to be 80 m^3 h^{-1} (47 cfm).

Selection of Interzonal and Exhaust Airflows: Interzonal airflows are scaled by the air exchange rate using the algorithm developed by Koontz and Rector (1995). Exhaust flows for the kitchen and bathrooms will be assigned in conformance with the NIST study (170 m3 h-1 in the kitchen, 80 m3 h-1 in each bath, under user control). These flows will be superimposed on the airflows that prevail when the fans are not operating.

3.4.3 Model Representation of Building

As described in Section 3.4.1, the house is idealized as a collection of compartments where water-use zones are explicitly represented and the remaining indoor zones are lumped into a common zone called "Rest of House", ROH. The volume parameters and the air exchange rate parameters are specified in accordance with Sections 3.4.1 and 3.4.2. The idealized representation of the house is presented in Figure 5.

3.5 Concentrations in Water Supply

The concentrations of DBPs in U.S. water supplies varies significantly across utilities. Several surveys have reported the concentrations of some DBPs (Krasner et al., 1989, Westrick et al., 1984, Miller et al., 1990, Richardson, 1998). In addition, a recent case study in two U.S. municipal water systems shows wide variation across the system (Lynberg et al., 2000, Miles et al., 2000). Also, USEPA has recently completed analysis of the Information Collection Rule (ICR). U.S. EPA had collected data required by the Information Collection Rule (ICR) from

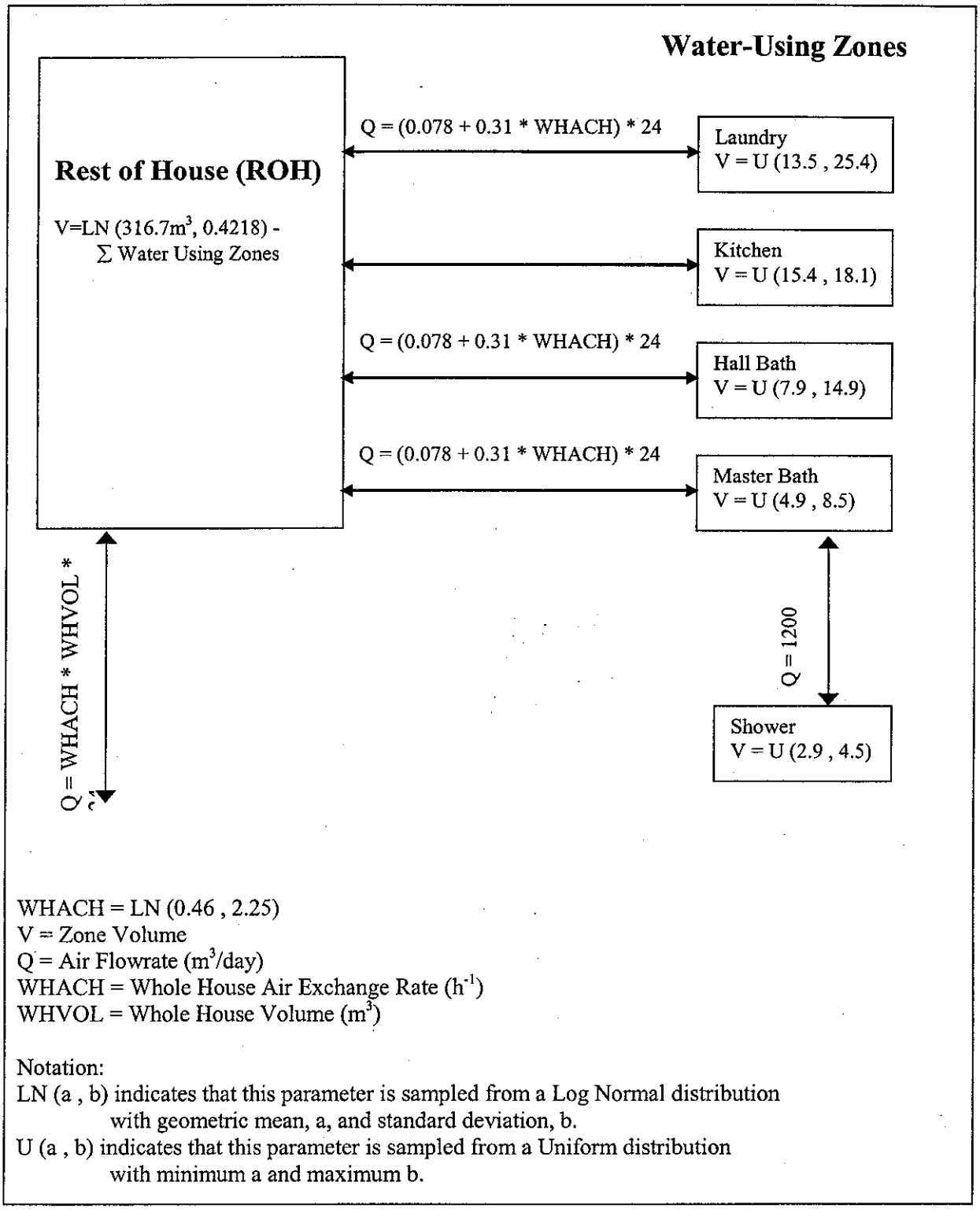


Figure 5. Schematic Representation of House Interzonal Air Flows

drinking water utilities to support future regulation of disinfectants, and disinfection byproducts. The rule intended to provide U.S. EPA with information on chemical byproducts that form when disinfectants react with chemicals already present in source water. The following sections present the results of various studies identifying concentrations in the water supplies of the 15 disinfection byproducts of interest listed in Table 1. The results from these studies are presented in the following Tables 32 through 34. The results from these studies serve to help define a set of concentrations to be used in this modeling study (Table 35).

With the exception of bromate, the results reported by Miltner et al. (1990) may be used to quantify DBP concentrations in a distribution system. Section 3.5.1 discusses the concentration of identified DBPs reported by Miltner et al. Section 3.5.2 discusses results from Miltner et al. (1992), which modeled ozonation, and thus could be used to quantify bromate concentrations. Table 32 summarizes the assumed concentration distributions 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.

Table 32. Summary of DBP Concentrations Reported by Miltner et al. (1990)

Chemical	Filter-Cl		O_3-Filter-Cl	
	Mean (μg/L)	Standard Deviation (μg/L)	Mean (μg/L)	Standard Deviation (μg/L)
Chloroform	55.50	2.01	39.55	2.95
BDCM	24.40	1.52	21.10	0.18
DBCM	10.20	0.85	13.00	0.49
Bromoform	0.35	0.30	1.50	0.18
MCA	1.44	0.10	1.46	0.05
DCA	30.85	1.49	19.30	0.79
TCA	20.10	0.97	10.00	0.73
MBA	0.29	0.02	0.28	0.04
DBA	1.50	0.12	1.98	0.13
BCA	8.50	0.06	6.70	0.12
DCAN	3.50	0.43	2.60	0.24
TCAN	0.20	0.06	0.05	0.00
BCAN	1.90	0.24	1.65	0.12
DBAN	0.15	0.07	0.55	0.14
Bromate	0.00	0.00	4.00	0.36

a. Based on Miltner et al. (1990; 1992)
b. The concentration of each DBP is assumed to be normal.
c. The standard deviation was calculated using mean and 95th percentile values developed below, along with the assumption of normality.
d. Bromate is not an organic halogen and therefore this fraction is zero.

3.5.1 DBPs (Excluding Bromate)

U.S. 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. For this study, raw Ohio River water was trucked to the USEPA 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 33 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 of a recalculation of 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.

Table 33. Mean and 95th Percentile Concentrations for Identified DBPs (Excluding Bromate) from Miltner et al. (1990)

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)
Chloroform	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
DBCM	10.20	8.80	11.60	13.00	12.20	13.80
Bromoform	0.35	0.00	0.84	1.50	1.10	1.80
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	0.00	0.00	0.00	4.00	3.40	4.60

3.5.2 Bromate

Under water treatment plant conditions, chlorine will not react with bromide to form bromate. Rather, chlorine reacts with bromide to form bromine, which reacts with organic compounds to form brominated DBPs. Hence, in the case of the filter-Cl treatment train, the assumed bromate concentration was 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 U.S. EPA Method 300.1 for bromate suggests that the expected deviation at 4 μg/L would be ± 0.6 μg/L. Table 34 describes the basis for the estimate.

Table 34. Estimated Bromate Formation in Ohio River Water by Ozonation, from Three Studies

Parameter	Study [a]		
	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 U.S. EPA method 300.1

3.5.3 Water Concentrations Selected as Model Inputs

Table 35 presents the selected water concentrations that are used as inputs for the modeling study. The concentration values were selected based on data presented in the "Stage 2 Occurrence and Exposure Assessment for Disinfectants and Disinfection Byproducts (D/DBPs)" (The Cadmus Group, Inc. 2001). For each chemical, the value was selected based on the 90th percentile concentration for surface water supply systems.

Table 35. List of Selected Concentrations for Chemicals in Modeling Study

DBP Subclass	Chemical Name	Concentration (mg/Liter)
Trihalomethanes	Chloroform	0.070
(THMs)	Bromodichloromethane (BDCM)	0.023
	Chlorodibromomethane (DBCM)	0.015
	Bromoform	0.0077
Haloacetic Acids	Chloroacetic acid (MCA)	0.0051
(HAAs)	Dichloroacetic acid (DCA)	0.032
	Trichloroacetic acid (TCA)	0.034
	Bromoacetic acid (MBA)	0.01 (Guess)
	Dibromoacetic acid (DBA)	0.0043
	Bromochloroacetic acid (BCA)	0.0091
Haloacetonitriles	Dichloroacertonitrile (DCAN)	0.0020
(HANs)	Trichloroacetonitrile (TCAN)	0.00014
	Bromochloroacetonitrile (BCAN)	0.0011
	Dibromoacertonitrile (DBAN)	0.00081
Miscellaneous	Bromate	0.0074

3.5.4 Estimated Concentrations in Consumed Tap Water

This section presents the development of reasonable representations of the chemical concentrations in consumed tap water for the 15 chemicals identified in Table 1. The volatilization of contaminant occurs during the filling activity, from the water surface while sitting in a glass or storage and as a result of any processing action. Each of these is analyzed below, and a combined volatilization is calculated for a number of scenarios. The results of this calculation are used to recommend estimated fractional volatilization and first order removal rate constants for each chemical.

3.5.4.1 Volatilization During Filling

Volatilization during a filling activity occurs in much the same way as during any other faucet use. There are differences in the volatilization occurring in the pool of water in a partially filled glass of water and the film of water in the bottom of a sink.

The experiments from Howard and Corsi (1996) as well as those performed by Batterman et. al. (2000) attempt to quantify this volatilization. Batterman et. al. implement an experiment meant to represent an "experimental procedure portray(ing) the filling of a pitcher from the tap and then the filling of a glass from the pitcher." The authors describe the procedure as follows: "The THM stock solution (2 mg/mL of each THM) was diluted in a filled 4 L black bottle to obtain the test mixture containing 100 μg/L of each THM compound and then transferred to a typical covered water pitcher (Rubbermaid, capacity = 2.34 L, filled to 1.96 L, height = 21.7 cm, dia = 12.2 cm, material = resin) and used to fill glasses and mugs." According to the authors, the "water transfers were done quickly (3 – 5 seconds) and at a minimal (2 cm) pouring height."

Unfortunately, neither the quick filling nor the filling height is typical of filling a glass of water for consumption. Filling 1.96 L in 3 to 5 seconds yields a flowrate in the range of 23.5 to 39.2 L/min. A typical faucet has a possible flowrate ranging from 0 (user controlled) to approximately 11 L/min, with a typical faucet use being in the range of about 2 – 8 L/min (Wilkes, 2002a). The large flowrate used by Batterman et. al. would significantly lower the opportunity for volatilization. Although no behavioral studies have been identified that quantify the distance the water must travel, it seems likely from personal experience that 2 cm would represent a reasonable minimum, and a reasonable maximum is probably on the order of 12 – 15 cm. The combination of the large flowrate and low height of the filling in the Batterman et. al. experiment has the effect of significantly lowering volatilization, and therefore this research is not useful in estimating the volatilization during filling.

Howard and Corsi (1996) conducted experiments measuring the volatilization resulting from using the kitchen faucet. The most consequential differences between the Howard and Corsi experiments and the filling of a glass or pitcher for consumption are the larger height of the drop and the potential splashing that could occur when the water lands in the sink. Both of these differences lead to a higher volatilization rate. Howard and Corsi measured the fractional volatilization for 3 compounds: cyclohexane, toluene, and acetone. The chemical properties impacting the volatilization rate for the three compounds measured by Howard and Corsi are given in Table 36. The chemical properties impacting volatilization for the compounds being modeled are given in Table 37. Table 38 summarizes the stripping efficiency measured by Howard and Corsi for the 3 compounds. Based on the low Henry's Law Constants, no significant volitilization is likely to occur for the non-THM DBPs. Therefore, the analysis of volatilization prior to consumption presented in the following sections, is limited to the THMs.

Table 36. Chemical Properties of Compounds Studied by Howard and Corsi (24° C)

Chemical	H (unitless)	D_l (cm^2/sec)[a]	D_g (cm^2/sec)[b]
Cyclohexane	7.1	9.0 E –6	0.088
Toluene	0.27	9.1 E –6	0.085
Acetone	0.0012	1.1 E –5	0.11

a. D_l is estimated using the Hayduk and Laudie method (Lyman etal, 1990, pp 17-20)
b. Dg is estimated using the Wilke and Lee method (Lyman etal, pp 17-13).

Table 37. Chemical properties of Compounds Being Modeled (24° C)

Chemical	H (unitless)	D_l (cm^2/sec)[a]	D_g (cm^2/sec)[b]
Chloroform	0.15	1.03 E –5	0.094
BDCM	0.088	1.01 E –5	0.089
DBCM	0.038	9.96 E –6	0.086
Bromoform	0.021	9.82 E –6	0.083
MCA	3.3 E-7	1.05 E –5	0.092
DCA	3.1 E-7	9.2 E –6	0.082
TCA	5 E-7	8.3 E –6	0.074
MBA	2.5 E-7	1.03 E –5	0.087
DBA	1.6 E-7	9.0 E –6	0.077
BCA	1.3 E-6	9.1 E –6	0.078
DCAN	1.6 E-4	9.9 E –6	0.090
TCAN	5.5 E-5	8.8 E –6	0.083
BCAN	5.3 E-4	8.8 E –6	??
Dibromoacetonitrile	1.7 E-5	9.6 E –6	0.082

a. D_l is estimated using the Hayduk and Laudie method (Lyman et. al., 1990, pp 17-20)
b. Dg is estimated using the Wilke and Lee method (Lyman et. al., pp 17-13).

Table 38. Summary of Experimental Stripping Efficiencies for Cyclohexane, Toluene , and Acetone

Flowrate	Aerator	Stripping Efficiency (%) [a]		
		Cyclohexane	Toluene	Acetone
4.8	None	24	21	4.9
7.9	None	19	17	2.2
4.8	Screen	19	13	1.7
7.9	Screen	18	14	1.1
4.8	Bubble Aerator	33	23	1.4
6.3	Bubble Aerator	35	22	1.5
7.9	Bubble Aerator	44	23	1.6

a. Measured by Howard and Corsi for Kitchen Sink Experiments; water temperature approximately 23° C.

3.5.4.2 Volatilization During Storage

After preparation and prior to consumption, the water may sit in a pitcher in the refrigerator or in a glass or cup on the table. During this period, volatilization occurs at the liquid/air interface. Batterman et. al. studied the rate at which this occurred for the four trihalomethanes at a variety

of temperatures (4, 25, 30, and 100 degrees C) and in two containers (tall glass, wide mouth glass) for a two hour period. Batterman et. al. fit the resulting measurements to an exponential decay model with good results (R^2 values for chloroform ranged from 0.59 to 0.86). Table 39 summarizes these results. The recommended fractions volatilized as a function of time are summarized in Table 40 for three conditions (cold water, room temperature water, and hot water).

Table 39. Estimated Rate Constants from Batterman et. al.

Condition	Chloroform		BDCM		DBCM		Bromoform	
	k (h^{-1})	R^2	k (h^{-1})	R^2	k (h^{-1})	R^2	k (h^{-1})	R^2
Tall glass, full, water at 4 °C	0.088	0.77	0.076	0.78	0.080	0.75	0.080	0.84
Tall glass, full, water at 25 °C	0.055	0.63	0.046	0.53	0.047	0.47	0.044	0.33
Tall glass, half full, water at 25 °C	0.070	0.77	0.064	0.64	0.063	0.76	0.062	0.56
Wide mouth glass, full, water at 25 °C	0.180	0.59	0.110	0.30	0.108	0.61	0.140	0.71
Tall glass, full, water at 30 °C	0.183	0.69	0.135	0.65	0.142	0.74	0.158	0.85
Tall glass, half full, water at 30 °C	0.248	0.83	0.205	0.90	0.177	0.90	0.193	0.89
Wide mouth glass, full, water at 30 °C	0.411	0.62	0.427	0.80	0.392	0.82	0.332	0.76
Coffee mug, full, water at 100 °C	1.50	0.86	1.52	0.82	1.41	0.80	1.40	0.85

Table 40. Estimated Fractional Volatilization as a Function of Time for THMs for Cold, Room Temperature, and Hot Water

Condition	Chemical	Rate Const, k (h^{-1})	Fraction Volatilized														
			Time, minutes														
			0	5	10	15	30	60	75	90	105	120	180	240	360	420	480
Cold Water (4 C)	Chloroform	0.09	0	0.007	0.015	0.022	0.044	0.086	0.11	0.13	0.15	0.16	0.24	0.30	0.42	0.47	0.51
	BDCM	0.076	0	0.006	0.013	0.019	0.037	0.073	0.091	0.11	0.13	0.14	0.20	0.26	0.37	0.41	0.46
	DBCM	0.080	0	0.07	0.013	0.020	0.039	0.077	0.095	0.11	0.13	0.15	0.21	0.27	0.38	0.43	0.47
	Bromoform	0.080	0	0.07	0.013	0.020	0.039	0.077	0.095	0.11	0.13	0.15	0.21	0.27	0.38	0.43	0.47
Room Temp (25 C)	Chloroform	0.18	0	0.015	0.030	0.044	0.086	0.16	0.20	0.24	0.27	0.30	0.42	0.51	0.66	0.72	0.76
	BDCM	0.11	0	0.009	0.018	0.027	0.054	0.104	0.13	0.15	0.18	0.20	0.28	0.36	0.48	0.54	0.59
	DBCM	0.108	0	0.009	0.018	0.027	0.053	0.102	0.13	0.15	0.17	0.19	0.28	0.35	0.48	0.53	0.58
	Bromoform	0.14	0	0.012	0.023	0.034	0.068	0.13	0.16	0.19	0.22	0.24	0.34	0.43	0.57	0.62	0.67
Hot Water (100 C)	Chloroform	1.50	0	0.12	0.22	0.31	0.53	0.78	0.85	0.89	0.93	0.95	0.99	1.0	1.0	1.0	1.0
	BDCM	1.52	0	0.12	0.22	0.32	0.53	0.78	0.85	0.90	0.93	0.95	0.99	1.0	1.0	1.0	1.0
	DBCM	1.41	0	0.11	0.21	0.30	0.51	0.76	0.83	0.88	0.92	0.94	0.99	1.0	1.0	1.0	1.0
	Bromoform	1.40	0	0.11	0.21	0.30	0.50	0.75	0.83	0.88	0.91	0.94	0.99	1.0	1.0	1.0	1.0

3.5.4.3 Volatilization During Processing

A wide variety of activities influence the removal of compounds from tap water. These activities include primarily heating and mixing activities that occur when using the water to make coffee, tea, other water based beverages, and in the process of preparing food. Beverages made from tap water fall into 2 primary categories: heated and non heated beverages. The non heated beverages undoubtedly have some volatilization due to the process of mixing the water with any additives, such as orange juice from concentrate. These losses have not been quantified in the literature sources identified above. The heating of water greatly reduces the concentration of volatile constituents. Batterman et. al. report a average chloroform loss of 81% resulting from bringing

water to 100 °C (presumably from room temperature, although this is not stated) in a kettle. After pouring the water into a mug, the measured fraction volatilized is an average of 85%.

3.5.4.4 Recommendations

The volatilization during filling appears to be correlated with the chemicals Henry's Law constant, the liquid phase diffusivity, and the gas phase diffusivity. Table 41 presents a variety of consumption scenarios and estimated volatilization fraction as a result of each scenario for each of the THMs. Table 42 presents recommended values for model inputs for the THMs, DCA, and TCA. The model uses an initial fraction volatilized and a rate constant to estimate the amount of contaminant remaining at the time of consumption. The values presented in Table 42 for the fraction of the compound remaining prior to consumption or storage accounts for an estimate of the average amount volatilized as a result of filling a container with tap water. The rate constant is used by the model to estimate the volatilization during storage or while a glass of water is consumed over an extended period (e.g., used to represent the volatilization from a glass of water over a period like 30 minutes when someone slowly sips the water). Except for the THMs, the compounds presented in Table 37 have extremely low Henry's Law constants, and therefore the amount volatilized is expected to be negligible. For this reason, it is assumed that no volatilization occurs prior to consumption.

Table 41. THM Consumption Scenarios

Scenario	Chemical	Fraction Volatilized			
		Filling	Storage [a]	Processing	Total [b]
Glass of water, room temperature, immediate consumption (over 5 – 10 minutes)	Chloroform	0.12	0.013	0	0.13
	BDCM	0.075	0.008	0	0.08
	DBCM	0.044	0.008	0	0.05
	Bromoform	0.035	0.010	0	0.04
Glass of water, room temperature, consumption over 1 hour	Chloroform	0.12	0.084	0	0.19
	BDCM	0.075	0.053	0	0.12
	DBCM	0.044	0.052	0	0.09
	Bromoform	0.035	0.067	0	0.10
Glass of ice water, immediate consumption (over 5 – 10 minutes)	Chloroform	0.12	0.007	0	0.13
	BDCM	0.075	0.006	0	0.08
	DBCM	0.044	0.006	0	0.05
	Bromoform	0.035	0.006	0	0.04
Glass of ice water, consumption over 1 hour	Chloroform	0.12	0.044	0	0.16
	BDCM	0.075	0.037	0	0.11
	DBCM	0.044	0.039	0	0.08
	Bromoform	0.035	0.039	0	0.07
Hot beverage (e.g., coffee or tea), consumed immediately (over 5 – 10 minutes)	Chloroform	0.12	0.11	0.85 [g]	0.88
	BDCM	0.075	0.11	0.80 [g]	0.84
	DBCM	0.044	0.11	0.72 [g]	0.76
	Bromoform	0.035	0.11	0.63 [g]	0.68
Hot beverage (e.g., coffee or tea), consumed immediately (over 20 minutes)	Chloroform	0.12	0.23	0.85 [g]	0.90
	BDCM	0.075	0.23	0.80 [g]	0.86
	DBCM	0.044	0.22	0.72 [g]	0.79
	Bromoform	0.035	0.22	0.63 [g]	0.72
Prepared and stored beverages (e.g., pitcher of orange juice), prepared, stored cold (assume average = 4 hours), poured, consumed over 5-10 minutes	Chloroform	0.12 [c] 0.12 [d]	0.29 [e] 0.007 [f]	0	0.38
	BDCM	0.075 [c] 0.075 [d]	0.25 [e] 0.006 [f]	0	0.36
	DBCM	0.044 [c] 0.044 [d]	0.26 [e] 0.006 [f]	0	0.33
	Bromoform	0.035 [c] 0.035 [d]	0.26 [e] 0.006 [f]	0	0.32
Prepared and stored beverages (e.g., pitcher of orange juice), prepared, stored cold (assume average = 4 hours), poured, consumed over 30 minutes	Chloroform	0.12 [d] 0.12 [d]	0.29 [e] 0.02 [f]	0	0.39
	BDCM	0.075 [c] 0.075 [d]	0.25 [e] 0.02 [f]	0	0.37
	DBCM	0.044 [c] 0.044 [d]	0.25 [e] 0.02 [f]	0	0.33
	Bromoform	0.035 [c] 0.035 [d]	0.26 [e] 0.02 [f]	0	0.32

a. Calculated using weighted averages for the appropriate time categories, with fractional volatilization as given in Table 40;
b. Total is calculated in a consecutive manner by multiplying fraction remaining after each activity (i.e., for coffee, hot, consumed immediately; the initial concentration is reduced for filling by 18% to yield 82%, then the 82% is reduced by 85% because of heating to yield 12.3%, and finally the 12.3% is reduced by 23% to account for storage losses to yield 9%, or a fractional volatilization of .91);
c. Volatilization attributed to preparation;
d. Volatilization attributed to pouring from the pitcher into the glass;
e. Volatilization attributed to storage in the pitcher; f. Volatilization while in the glass; g. Taken from Batterman et. al.

Table 42. Recommended Consumption Model Inputs for the THMs, DCA, and TCA

Chemical	Average Fraction Remaining Prior to Storage or Consumption		Volatilization Rate Constant (h^{-1})	
	Direct	Indirect	Direct	Indirect
Chloroform	0.80	0.15	0.07	0.4
BDCM	0.90	0.2	0.06	0.4
DBCM	0.95	0.25	0.06	0.4
Bromoform	0.95	0.3	0.06	0.4
MCA	1	1	0	0
DCA	1	1	0	0
TCA	1	1	0	0
MBA	1	1	0	0
DBA	1	1	0	0
BCA	1	1	0	0
DCAN	1	1	0	0
TCAN	1	1	0	0
BCAN	1	1	0	0
Dibromoacetonitrile	1	1	0	0

3.6 Physiological Parameters

The ERDEM model requires sets of input parameters by chemical, by exposure, by compartment, by demographic group, and by activity.

3.6.1 Compartment Volumes by Demographic Group

The user chooses the compartments to be modeled in ERDEM based on the information available for the exposure chemical(s) and the metabolites. The compartments used for a metabolite may be a subset of those used for the parent chemical. The body volume is first chosen for each demographic group. The compartment volumes are then usually chosen as a percentage of the body volume. The normally suggested compartments are the Arterial Blood, Liver, Static Lung, Kidney, Fat, Slowly Perfused Tissue (muscle), Rapidly Perfused Tissue, Ovaries or Testes, and the Venous Blood. The volume percentages depend on the chosen compartments. Table 43 presents the values used for the PBPK modeling presented in this report.

Table 43. Volumes of Compartments by Percentage for PBPK Modeling with ERDEM

Parameter/Compartment	Male (Age 15 – 45)	Female (Age 15 – 45)	Child (Age 6)
Volume of the Body (L) [a]	77.6	63.8	22.5
Arterial Blood (%) (estimated)	3	3	3
Dermis (%) [b]	9	9	9
Fat (%) [c]	17	23	17
Kidney (%) [b]	0.4	0.4	0.4
Liver (%) [d]	2.6	2.6	2.6
Ovaries (%)	---	0.0063	---
Rapidly Perfused Tissue (%) [d]	4.6	4.6	4.6
Slowly Perfused Tissue (including Muscle) (%) [f]	55.95	49.99	55.99
Static Lung (%) [d]	1.4	1.4	1.4
Testes (%) [g]	0.046	---	0.0074
Venous Blood (%) (estimated)	6	6	6

a. Body volumes, calculated from the Exposure Factors Handbook, Tables 7.2 and 7.3 adjusted for weight of clothes.
b. Value from Corley, et al (1990)
c. Fat content based on measurements by Fisher, et al (1998).
d. Fisher, et al (1990).
e. The ovarian volume of 4g is presented for the adult woman (ages 15-45). This value is low for most women in our population group of 15-45. The value of 4g is consistent with the ovaries volume for a very young woman (approximately 15 years old), based on values reported in Publication 23 of the International Commission on Radiological Protection (ICRP, 1974). This value represents an approximate minimum value for the selected population group.
f. Value estimated from the Fat content using Fisher, et al (1998)
g. A value of 35.7g was used as the testes volume for the adult male (ages 15-45). This value is consistent with the mean value reported in ICRP-23 (1974) for a 20 to 30 year old male. A value of 1.67g was used as the testes volume for the male child (age ~6), the mean value reported by ICRP-23 (1974) for a male between the ages of 5 and 10.

In Table 43 above, a value of 4 grams is presented as the ovarian volume for the adult woman (ages 15-45). This value is low for most women in our population group of 15-45. The value of 4g is consistent with the ovaries volume for a very young woman (approximately 15 years old), based on values reported in Publication 23 of the International Commission on Radiological Protection (ICRP, 1974). This value represents an approximate minimum value for the selected population group. A value of 35.7g was used as the testes volume for the adult male (ages 15-45). This value is consistent with the mean value reported in ICRP-23 (1974) for a 20 to 30 year old male. A value of 1.67g was used as the testes volume for the male child (age ~6), the mean value reported by ICRP-23 (1974) for a male between the ages of 5 and 10.

3.6.2 Breathing Rates by Activity and Demographic Group

The breathing rates (alveolar ventilation rates, QA) based on the Exposure Factors Handbook, Table 5.6 (U.S. EPA, 1997b) are presented in Table 44 for an adult male and female (15 – 45 years old) and a child of approximately age six for two activity levels: resting and sedentary.

Table 44. Alveolar Ventilation Rates by Demographic Group and Activity

Activity Level	Alveolar Ventilation Rate (Liters/Hour)[a]		
	Male (Age 15 – 45)	Female (Age 15 – 45)	Child (Age 6)
Rest	540	430	410
Sedentary	600	480	435

a. From Exposure Factors Handbook, Table 5-6, U.S. EPA, 1997b

3.6.3 Compartment Blood Flows by Activity and Demographic Group

The Cardiac Output is chosen by activity for each demographic group. ERDEM can handle as many as nine activity scenarios. Usually only one is modeled. The compartment blood flows are usually chosen as a percentage of the Cardiac Output. The compartments requiring blood flow input are the Liver, Kidney, Fat, Dermis, Ovaries, Slowly Perfused Tissue (muscle), the Rapidly Perfused Tissue, and the Testes. The percentages depend on the chosen compartments. A proposed table of values is given in Table 45. The blood flows as a percentage of the Cardiac Output are the same for each of the two activities: resting and sedentary. In addition, the blood flows for the female were not adjusted from the male except for differences due to the Testes and Ovaries.

Table 45. Blood Flows to Compartments by Percentage for PBPK Modeling with ERDEM

Compartment	Blood Flows (Percentage of Cardiac Output) [c]					
	Male		Female		Child [a]	
	At Rest	Sedentary	At Rest	Sedentary	At Rest	Sedentary
Cardiac Output (L/hr)	461.34 [a]	512.60 [a]	423.55 [b]	472.8 [b]	350.28 [a]	371.64 [a]
Dermis (%)	4.8	4.8	4.8	4.8	4.8	4.8
Fat (%)	4.8	4.8	4.8	4.8	4.8	4.8
Kidney (%)	19.4	19.4	19.6	19.6	19.6	19.6
Liver (%)	23.7	23.7	24.0	24.0	24.0	24.0
Ovaries [d]	---	---	0.02	0.02		
Rapidly Perfused Tissue (%)	27.0	27.0	27.58	27.58	27.39	27.39
Slowly Perfused Tissue (including Muscle) (%)	19.0	19.0	19.2	19.2	19.2	19.2
Testes [d]	1.3	1.3	---	---	0.21	0.21

a. The ratio of male Cardiac Output to Alveolar Ventilation Rate was 0.85434 in Fisher, et al, (1998). This is used here to estimate male Cardiac Output.

b. The ratio of female Cardiac Output to Alveolar Ventilation Rate was 0.985 in Fisher, et al, (1998). This is used here to estimate the female Cardiac Output.

c. The blood flow percentages for the male are from Fisher, et al, (1998). The female was not modified except for the changes due to the Ovaries and Testes.

d. The blood flow for the Ovaries and Testes was determined from their volume relative to body weight.

3.6.4 Definition of the Exposure Scenarios for Each Exposure Route

The ERDEM simulations for exposure modeling will use time histories output from the TEM model. There will be dermal, inhalation, and ingestion time histories. In addition, there will be

an activity time history that supplies the alveolar ventilation rate as a function of time. The same blood flow percentages are used for each activity at this time. There may be up to nine different values for alveolar ventilation rate supplied. This method of inputs from TEM to ERDEM is in current use and has been completely tested.

3.6.5 Skin Permeability Coefficients for Each Chemical

The skin permeation coefficient, called the Permeability Coefficient of Stratum Corneum, Kp, is required for each chemical to be modeled. Kp values were calculated bases on biological and physiochemical characteristics of the skin and the chemicals, respectively. Computations were based on the method published by Poulin and Krishnana (2001), in which the value for the partition coefficient of the chemical for lipid is combined with the fractional lipid and water composition of human skin. For each of the 15 chemicals of interest, the Kp values used for TEM and ERDEM are given in Table 46. Separate values were calculated based on the range of lipid and water contents for human skin, accounting for the of Kp values demonstrated.

Table 46. Skin Permeability Coefficients

Chemical Name	Kp (cm/hr) (measured)	Kp (cm/hr) (Krishnan, 2001)	Kp [a] (cm/hr) (other predictions)	Kp [b] (cm/hr) (est. possible range)	Kp [c] Value Used as Model Input (cm/hr)
Chloroform	*0.13*	*0.0156 – 0.0393*	---	*0.015 – 0.15*	*0.13*
BDCM	---	0.0184 – 0.0478	---	0.018 – 0.18	0.0331
DBCM	---	0.0215 – 0.0577	---	0.021 – 0.22	0.0396
Bromoform	---	0.0247 – 0.0681	---	0.024 – 0.25	0.0464
MCA	---	0.0034 – 0.0040	---	1.8 E-6 – 0.01	0.0037
DCA	---	0.0036 – 0.0041	1.84E-6	1.8 E-6 – 0.01	1.84E-6
TCA	---	0.0062 – 0.0081	3.58E-6	3.5 E-6 – 0.01	3.58E-6
MBA	---	0.0036 – 0.0041	---	1 E-6 – 0.01	0.00385
DBA	---	0.0039 – 0.0046	---	1.0 E-6 – 0.01	0.00425
BCA	---	0.0037 – 0.0044	---	1.0 E-6 – 0.01	0.00405
DCAN	---	0.0029 – 0.0033	---	1.0 E-6 – 0.01	0.0031
TCAN	---	0.0051 – 0.0064	---	1.0 E-6 – 0.01	0.00575
BCAN	---	0.0031 – 0.0036	---	1.0 E-6 – 0.01	0.00335
DBAN	---	0.0033 – 0.0038	---	1.0 E-6 – 0.01	0.00355
Bromate	---	0.0049 – 0.0058	---	1.0 E-6 – 0.01	0.00535

a. Personal communications with James McDougal, 1999
b. Range of possible Kp values estimated based on predictions and on measured/predicted values for other compounds in the same class. For classes other than the THMs, no measurements have been identified, so the range itself is somewhat uncertain.
c. The midpoint of the estimate range by Krishnan was used unless alternative information was available.

3.6.6 Rate Constants for the Gastro-Intestinal Model for Each Chemical

There are two models for the gastro-intestinal (GI) tract. Normally a Stomach/Intestine model is used that requires absorption rate constants for the transport of chemical from the stomach to the intestine, stomach to portal blood, and intestine to portal blood. Often only the stomach to portal blood parameter is supplied. A second model, called the Full GI model may be used if bile flow

or chylomicron flow need to be modeled. The latter model would require blood flows for the GI compartment walls and food flow for the lumen (Stomach, Duodenum, Lower Small Intestine, and the Colon). One can use a subset of these compartments. The rate constants are, in general, different for each chemical. The four chemicals presented in Table 47 are the chemicals being evaluated by the PBPK model, ERDEM.

Table 47. Gastro-Intestinal Permeation Rate Constants.

	Chloroform	BDCM	DCA	TCA
Stomach to Portal Blood Rate Constant	5.0[a]	13.65[b]	13.65[b]	13.65[b]
Stomach to Intestine Rate Constant	2.0[a]	0.044[b]	0.044[b]	0.044[b]
Intestine to Portal Blood Rate Constant	6.0[a]	2.18[b]	2.18[b]	2.18[b]

a. Values used by Blancato, 2001 for $CHCL_3$ modeling

b. Values from Abbas and Fisher,1997 and modified based on Staats et.al., 1990

3.6.7 Partition Coefficients for Each Chemical

The partition coefficients between the skin and blood and between the blood and air are required for the fundamental uptake modeling in TEM. Partition coefficients for each physiological compartment are given in Table 48 for the 15 DBPs of interest.

Table 48. Partition Coefficients Required for Fundamental Uptake Modeling in TEM

Chemical Name	Skin/Blood [e]	Blood/Air [e]
Chloroform	1.62 [a]	7.43 [a]
BDCM	2.0 [b]	6.11 [b]
DBCM	3.82	10.26
Bromoform	5.51	25.89
MCA	0.96	46845.95
DCA	0.43 [c]	22995.65
TCA	0.52 [d]	387756.34
MBA	0.96	163836.96
DBA	0.97	1514909.77
BCA	0.97	349330.57
DCAN	0.96	4110.45
TCAN	1.02	8467.35
BCAN	0.96	18035.71
DBAN	0.96	31960.96
Bromate	0.97	0.5

a. Estimates for $CHCl_3$ from Corley et.al., 1990

b. Estimates from Krishnan, 2001 and Lipscomb, 2001

c. Estimates for DCA and TCA from Fisher et.al., 1998

d. These values were estimated. Compartments were not used by Fisher et.al., 1998 for TCA modeling.

e. All other estimates from personal communication with John Lipscomb, 2001

The partition coefficients for each physiological compartment in relation to the blood is presented in Table 49 for each of the four chemicals that are modeled by ERDEM.

Table 49. Partition Coefficients Used by ERDEM

Compartmental Relationship to Venous Blood	Chloroform[a]	BDCM[b]	DCA[c]	TCA[c]
Dermis/Blood	1.62	2.0 [e]	0.43 [f]	0.52 [f]
Fat/Blood	37.69	16.75	2.8 [f]	0.5 [f]
Kidney/Blood	1.48	1.05	0.8	0.66
Liver/Blood	2.29	0.975	0.8	0.66
Ovaries/Blood [d]	1.37	1.45	0.95	0.98
Rapidly Perfused Tissue/Blood	2.29	0.975	0.8 [f]	0.66 [f]
Slowly Perfused Tissue/Blood	1.62	0.395	0.43	0.52
Static Lung/Air	7.43	6.11	NA	NA
Static Lung/Blood	1.0	1.0 (Est)	0.16	0.47
Testes/Blood [d]	1.89	2.06	0.99	1.04

a. Estimates for $CHCl_3$ from Corley et.al.
b. Estimates for BDCM from Gargas et.al., 1989
c. Estimates for DCA and TCA from Fisher et.al., 1998
d. Ovaries/Blood and Testes/Blood estimates determined by Krishnan, 2001, and Lipscomb, 2001
e. Estimates from Krishnan, 2001, and Lipscomb, 2001
f. These values were estimated. Fisher, et al, 1998 did not use these Compartments for TCA and DCA modeling.

3.6.8 Metabolism Pathways and Rate Constants

There may be many different pathways hypothesized for a given chemical. A particular metabolism definition must be chosen for each chemical for modeling purposes. The metabolism processes are defined by rate constants if the metabolism is linear, or V-Max and Km (Michaelis-Menten constant) if the metabolism is saturable. In addition, there may be additional parameters required if the metabolism is inhibited by another chemical. Usually the metabolism is modeled in the Liver compartment but it may be important to model metabolism in other compartments such as the Kidney or Static Lung compartments. Chloroform is modeled as metabolizing in the liver and kidney to Phosgene (CG) and Carbon Dioxide (CO_2). The metabolism rate constants for the four chemicals modeled by ERDEM are presented in Table 50.

Table 50. Metabolism Rate Constants

Variable	Chloroform	BDCM [d]	DCA	TCA
Liver Linear Metabolism Rate Constant (/hr/kg)	Metab to CO_2: [a] 0.39917	--	--	--
Kidney Linear Metabolism Rate Constant (/hr/kg)	Metab. to CO_2: [a] 0.001857	--	--	--
Liver Metabolism Vmax (mg/hr/kg)	Metab. to CG: [a,b] 15.7	12.8 [d]	--	--
Kidney Metabolism Ratio of Kidney to Liver Vmax (mg/hr/kg)	Metab. to CG: [a,b] 0.033	--	--	--
Liver Metabolism Michaelis-Mentin Constant (mg/Liter)	0.448 [c]	0.5 [d]	--	--
Kidney Metabolism Michaelis-Mentin Constant (mg/Liter)	0.448 [c]	--	--	--

a. Dr. Jerry Blancato, personal communication.
b. Phosgene.
c. Corley, et al , (1990).
d. John Lipscomb, personal communication.

3.6.9 Elimination Parameters

Many chemicals will have measurable elimination in the kidney and a few from the feces. Often an elimination process is defined by chemical for other compartments when a reaction occurs that does not result in a chemical that must be modeled further (such as a metabolite that stays in the current compartment and is of no further interest). The elimination is usually linear but it can also be of the saturable form. The elimination rate constants for the four chemicals modeled by ERDEM are presented in Table 51.

Table 51. Elimination Rate Constants

Variable	Chloroform	BDCM	DCA	TCA
Urine Elimination Rate Constant (/hr/kg)	--	--	0.023 [a]	2.169 [b]
Liver Elimination Rate Constant (/hr/kg)	--	--	20.5 [c]	0.5785 [d]

a. Clewell, et al (1997)
b. Estimated from urine measurement data from Fisher, et al, (1998)
c. Estimated from mouse data of Abbas and Fisher, (1997)
d. Power, personal communication, from TCA PBPK model results fitted to data from Fisher, et all, (1998). (to be reported)

3.7 Uptake Calculations

The dermal uptake calculation implemented in TEM is based on membrane equations developed by Cleek and Bunge (Olin, 1999). This representation uses two simple functions, representing the non-steady-state and steady-state periods. The dermal uptake does not account for issues such as skin hydration and skin temperature.

The ingestion uptake calculation implemented in TEM is based on the estimated water concentrations at the time the water is consumed, and assumes that the entire mass of the chemical in the consumed water is absorbed into the bloodstream.

The inhalation uptake calculation implemented in TEM is based on the predicted air concentrations in the breathing zone. TEM implements an equilibrium calculation between the inhaled air and the bloodstream. This calculation is described in Wilkes, 1999.

4.0 Modeling Results

4.1 Model Execution

The Total Exposure Model, TEM, was set up as described in the above sections. Table 52 presents a summary of the chemical specific model parameters, Table 53 presents a summary of the behavioral model inputs, and Table 54 presents a summary of the building related parameters. The model is initiated with the inputs described in these tables, identifying the structure of the household, the characteristics and locations of the water appliances, and the population groups for the three-person household. For each simulation, activity patterns are sampled from the NHAPS for the three defined population groups, the activities are mapped into the household, and the appropriate water uses are simulated consistent with the activity patterns, as described in Section 2.1. The model is executed for 1000 simulations.

Subsequent to executing the exposure model, the results were interfaced with the PBPK model, ERDEM. This was accomplished by creating a series of transfer files containing information on breathing zone concentrations, respiratory rates, skin contact concentrations, skin contact area, ingestion concentrations and quantities as a function of time for each of the simulations. These results are input into ERDEM for 250 of the simulations to predict blood and organ concentrations.

The results of the exposure modeling study are presented in Section 4.2, and the results of the PBPK modeling study are presented in Section 4.3.

4.2 Exposure and Uptake Modeling Results

The exposure model, TEM, was initiated as described in earlier sections, and executed. The results are in several forms:

1) An MS-Access database containing the results of:
   - Each sampled parameter (eg., building volumes, building interzonal, etc.).
   - Sampled activity pattern
   - Simulated activities (eg., water uses simulated within each sampled activity pattern, ingestion behavior, etc.)
   - Predicted air and water concentrations
   - Predicted exposure and potential dose
   - Predicted absorbed dose.

2) Transfer files to be used as input to the PBPK model (ERDEM)

These results are analyzed and presented in the following sections.

Table 52. *Summary of Chemical Specific Model Parameters*

Parameter	Chloroform	BDCM	DBCM	Bromoform	MCA	DCA	TCA	MBA	DBA	BCA	DCAN	TCAN	DBAN
Henry's Law @ 25 ° C	0.153	0.0929	0.0397	0.0227	3.7E-7	3.4E-7	5.5E-7	2.7E-7	1.8E-7	1.31E-6	1.55E-4	5.4E-7	1.66E-5
Henry's Law @ 30 ° C	0.195	0.119	0.0512	0.030	6.2E-7	5.2E-7	8.8E-7	4.5E-7	2.9E-7	--[c]	--[c]	--[c]	--[c]
Henry's Law @ 35 ° C	0.238	0.150	0.0654	0.0393	1.0E-6	7.9E-7	1.4E-6	7.3E-7	4.5E-7	--[c]	--[c]	--[c]	--[c]
Henry's Law @ 40 ° C	0.287	0.188	0.0830	0.0511	1.9E-6	1.2E-6	2.1E-6	1.2E-6	7.1E-7	--[c]	--[c]	--[c]	--[c]
$K_{OL}A$ Shower (m^3/h)	0.432	0.428	0.415	0.402	4.49E-4	4.37E-4	4.53E-4	4.41E-4	4.28E-4	4.39E-4	0.00381	0.00143	7.24E-4
$K_{OL}A$ Bath, Fill (m^3/h)	0.243	0.228	0.186	0.153	1.05E-5	7.42E-6	1.22E-5	1.33E-5	4.12E-6	1.20E-5	0.00290	5.18E-4	1.57E-4
$K_{OL}A$ Bath, Pool (m^3/h)	0.078	0.0735	0.0625	0.0531	4.64E-6	3.27E-6	5.39E-6	3.56E-6	1.81E-6	5.28E-6	7.71E-4	2.28E-4	6.90E-5
$K_{OL}A$ Clothes Washer, Fill (m^3/h)	0.317	0.265	0.174	0.124	5.24E-6	3.69E-6	6.08E-6	3.54E-6	2.05E-6	5.97E-6	7.73E-4	2.59E-4	7.81E-5
$K_{OL}A$ Clothes Washer, Wash (m^3/h)	0.113	0.0637	0.0293	0.0177	5.21E-7	3.67E-7	6.05E-7	2.69E-7	2.04E-7	5.94E-7	8.95E-5	2.58E-5	7.78E-6
$K_{OL}A$ Clothes Washer, Rinse (m^3/h)	0.403	0.265	0.122	0.0735	2.16E-6	1.52E-6	2.51E-6	1.14E-6	8.46E-7	2.46E-6	2.51E-4	1.07E-4	3.23E-5
$K_{OL}A$ Toilet (m^3/h)	0.00468	0.00368	0.00312	0.00265	2.32E-7	1.63E-7	2.69E-7	1.78E-7	9.06E-8	2.64E-7	3.26E-5	1.14E-5	3.45E-6
$K_{OL}A$ Faucets @ 35 ° C (m^3/h)	0.128	0.116	0.0913	0.0731	5.07E-6	3.58E-6	5.89E-6	4.26E-6	1.99E-6	5.78E-6	9.28E-4	2.50E-4	7.58E-5
$K_{OL}A$ Faucets @ 30 ° C (m^3/h)	0.117	0.104	0.0792	0.0613	3.01E-6	2.32E-6	3.68E-6	2.58E-6	1.23E-6	5.67E-6	9.08E-4	2.44E-4	7.41E-4
Blood/Air Partition Coeff.	0.135	0.164	0.0975	0.0386	2.13E-5	4.35E-5	2.59E-6	6.1E-6	6.6E-7	2.86E-6	2.43E-4	1.18E-4	3.13E-5
Skin Permeability Coeff., K_p (cm/h)	0.13	0.0330	0.0396	0.0464	0.00370	1.84E-6	3.58E-6	0.00385	0.00425	0.00405	0.00310	0.00575	0.00355
Skin/Blood Partition Coefficient	1.62	2.0	3.82	5.51	0.96	0.43	0.52	0.96	0.97	0.97	0.96	1.02	0.96
Ingestion Direct: Initial Fraction Volatilized [a]	0.80	0.9	0.95	0.95	1	1	1	1	1	1	1	1	1
Ingestion Indirect: Initial Fraction Volatilized [a]	0.15	0.2	0.25	0.3	1	1	1	1	1	1	1	1	1
Ingestion Direct: Rate Const. for Volatilization [b]	0.07	0.06	0.06	0.06	0	0	0	0	0	0	0	0	0
Ingestion Indirect: Rate Const. for Volatilization [b]	0.4	0.1	0.4	0.4	0	0	0	0	0	0	0	0	0

NOTES: BCAN and Bromate were not modeled because of a lack of chemical parameters. a. The initial fraction volatilized is the assumed amount volatilized during the filling activity; b. The rate constant for volatilization is the rate at which the chemical is assumed to volatilize during storage; c. These values are not available, therefore the values for H at 25 ° C are used. .

Table 53. Summary of Water-Use Behavioral Model Inputs

Water Use	Water Temperature (° C)	Frequency (events per person per day)	Duration		Flowrate (gpm)	Volume (gal)	Fill Duration (min)	Cycle Duration (min)
			Geometric Mean (min)	Geometric Std Dev				
Female, Ages 15-45								
Shower	40	1.12	???	???	2.40	NA	NA	NA
Bath	35	0.38	???	???	NA	50	8	NA
Toilet	25	6	NA	NA	NA	3.5	NA	NA
Faucet - Kitchen	35	6.1	???	???	1.2	NA	NA	NA
Faucet - Bathroom	35	6.1	???	???	1.2	NA	NA	NA
Faucet - Laundry	30	3.4	???	???	1.2	NA	NA	NA
Male, Ages 15-45								
Shower	40	1.24	???	???	2.40	NA	NA	
Bath	35	0.21	???	???	NA	50	8	
Toilet	25	6	NA	NA	NA	3.5	NA	NA
Faucet - Kitchen	35	6.1	???	???	1.2	NA	NA	NA
Faucet - Bathroom	35	6.1	???	???	1.2	NA	NA	NA
Faucet - Laundry	30	3.4	???	???	1.2	NA	NA	NA
Child, Age 6								
Shower	40	0.55	???	???	2.40	NA	NA	NA
Bath	35	0.48	???	???	NA	50	8	NA
Toilet	25	6	NA	NA	NA	3.5	NA	NA
Faucet - Kitchen	35	6.1	???	???	1.2	NA	NA	NA
Faucet - Bathroom	35	6.1	???	???	1.2	NA	NA	NA
Faucet - Laundry	30	3.4	???	???	1.2	NA	NA	NA
Household Water Uses								
Clothes Washer	35	0.99 events per 3 person household per day	NA	NA		16.6 (Wash) 21.0 (Rinse)	3.3 (Wash) 4.2 (Rinse)	7.4 (Wash) 9.8 (Rinse)
Dishwasher	35	0.54 events per 3 person household per day	NA	NA	NA	4.25 (Wash) 4.25 (Rinse)	NA	30 (Wash) 30 (Rinse)

Table 54. Summary of Building Related Model Inputs

Parameter	Representation
Whole House Volume	Lognormal, Geometric Mean = 316.7 m^3; Geometric Standard Deviation = 0.4218
Laundry Room Volume	Uniform Distribution, Minimum = 13.5 m^3; Maximum = 25.4 m^3
Kitchen Room Volume	Uniform Distribution, Minimum = 15.4 m^3; Maximum = 18.1 m^3
Hall Bath Room Volume	Uniform Distribution, Minimum = 7.9 m^3; Maximum = 14.9 m^3
Master Bath Room Volume	Uniform Distribution, Minimum = 4.9 m^3; Maximum = 8.5 m^3
Shower Room Volume	Uniform Distribution, Minimum = 2.9 m^3; Maximum = 4.5 m^3
Rest of House (ROH) Volume	Whole House Volume - ΣWater Using Zone Volumes
Whole House ACH (h^{-1})	Lognormal, Geometric Mean = 0.46 h^{-1}; Geometric Standard Deviation = 2.25
ROH Airflow	Whole House ACH * Whole House Volume
ROH to Laundry Airflow	0.078 +0.31 * Whole House ACH
ROH to Kitchen Airflow	0.078 +0.31 * Whole House ACH
ROH to Hall Bath Airflow	0.078 +0.31 * Whole House ACH
ROH to Master Bath Airflow	0.078 +0.31 * Whole House ACH
Bath to Shower Airflow	0.078 +0.31 * Whole House ACH

4.2.1 Analysis of Results of Water Use Behavior

The water-use parameters presented in Section 3.2 are entered as model inputs to the exposure model. Under ideal conditions, the model would simulate water uses with characteristics essentially identical to these parameters. However, shortcomings or inconsistencies between these specified water use characteristics and the behavioral characteristics recorded in the activity patterns result in the inability to simulate all the desired water uses. For example, many activity pattern records report virtually no bathroom visits, and many others never report entering the kitchen.

TEM adjusts for activity patterns that have no opportunity for a particular water use to occur by calculating a "conditional" frequency. The conditional frequency is calculated by pre-processing the sampled activity patterns to determine the number that have an opportunity for each water use to occur, and then adjusting the desired frequency to account for the records that do not have eligible locations and activities. However, in many records, an opportunity exists, but the duration is very brief, which also results in a lower simulated frequency, and duration of water use.

4.2.2 Uptake Modeling Results

The simulation results for absorbed dose are analyzed for each chemical as a function of route (dermal, ingestion, and inhalation) and presented in the following sections. For each chemical, a table containing the absorbed does is presented as a function of route, population group, and percentile of the population. The route-specific and total absorbed dose given for various percentiles of the population, are calculated for the specific route, and therefore, for a given percentile, the member of the population is likely to be different for each route (e.g., the person who has the 50th percentile absorbed dose by the inhalation route is not the same person as has the

50th percentile dermal absorbed dose). For each chemical, the cumulative distribution function for absorbed dose is plotted along with histograms of the route specific absorbed dose.

4.2.2.1 Uptake Results for Chloroform

The following Table 55 presents the resultant absorbed dose of chloroform from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 6 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of chloroform and Figures 7, 8, and 9 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 10 presents the total absorbed chloroform dose.

Table 55. Chloroform Absorbed Dose Results

	Chloroform Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	1.95E-02	0[a]	2.79E-03	1.25E-03	6.04E-03	4.37E-04
5	4.02E-02	0[a]	4.95E-03	1.67E-03	8.75E-03	1.00E-02
10	6.40E-02	9.54E-04	6.64E-03	1.93E-03	1.05E-02	3.09E-02
25	1.42E-01	2.44E-03	1.13E-02	2.65E-03	1.54E-02	8.33E-02
50	3.00E-01	2.51E-02	2.09E-02	3.76E-03	2.52E-02	2.19E-01
75	6.04E-01	5.13E-02	4.09E-02	5.16E-03	4.47E-02	5.01E-01
90	1.03E+00	9.18E-02	7.45E-02	6.94E-03	7.86E-02	9.41E-01
95	1.52E+00	1.31E-01	9.46E-02	7.88E-03	9.95E-02	1.41E+00
99	8.56E+00	2.12E-01	2.30E-01	1.11E-02	2.32E-01	8.47E+00
Male, Age 15-45						
1	1.76E-02	0[a]	2.07E-03	6.07E-04	5.31E-03	3.75E-04
5	3.76E-02	0[a]	4.19E-03	1.10E-03	8.54E-03	9.69E-03
10	6.07E-02	0[a]	5.78E-03	1.42E-03	1.10E-02	2.16E-02
25	1.43E-01	2.04E-03	1.10E-02	2.26E-03	1.64E-02	6.70E-02
50	3.02E-01	2.62E-02	2.16E-02	4.00E-03	2.84E-02	2.13E-01
75	6.17E-01	5.40E-02	4.19E-02	7.29E-03	4.83E-02	5.20E-01
90	1.07E+00	8.92E-02	7.87E-02	1.22E-02	8.42E-02	9.69E-01
95	1.56E+00	1.18E-01	1.17E-01	1.75E-02	1.25E-01	1.52E+00
99	6.99E+00	2.02E-01	1.93E-01	2.88E-02	1.96E-01	6.88E+00
Child, Age 6						
1	8.96E-03	0[a]	1.26E-03	9.66E-05	1.97E-03	2.17E-04
5	1.86E-02	0[a]	2.34E-03	1.90E-04	3.39E-03	4.00E-03
10	3.07E-02	0[a]	3.15E-03	2.76E-04	4.36E-03	1.03E-02
25	6.70E-02	6.03E-04	5.60E-03	5.15E-04	7.11E-03	3.75E-02
50	1.56E-01	1.87E-03	1.09E-02	9.19E-04	1.26E-02	1.19E-01
75	3.40E-01	2.79E-02	2.08E-02	1.83E-03	2.24E-02	3.04E-01
90	6.55E-01	4.84E-02	3.56E-02	3.20E-03	3.70E-02	6.18E-01
95	8.63E-01	6.11E-02	4.73E-02	4.45E-03	4.80E-02	7.74E-01
99	1.32E+00	8.89E-02	8.78E-02	6.99E-03	9.01E-02	1.30E+00

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.

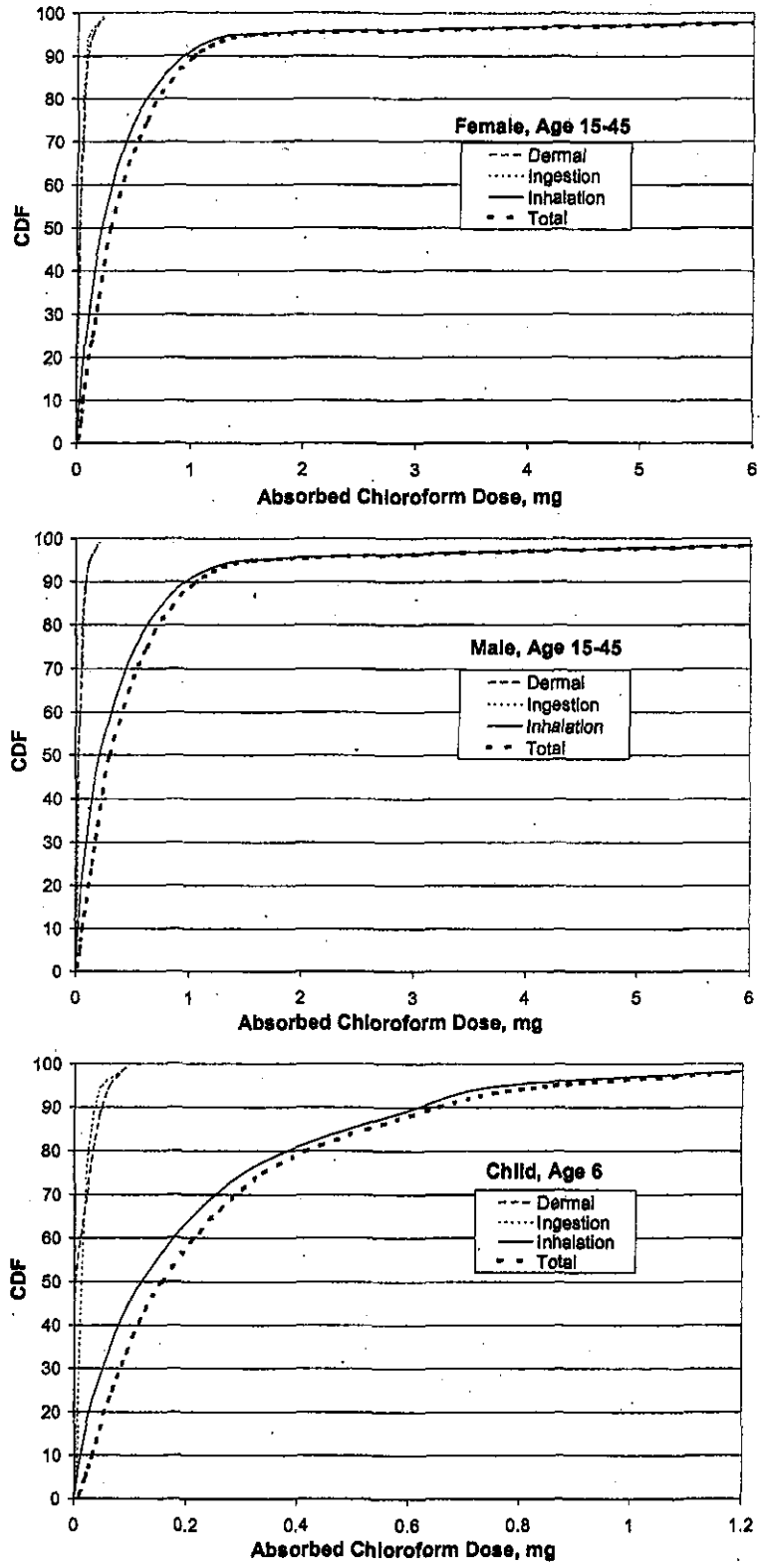


Figure 6. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed Chloroform Dose for Females, Males and Children.

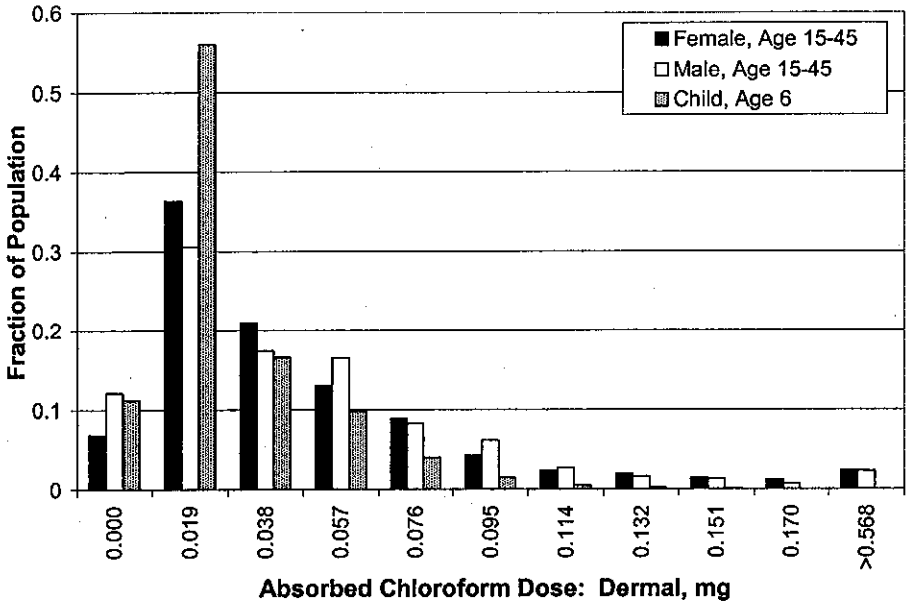


Figure 7. Histogram for Absorbed Dermal Chloroform Dose for Females, Males and Children.

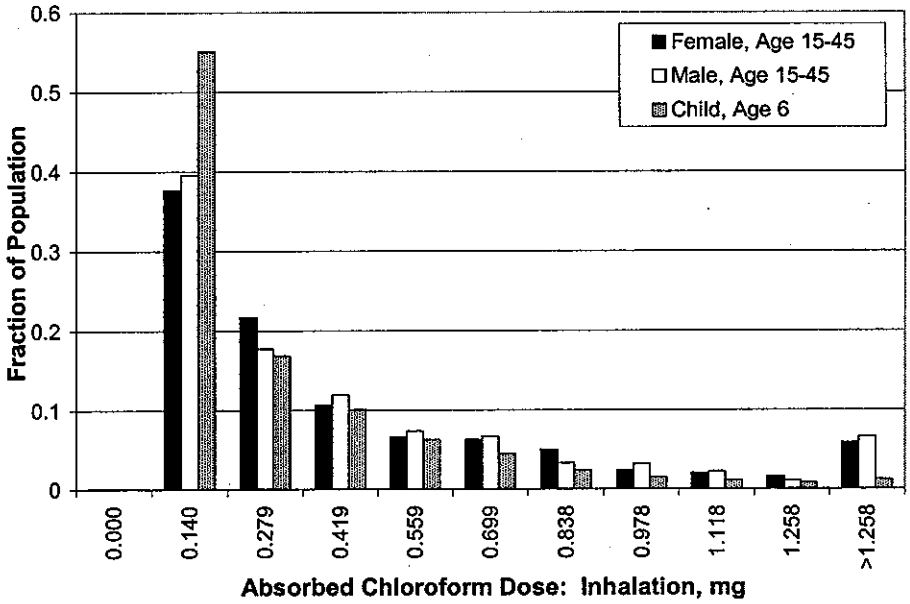


Figure 8. Histogram for Absorbed Inhalation Chloroform Dose for Females, Males and Children.

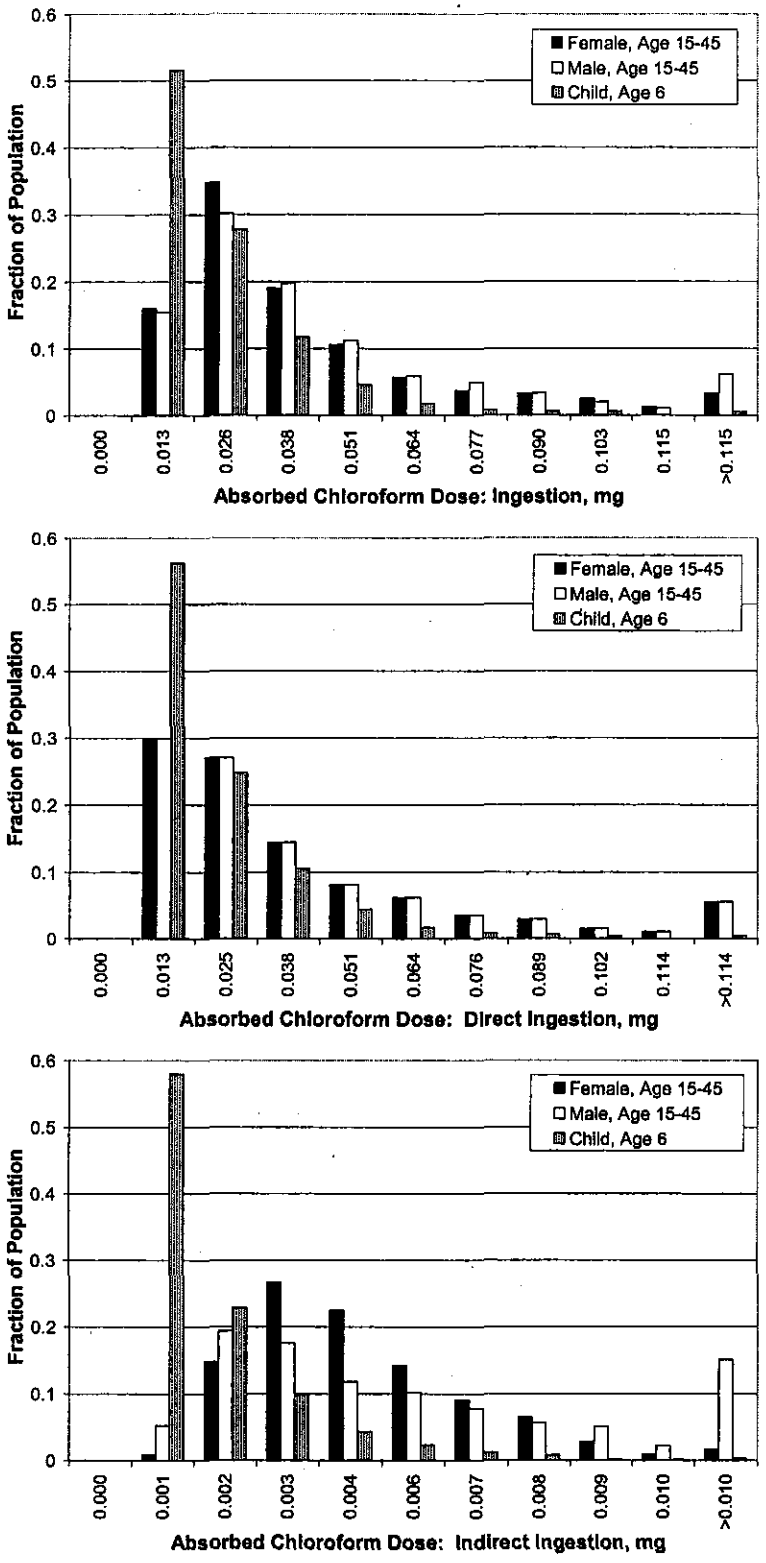


Figure 9. Histograms for the Absorbed Chloroform Ingestion Dose for Females, Males and Children.

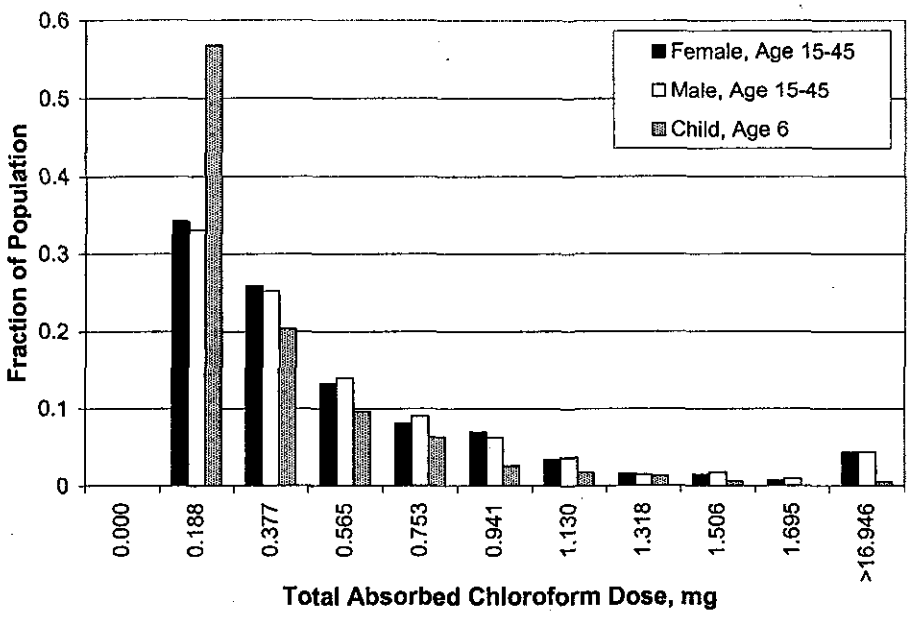


Figure 10. Histogram for the Total Absorbed Chloroform Dose for Females, Males and Children.

4.2.2.2 Uptake Results for BDCM

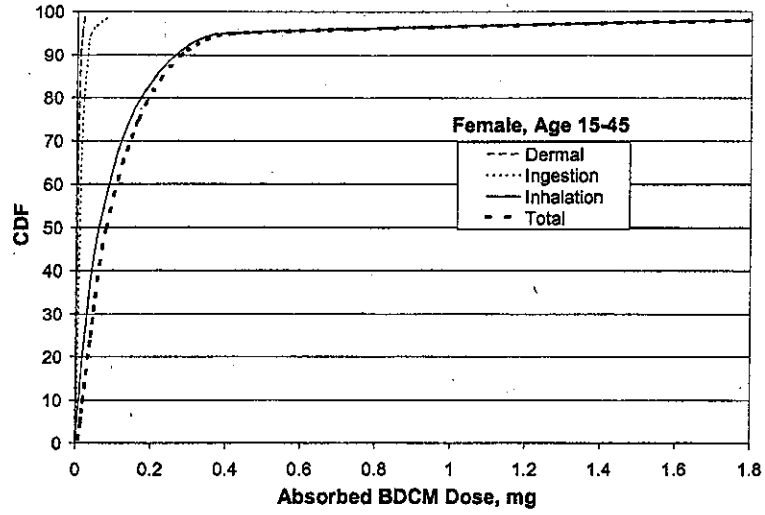
The following Table 56 presents the resultant absorbed dose of BDCM from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 11 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of BDCM and Figures 12, 13, and 14 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 15 presents the total absorbed BDCM dose.

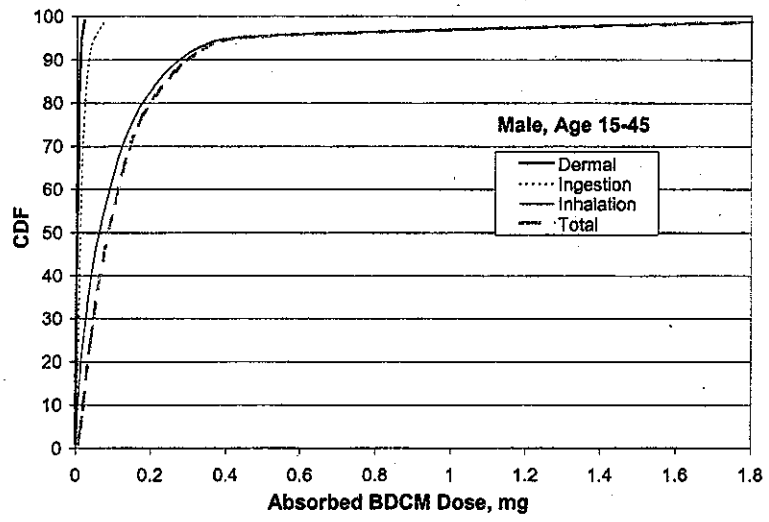
Table 56. BDCM Absorbed Dose Results

	BDCM Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	7.20E-03	0 [a]	1.03E-03	5.64E-04	2.49E-03	1.12E-04
5	1.35E-02	0 [a]	1.83E-03	7.64E-04	3.51E-03	2.66E-03
10	1.92E-02	1.54E-04	2.46E-03	8.86E-04	4.14E-03	8.78E-03
25	3.96E-02	3.71E-04	4.19E-03	1.23E-03	6.05E-03	2.35E-02
50	8.00E-02	2.70E-03	7.73E-03	1.71E-03	9.72E-03	6.12E-02
75	1.66E-01	5.21E-03	1.51E-02	2.37E-03	1.69E-02	1.42E-01
90	2.79E-01	8.67E-03	2.76E-02	3.18E-03	2.95E-02	2.64E-01
95	4.13E-01	1.21E-02	3.50E-02	3.61E-03	3.70E-02	3.88E-01
99	2.41E+00	1.87E-02	8.49E-02	5.05E-03	8.60E-02	2.38E+00
Male, Age 15-45						
1	6.25E-03	0 [a]	7.64E-04	2.79E-04	2.18E-03	1.01E-04
5	1.27E-02	0 [a]	1.55E-03	4.95E-04	3.42E-03	2.64E-03
10	1.97E-02	0 [a]	2.14E-03	6.49E-04	4.35E-03	6.07E-03
25	3.88E-02	3.09E-04	4.05E-03	1.05E-03	6.52E-03	1.89E-02
50	8.43E-02	2.90E-03	7.98E-03	1.85E-03	1.11E-02	6.05E-02
75	1.64E-01	5.57E-03	1.55E-02	3.37E-03	1.86E-02	1.46E-01
90	2.95E-01	8.73E-03	2.91E-02	5.67E-03	3.19E-02	2.74E-01
95	4.36E-01	1.13E-02	4.31E-02	7.93E-03	4.68E-02	4.23E-01
99	1.93E+00	1.84E-02	7.14E-02	1.31E-02	7.28E-02	1.91E+00
Child, Age 6						
1	3.51E-03	0 [a]	4.66E-04	1.13E-04	1.10E-03	5.71E-05
5	6.98E-03	0 [a]	8.66E-04	2.26E-04	1.73E-03	1.13E-03
10	1.00E-02	0 [a]	1.17E-03	3.28E-04	2.27E-03	2.98E-03
25	1.95E-02	9.26E-05	2.07E-03	6.03E-04	3.50E-03	1.07E-02
50	4.38E-02	2.66E-04	4.02E-03	1.07E-03	6.03E-03	3.36E-02
75	9.48E-02	2.67E-03	7.68E-03	2.17E-03	9.89E-03	8.56E-02
90	1.81E-01	4.48E-03	1.32E-02	3.80E-03	1.53E-02	1.73E-01
95	2.29E-01	5.63E-03	1.75E-02	5.37E-03	1.88E-02	2.19E-01
99	3.58E-01	8.03E-03	3.25E-02	8.16E-03	3.54E-02	3.51E-01

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.





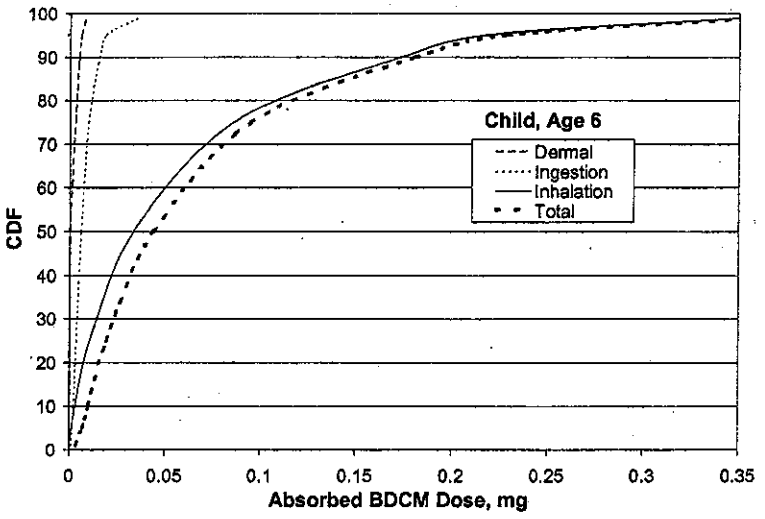


Figure 11. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed BDCM Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

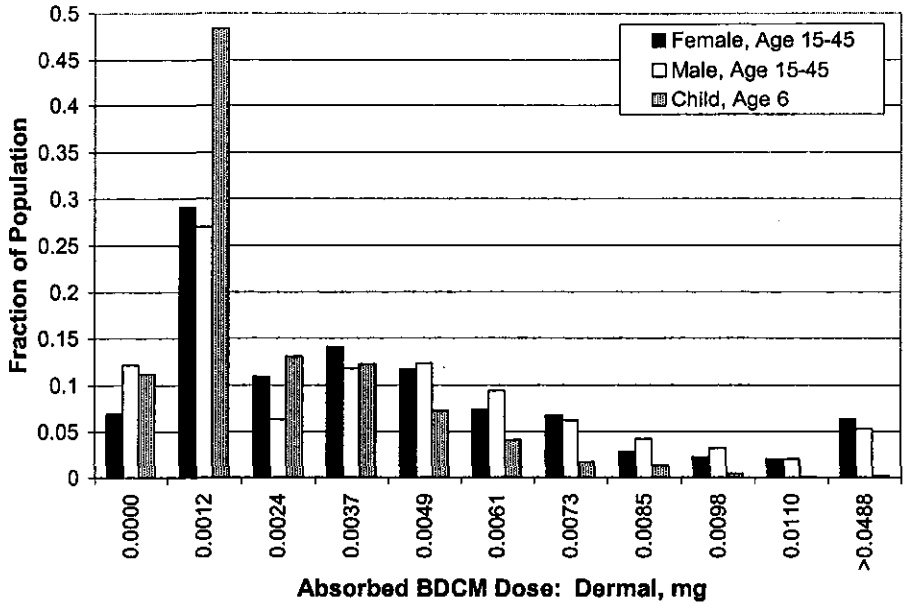


Figure 12. Histogram for Absorbed Dermal BDCM Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

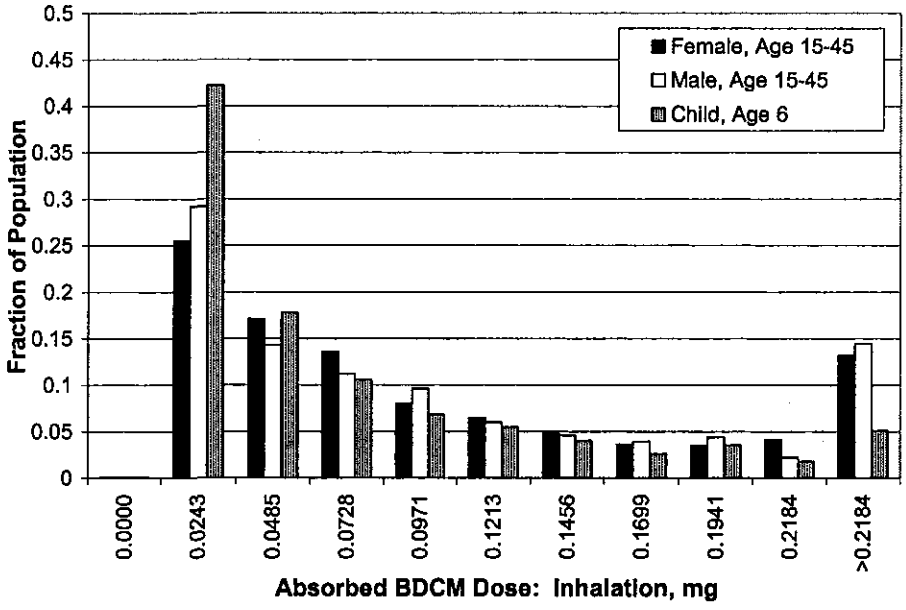
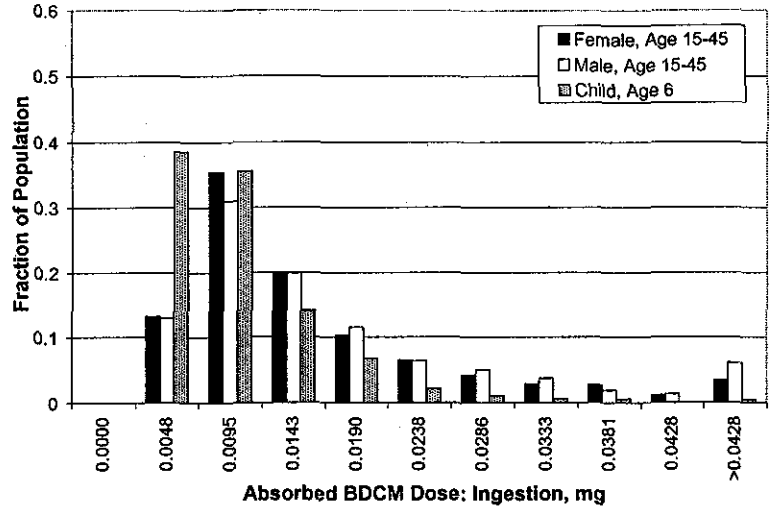
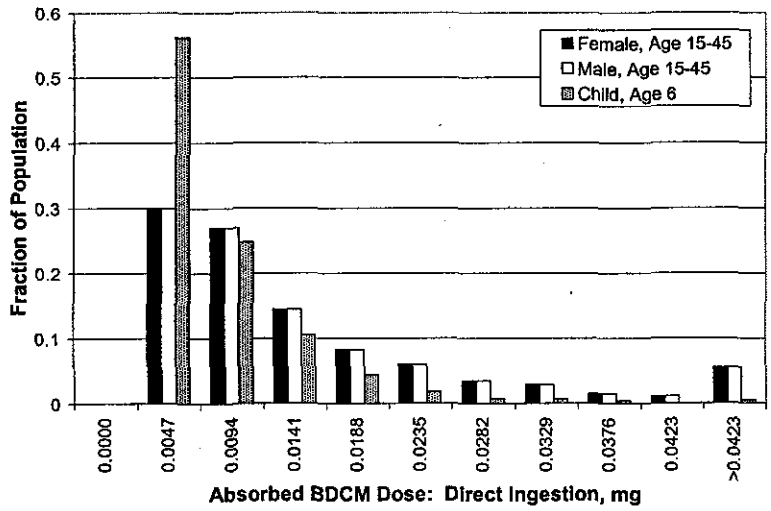


Figure 13. Histogram for Absorbed Inhalation BDCM Dose for Females, Males and Children.





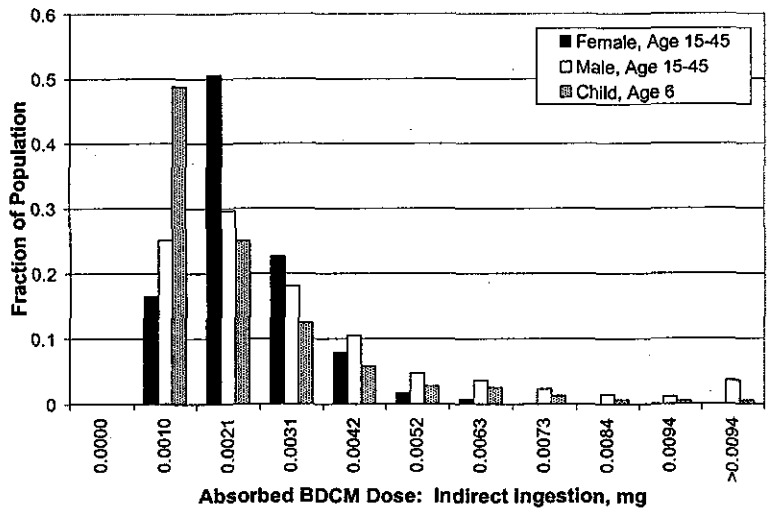


Figure 14. Histograms for the Absorbed BDCM Ingestion Dose for Females, Males and Children.

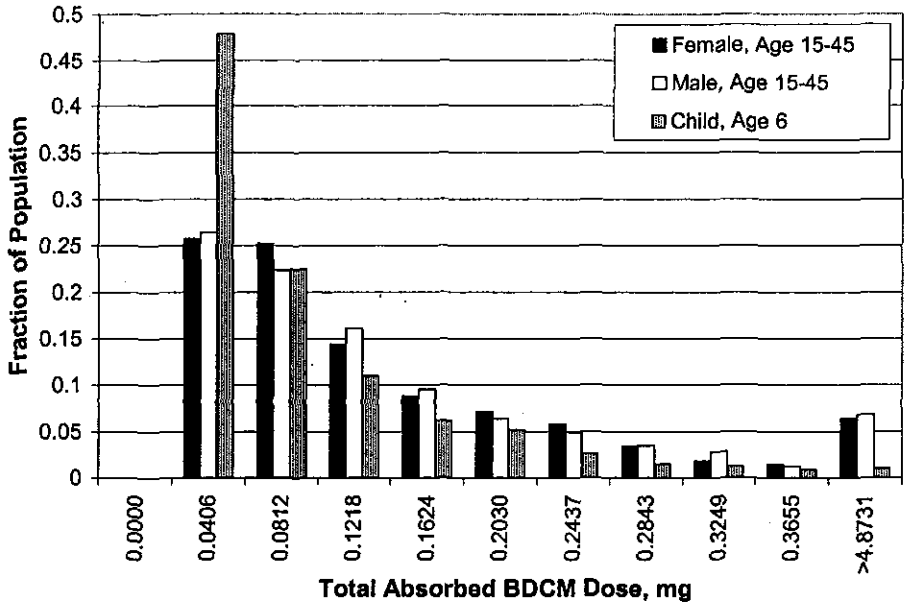


Figure 15. Histogram for the Total Absorbed BDCM Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.3 Uptake Results for DBCM

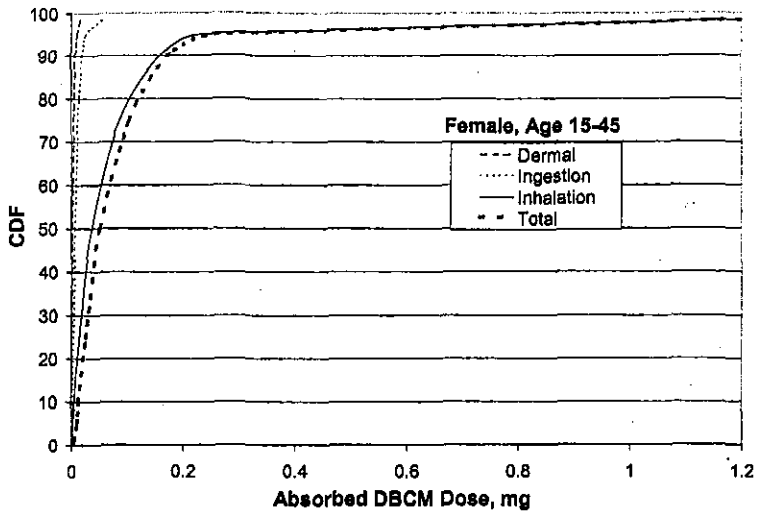
The following Table 57 presents the resultant absorbed dose of DBCM from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 16 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of DBCM and Figures 17, 18, and 19 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 20 presents the total absorbed DBCM dose.

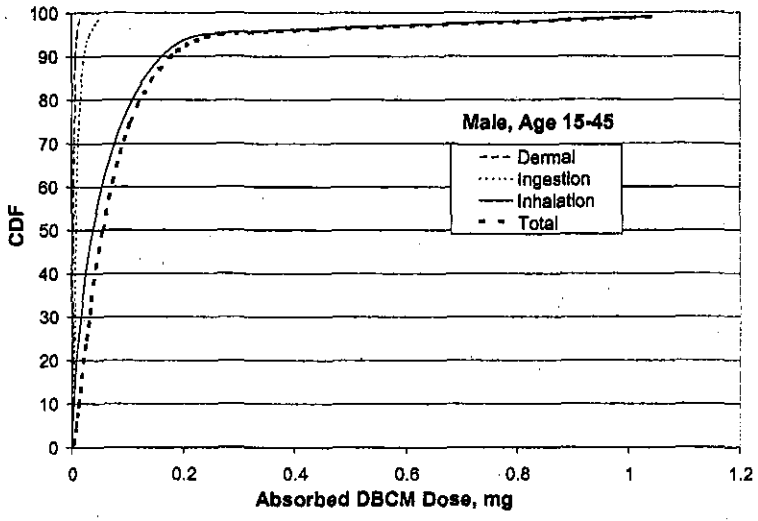
Table 57. DBCM Absorbed Dose Results

	DBCM Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	5.02E-03	0 [a]	7.11E-04	4.60E-04	1.90E-03	9.36E-05
5	9.23E-03	0 [a]	1.26E-03	6.24E-04	2.60E-03	1.67E-03
10	1.32E-02	1.52E-04	1.69E-03	7.25E-04	3.07E-03	5.29E-03
25	2.60E-02	3.64E-04	2.89E-03	1.01E-03	4.45E-03	1.43E-02
50	5.12E-02	2.47E-03	5.33E-03	1.40E-03	7.03E-03	3.73E-02
75	1.03E-01	4.48E-03	1.04E-02	1.94E-03	1.19E-02	8.58E-02
90	1.74E-01	7.34E-03	1.90E-02	2.60E-03	2.05E-02	1.60E-01
95	2.56E-01	9.88E-03	2.41E-02	2.95E-03	2.57E-02	2.31E-01
99	1.38E+00	1.52E-02	5.85E-02	4.14E-03	5.94E-02	1.36E+00
Male, Age 15-45						
1	4.56E-03	0 [a]	5.26E-04	2.28E-04	1.65E-03	6.59E-05
5	8.95E-03	0 [a]	1.07E-03	4.04E-04	2.54E-03	1.61E-03
10	1.34E-02	0 [a]	1.47E-03	5.30E-04	3.21E-03	4.06E-03
25	2.62E-02	3.03E-04	2.79E-03	8.57E-04	4.71E-03	1.22E-02
50	5.49E-02	2.64E-03	5.50E-03	1.52E-03	8.10E-03	3.79E-02
75	1.05E-01	4.93E-03	1.07E-02	2.75E-03	1.34E-02	9.06E-02
90	1.79E-01	7.34E-03	2.00E-02	4.63E-03	2.27E-02	1.63E-01
95	2.68E-01	9.58E-03	2.97E-02	6.48E-03	3.24E-02	2.42E-01
99	1.04E+00	1.51E-02	4.92E-02	1.07E-02	5.04E-02	1.03E+00
Child, Age 6						
1	2.34E-03	0 [a]	3.21E-04	8.09E-05	7.74E-04	4.16E-05
5	4.83E-03	0 [a]	5.96E-04	1.63E-04	1.21E-03	6.75E-04
10	6.98E-03	0 [a]	8.02E-04	2.36E-04	1.58E-03	2.00E-03
25	1.35E-02	9.05E-05	1.43E-03	4.33E-04	2.45E-03	6.91E-03
50	2.91E-02	2.59E-04	2.77E-03	7.72E-04	4.18E-03	2.21E-02
75	6.35E-02	2.26E-03	5.29E-03	1.56E-03	6.92E-03	5.64E-02
90	1.19E-01	3.69E-03	9.06E-03	2.73E-03	1.05E-02	1.11E-01
95	1.55E-01	4.68E-03	1.20E-02	3.88E-03	1.32E-02	1.48E-01
99	2.51E-01	6.47E-03	2.24E-02	5.86E-03	2.44E-02	2.50E-01

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.





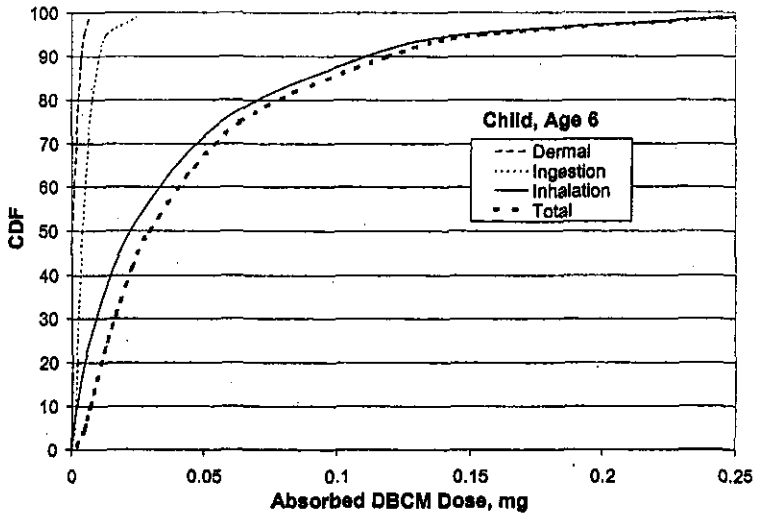


Figure 16. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed DBCM Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

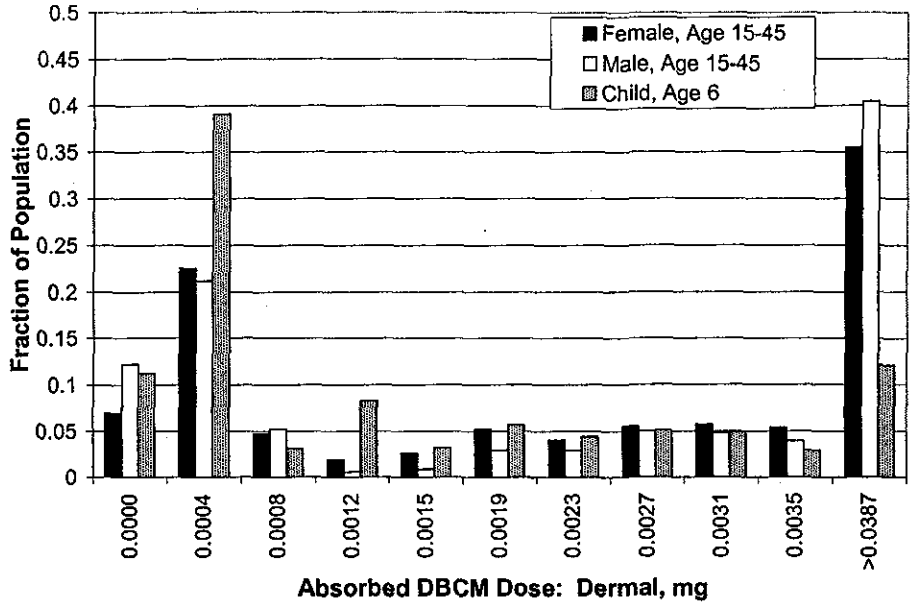


Figure 17. Histogram for Absorbed Dermal DBCM Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

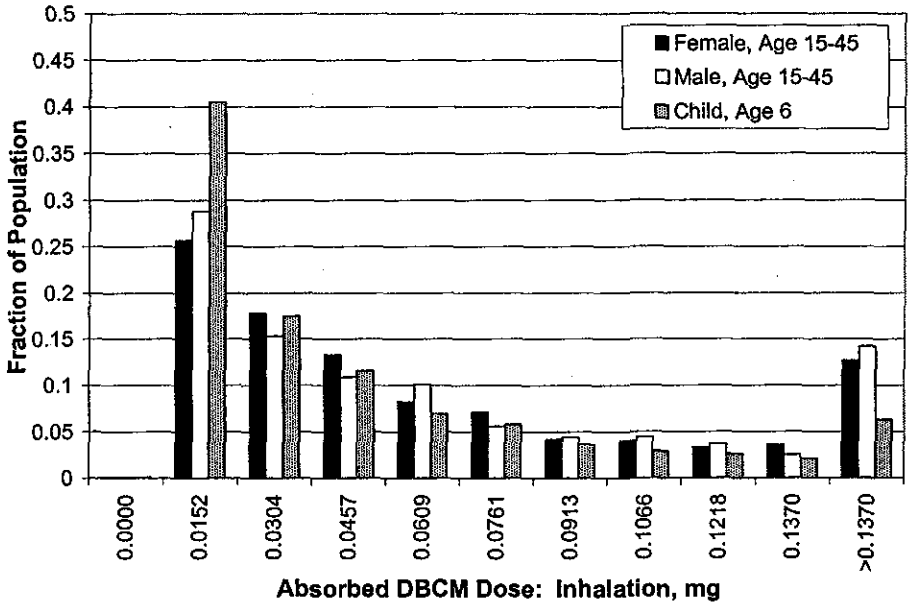
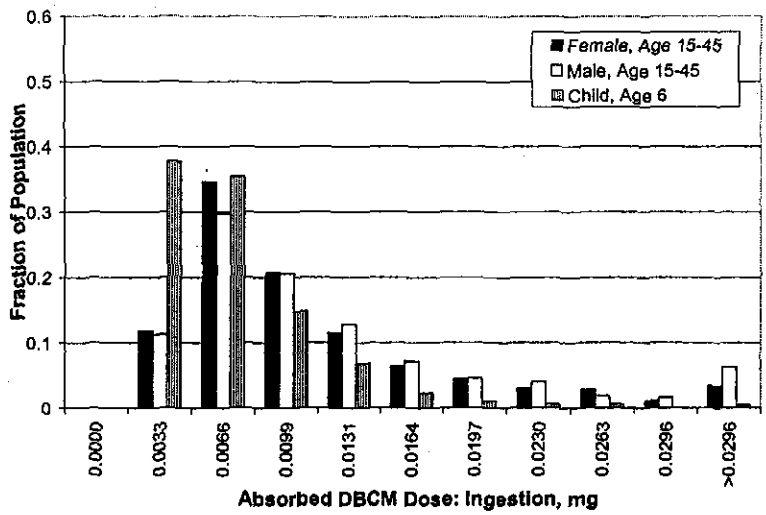
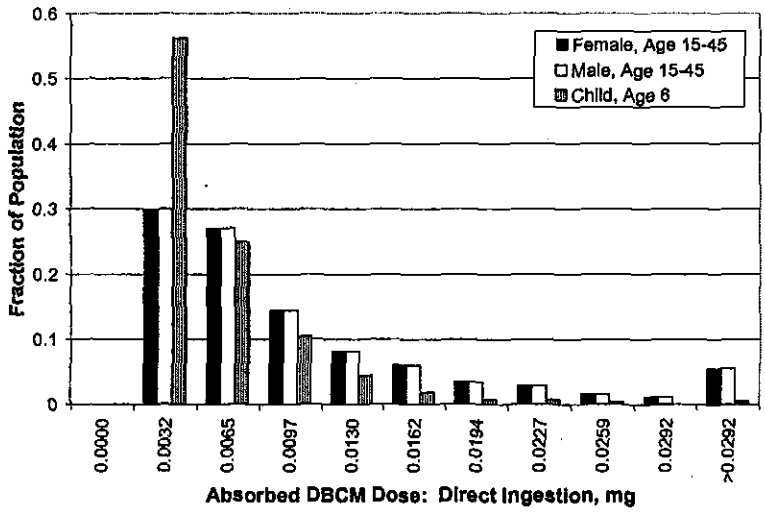


Figure 18. Histogram for Absorbed Inhalation DBCM Dose for Females, Males and Children.





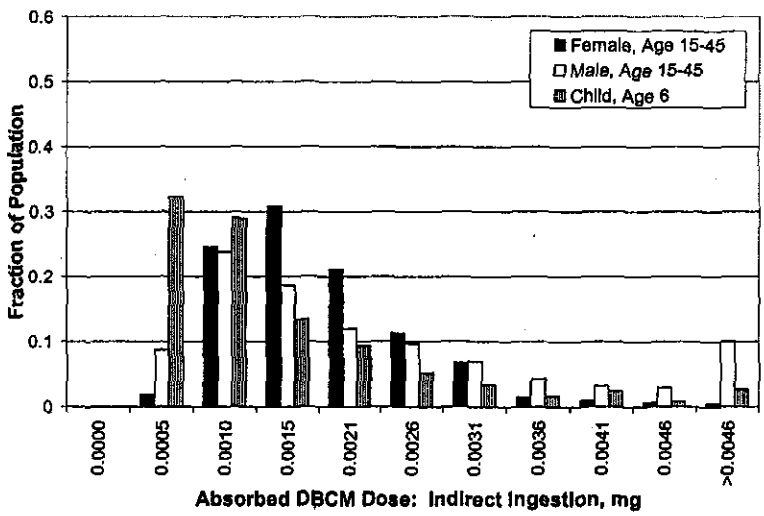


Figure 19. Histograms for the Absorbed DBCM Ingestion Dose for Females, Males and Children.

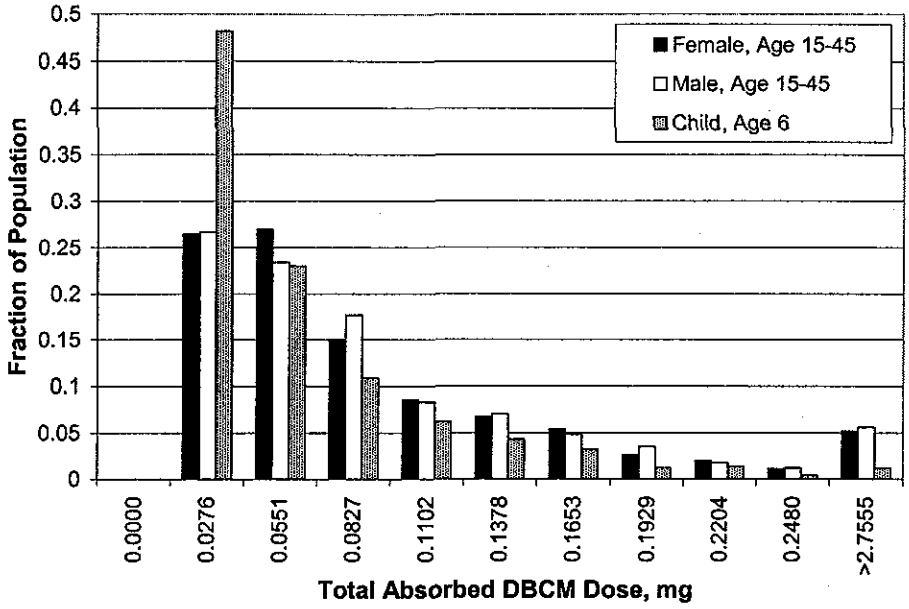


Figure 20. Histogram for the Total Absorbed DBCM Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.4 Uptake Results for Bromoform

The following Table 58 presents the resultant absorbed dose of Bromoform from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 21 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of Bromoform and Figures 22, 23, and 24 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 25 presents the total absorbed Bromoform dose.

Table 58. Bromoform Absorbed Dose Results

	Bromoform Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	4.55E-03	0 [a]	3.84E-04	9.53E-04	2.15E-03	3.01E-05
5	6.83E-03	0 [a]	6.82E-04	1.34E-03	2.83E-03	6.89E-04
10	9.23E-03	1.02E-04	9.14E-04	1.56E-03	3.43E-03	2.30E-03
25	1.54E-02	2.43E-04	1.56E-03	2.18E-03	4.60E-03	6.46E-03
50	2.65E-02	1.60E-03	2.88E-03	3.00E-03	6.55E-03	1.63E-02
75	4.94E-02	2.84E-03	5.62E-03	4.16E-03	9.40E-03	3.63E-02
90	7.79E-02	4.64E-03	1.03E-02	5.61E-03	1.39E-02	6.71E-02
95	1.12E-01	6.24E-03	1.30E-02	6.28E-03	1.69E-02	9.85E-02
99	6.28E-01	9.45E-03	3.16E-02	8.82E-03	3.43E-02	6.16E-01
Male, Age 15-45						
1	3.97E-03	0 [a]	2.84E-04	4.82E-04	1.70E-03	2.99E-05
5	6.49E-03	0 [a]	5.76E-04	8.86E-04	2.60E-03	6.76E-04
10	9.21E-03	0 [a]	7.95E-04	1.15E-03	3.29E-03	1.69E-03
25	1.68E-02	2.03E-04	1.51E-03	1.84E-03	4.82E-03	5.45E-03
50	3.00E-02	1.70E-03	2.97E-03	3.24E-03	7.55E-03	1.68E-02
75	5.18E-02	3.19E-03	5.77E-03	5.84E-03	1.18E-02	3.79E-02
90	8.26E-02	4.59E-03	1.08E-02	1.00E-02	1.91E-02	6.90E-02
95	1.20E-01	5.99E-03	1.60E-02	1.38E-02	2.48E-02	1.07E-01
99	4.87E-01	9.33E-03	2.66E-02	2.28E-02	3.50E-02	4.73E-01
Child, Age 6						
1	1.45E-03	0 [a]	1.73E-04	7.65E-05	5.15E-04	1.63E-05
5	2.75E-03	0 [a]	3.22E-04	1.59E-04	8.69E-04	2.86E-04
10	3.79E-03	0 [a]	4.34E-04	2.22E-04	1.06E-03	8.37E-04
25	6.99E-03	6.01E-05	7.70E-04	4.21E-04	1.61E-03	2.85E-03
50	1.34E-02	1.73E-04	1.50E-03	7.42E-04	2.70E-03	8.77E-03
75	2.64E-02	1.42E-03	2.86E-03	1.51E-03	4.43E-03	2.22E-02
90	4.90E-02	2.30E-03	4.90E-03	2.62E-03	6.57E-03	4.41E-02
95	6.28E-02	2.91E-03	6.51E-03	3.73E-03	8.14E-03	5.84E-02
99	9.18E-02	4.03E-03	1.21E-02	5.58E-03	1.32E-02	9.00E-02

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.

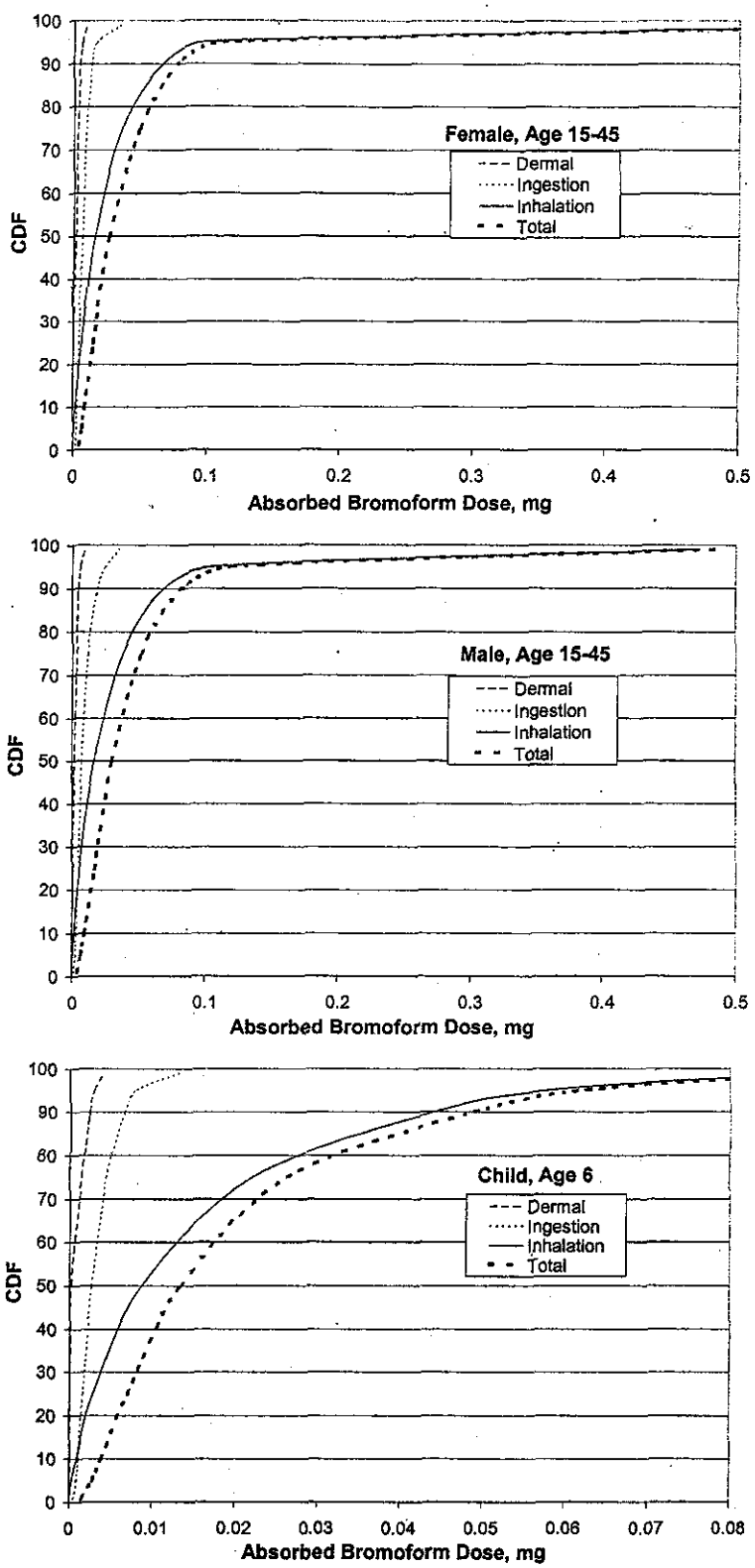


Figure 21. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed Bromoform Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

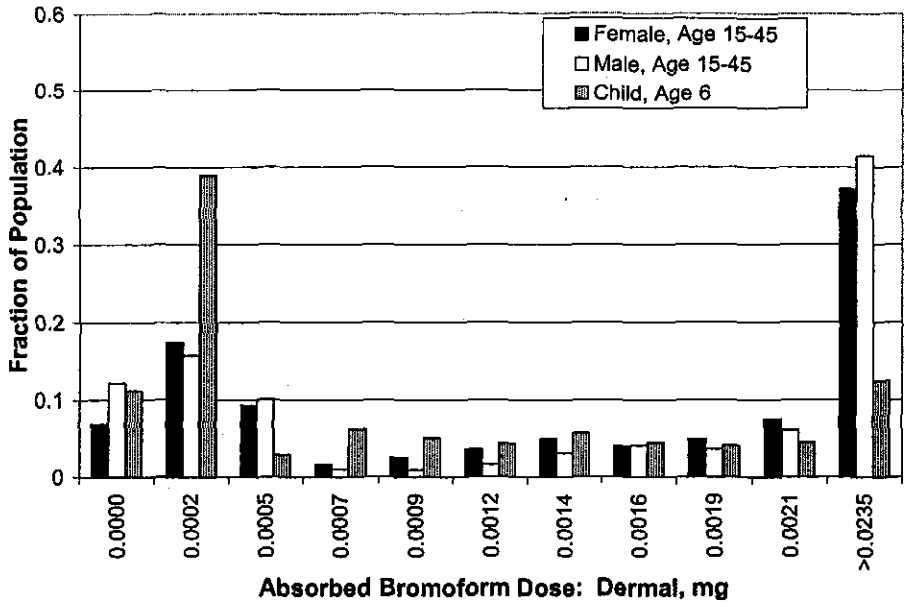


Figure 22. Histogram for Absorbed Dermal Bromoform Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

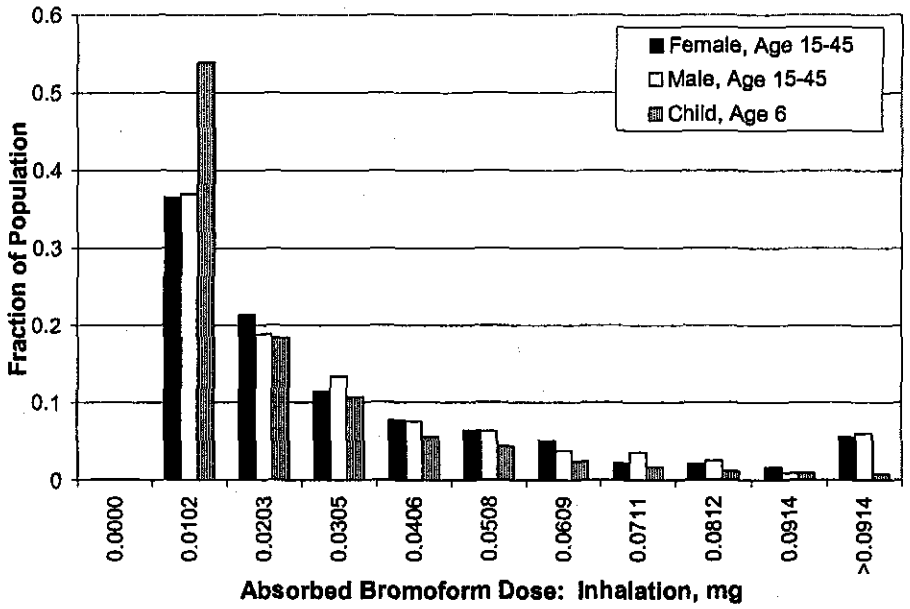
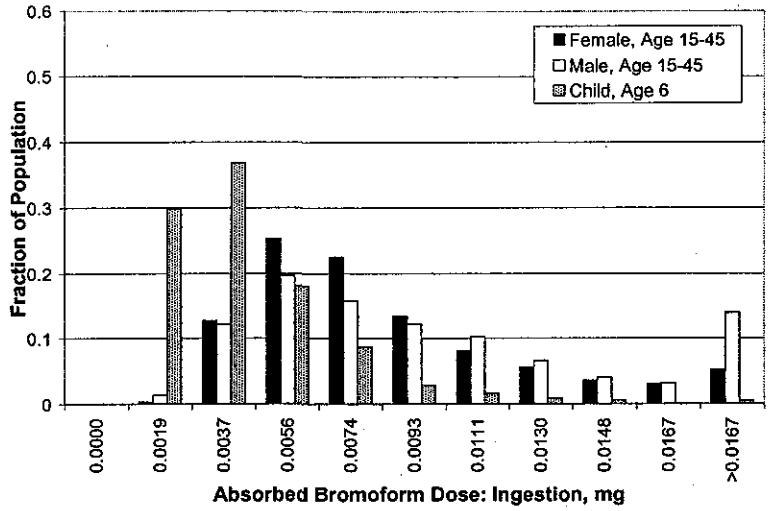
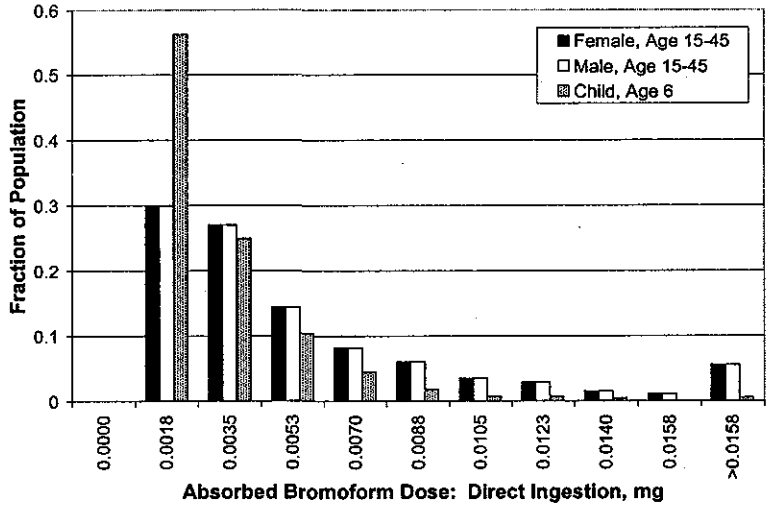


Figure 23. Histogram for Absorbed Inhalation Bromoform Dose for Females, Males and Children.





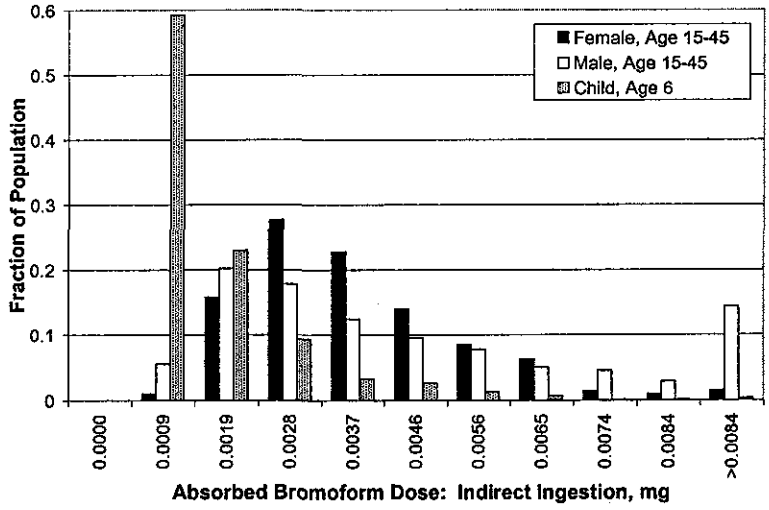


Figure 24. Histograms for the Absorbed Bromoform Ingestion Dose for Females, Males and Children.

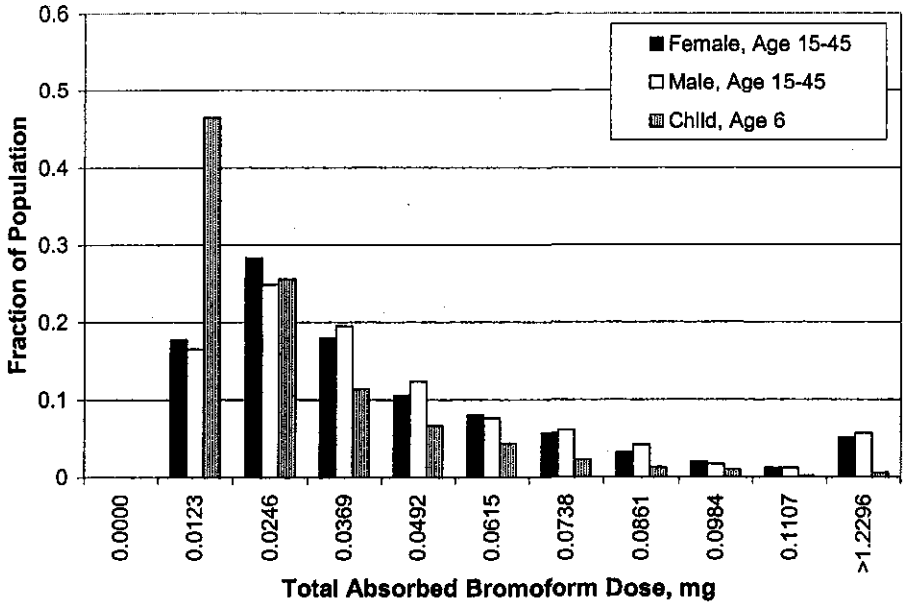


Figure 25. Histogram for the Total Absorbed Bromoform Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.5 Uptake Results for MCA

The following Table 59 presents the resultant absorbed dose of MCA from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 26 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of MCA and Figures 27, 28, and 29 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 30 presents the total absorbed MCA dose.

Table 59. MCA Absorbed Dose Results

	MCA Absorbed Dose, mg					
Percentile	**Total [b]**	**Dermal Total**	**Ingestion Direct**	**Ingestion Indirect**	**Ingestion Total**	**Inhalation Total**
Female, Age 15-45						
1	1.52E-03	0 [a]	2.54E-04	6.31E-04	1.42E-03	1.94E-09
5	1.99E-03	0 [a]	4.51E-04	8.88E-04	1.88E-03	3.54E-08
10	2.40E-03	7.93E-06	6.05E-04	1.03E-03	2.27E-03	1.30E-07
25	3.21E-03	1.89E-05	1.03E-03	1.44E-03	3.05E-03	4.74E-07
50	4.45E-03	1.16E-04	1.91E-03	1.99E-03	4.34E-03	1.15E-06
75	6.32E-03	1.98E-04	3.73E-03	2.76E-03	6.22E-03	2.34E-06
90	9.38E-03	3.13E-04	6.79E-03	3.71E-03	9.24E-03	3.86E-06
95	1.13E-02	3.91E-04	8.63E-03	4.16E-03	1.12E-02	5.29E-06
99	2.27E-02	5.78E-04	2.09E-02	5.84E-03	2.27E-02	3.18E-05
Male, Age 15-45						
1	1.27E-03	0 [a]	1.88E-04	3.19E-04	1.13E-03	2.11E-09
5	1.84E-03	0 [a]	3.82E-04	5.87E-04	1.72E-03	3.86E-08
10	2.27E-03	0 [a]	5.27E-04	7.60E-04	2.18E-03	9.84E-08
25	3.35E-03	1.58E-05	1.00E-03	1.22E-03	3.19E-03	4.40E-07
50	5.09E-03	1.25E-04	1.97E-03	2.14E-03	5.00E-03	1.33E-06
75	7.93E-03	2.20E-04	3.82E-03	3.87E-03	7.82E-03	2.39E-06
90	1.30E-02	3.12E-04	7.17E-03	6.62E-03	1.27E-02	3.99E-06
95	1.66E-02	3.93E-04	1.06E-02	9.16E-03	1.64E-02	5.97E-06
99	2.33E-02	5.82E-04	1.76E-02	1.51E-02	2.32E-02	2.74E-05
Child, Age 6						
1	4.22E-04	0 [a]	1.15E-04	5.07E-05	3.41E-04	1.10E-09
5	6.27E-04	0 [a]	2.13E-04	1.05E-04	5.75E-04	1.80E-08
10	7.71E-04	0 [a]	2.87E-04	1.47E-04	7.00E-04	5.05E-08
25	1.14E-03	4.69E-06	5.10E-04	2.79E-04	1.07E-03	1.81E-07
50	1.84E-03	1.35E-05	9.92E-04	4.92E-04	1.79E-03	6.29E-07
75	2.99E-03	9.49E-05	1.89E-03	9.97E-04	2.94E-03	1.50E-06
90	4.39E-03	1.49E-04	3.24E-03	1.73E-03	4.35E-03	2.56E-06
95	5.51E-03	1.86E-04	4.31E-03	2.47E-03	5.39E-03	3.43E-06
99	8.76E-03	2.54E-04	8.00E-03	3.70E-03	8.75E-03	5.20E-06

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.

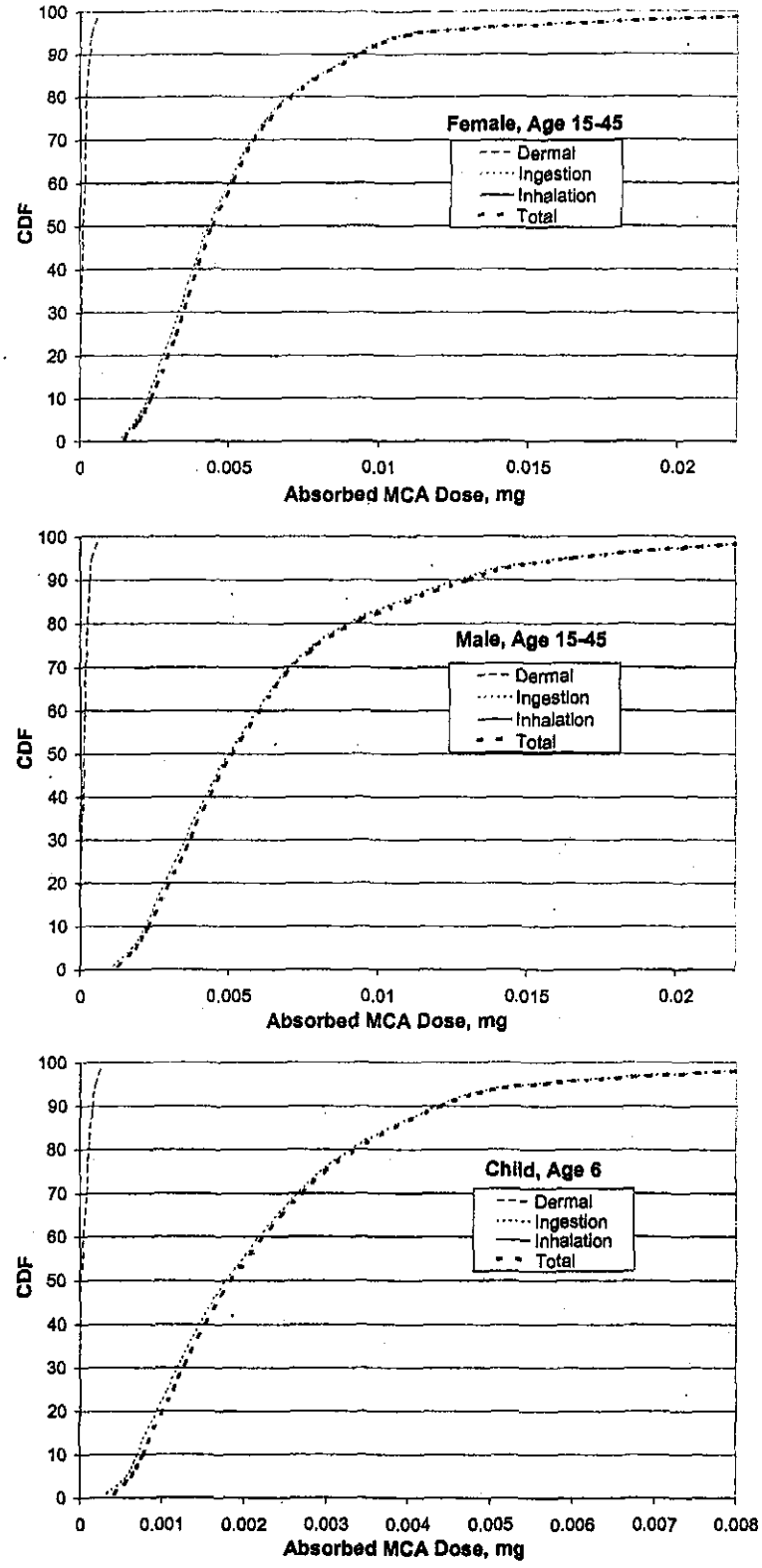


Figure 26. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed MCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

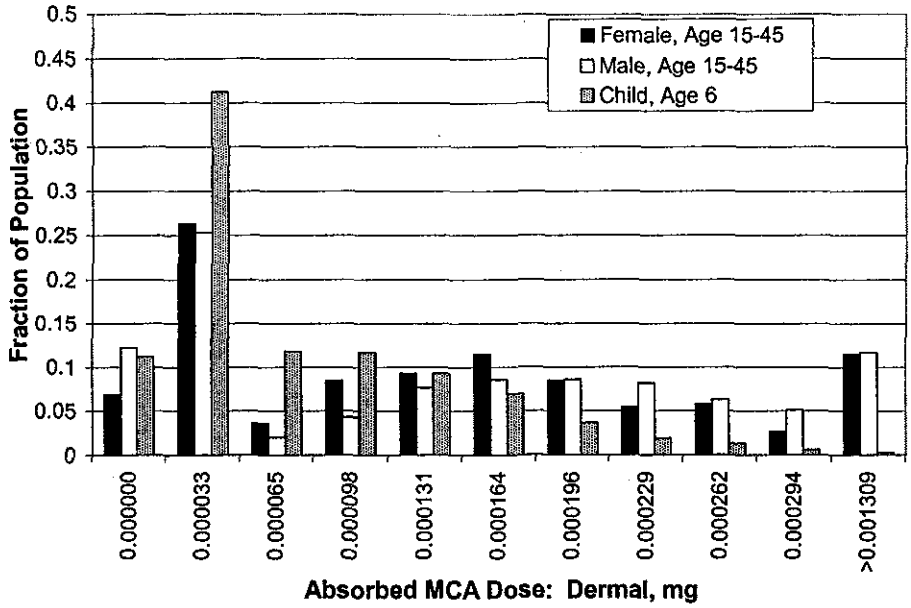


Figure 27. Histogram for Absorbed Dermal MCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

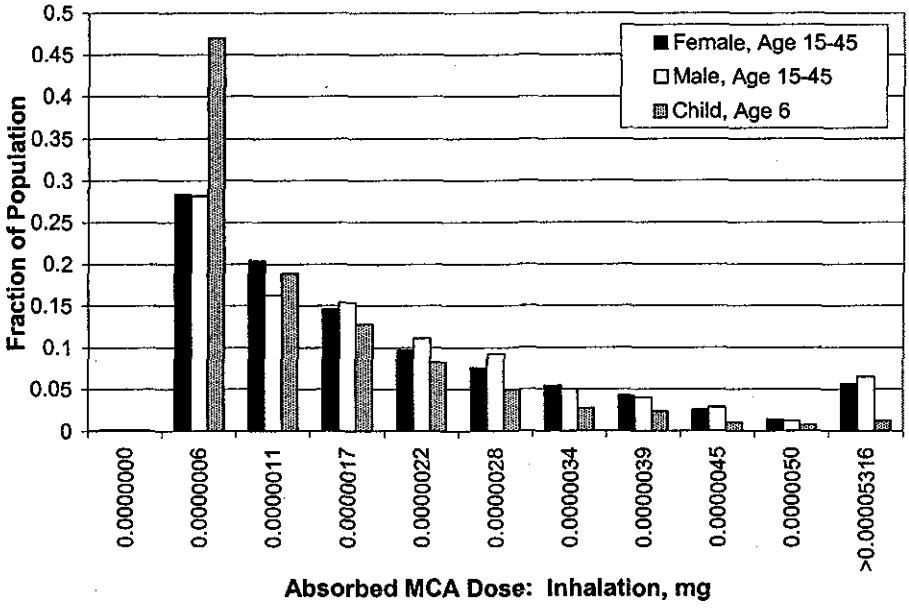
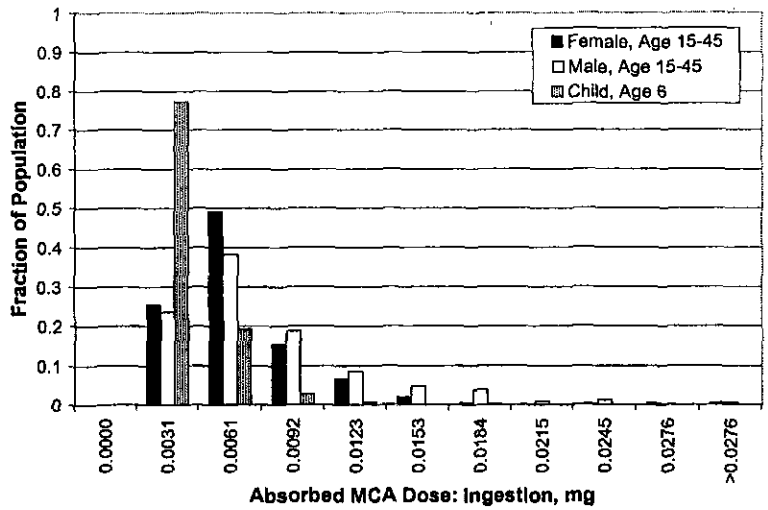
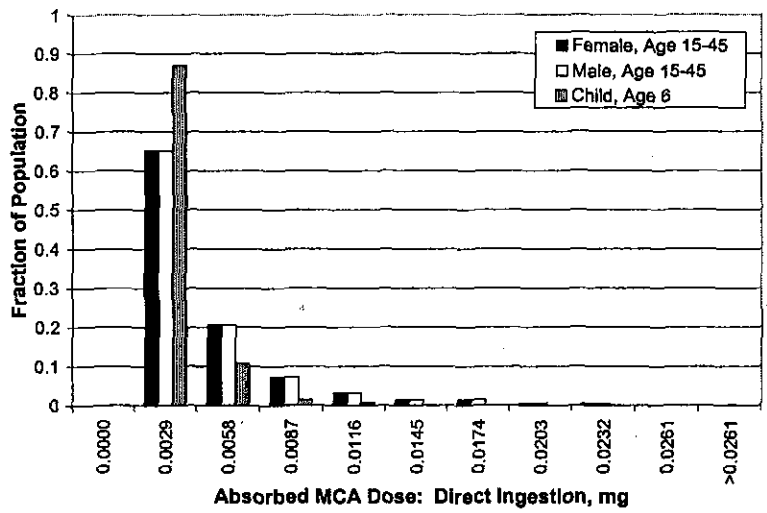


Figure 28. Histogram for Absorbed Inhalation MCA Dose for Females, Males and Children.





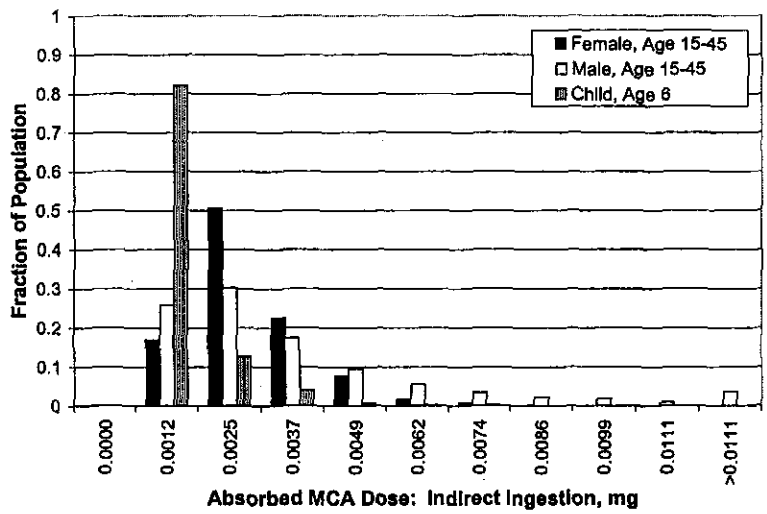


Figure 29. Histograms for the Absorbed MCA Ingestion Dose for Females, Males and Children.

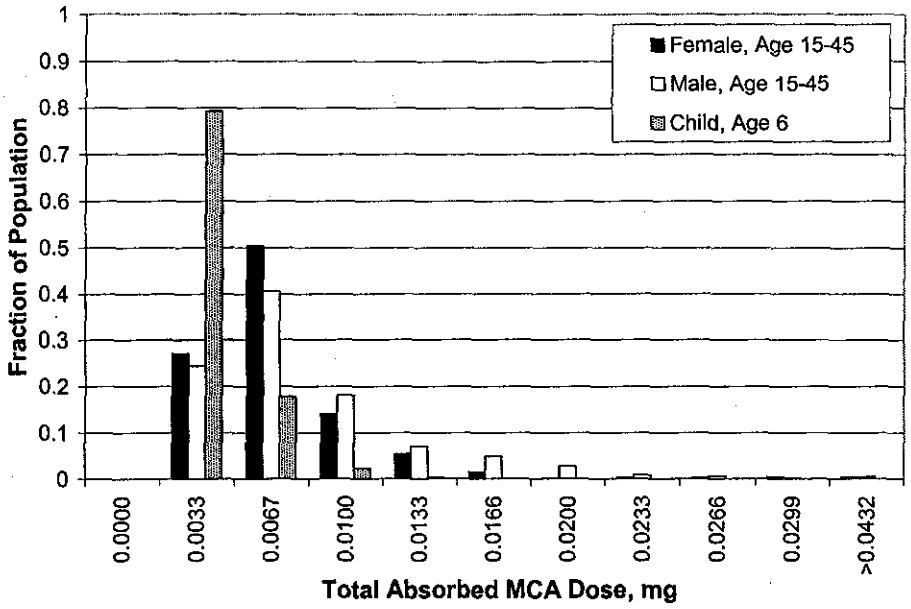


Figure 30. Histogram for the Total Absorbed MCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.6 Uptake Results for DCA

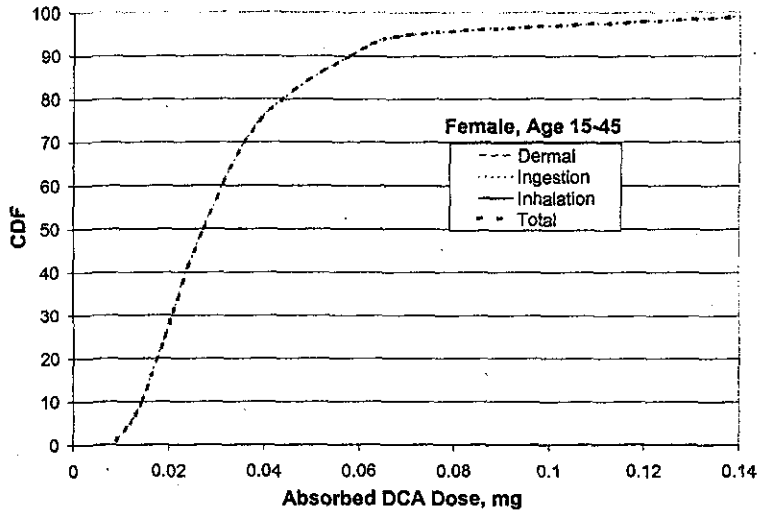
The following Table 60 presents the resultant absorbed dose of DCA from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 31 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of DCA and Figures 32, 33, and 34 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 35 presents the total absorbed DCA dose.

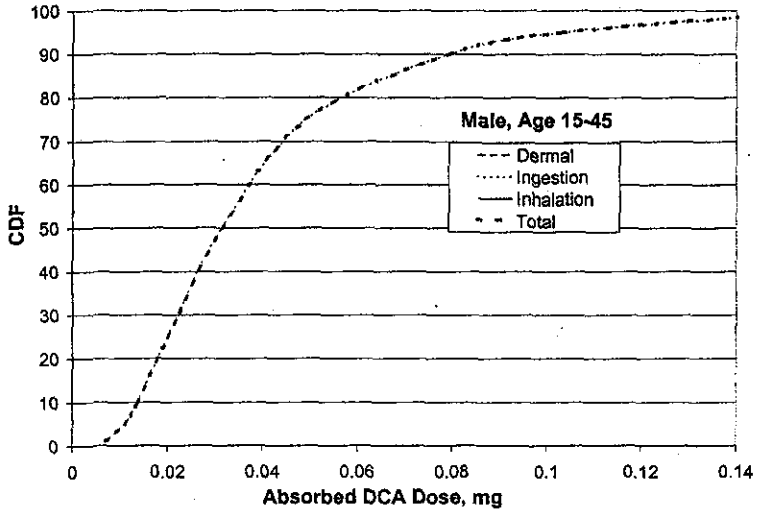
Table 60. DCA Absorbed Dose Results

	DCA Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	8.96E-03	0 [a]	1.60E-03	3.96E-03	8.92E-03	8.71E-09
5	1.18E-02	0 [a]	2.83E-03	5.57E-03	1.18E-02	1.63E-07
10	1.43E-02	7.42E-07	3.80E-03	6.47E-03	1.42E-02	5.87E-07
25	1.91E-02	1.77E-06	6.49E-03	9.05E-03	1.91E-02	2.24E-06
50	2.73E-02	1.05E-05	1.20E-02	1.25E-02	2.72E-02	5.46E-06
75	3.91E-02	1.76E-05	2.34E-02	1.73E-02	3.91E-02	1.10E-05
90	5.80E-02	2.58E-05	4.26E-02	2.33E-02	5.80E-02	1.83E-05
95	7.03E-02	3.04E-05	5.41E-02	2.61E-02	7.03E-02	2.51E-05
99	1.43E-01	4.04E-05	1.31E-01	3.67E-02	1.43E-01	1.58E-04
Male, Age 15-45						
1	7.09E-03	0 [a]	1.18E-03	2.00E-03	7.08E-03	9.72E-09
5	1.08E-02	0 [a]	2.39E-03	3.68E-03	1.08E-02	1.72E-07
10	1.37E-02	0 [a]	3.30E-03	4.77E-03	1.37E-02	4.66E-07
25	2.01E-02	1.48E-06	6.27E-03	7.65E-03	2.00E-02	2.03E-06
50	3.14E-02	1.16E-05	1.23E-02	1.35E-02	3.14E-02	6.20E-06
75	4.91E-02	1.96E-05	2.40E-02	2.43E-02	4.91E-02	1.13E-05
90	7.95E-02	2.72E-05	4.50E-02	4.16E-02	7.94E-02	1.89E-05
95	1.03E-01	3.34E-05	6.67E-02	5.75E-02	1.03E-01	2.85E-05
99	1.46E-01	4.41E-05	1.10E-01	9.47E-02	1.46E-01	1.32E-04
Child, Age 6						
1	2.15E-03	0 [a]	7.20E-04	3.18E-04	2.14E-03	4.89E-09
5	3.61E-03	0 [a]	1.34E-03	6.60E-04	3.61E-03	8.42E-08
10	4.40E-03	0 [a]	1.80E-03	9.24E-04	4.39E-03	2.29E-07
25	6.70E-03	4.39E-07	3.20E-03	1.75E-03	6.70E-03	8.44E-07
50	1.12E-02	1.26E-06	6.22E-03	3.08E-03	1.12E-02	3.01E-06
75	1.84E-02	8.15E-06	1.19E-02	6.26E-03	1.84E-02	7.05E-06
90	2.73E-02	1.23E-05	2.04E-02	1.09E-02	2.73E-02	1.23E-05
95	3.38E-02	1.51E-05	2.71E-02	1.55E-02	3.38E-02	1.63E-05
99	5.49E-02	2.00E-05	5.02E-02	2.32E-02	5.49E-02	2.51E-05

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.





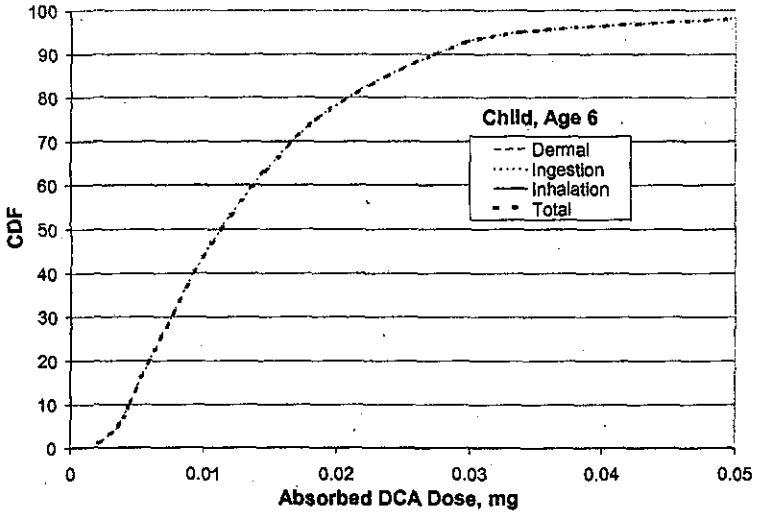


Figure 31. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed DCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

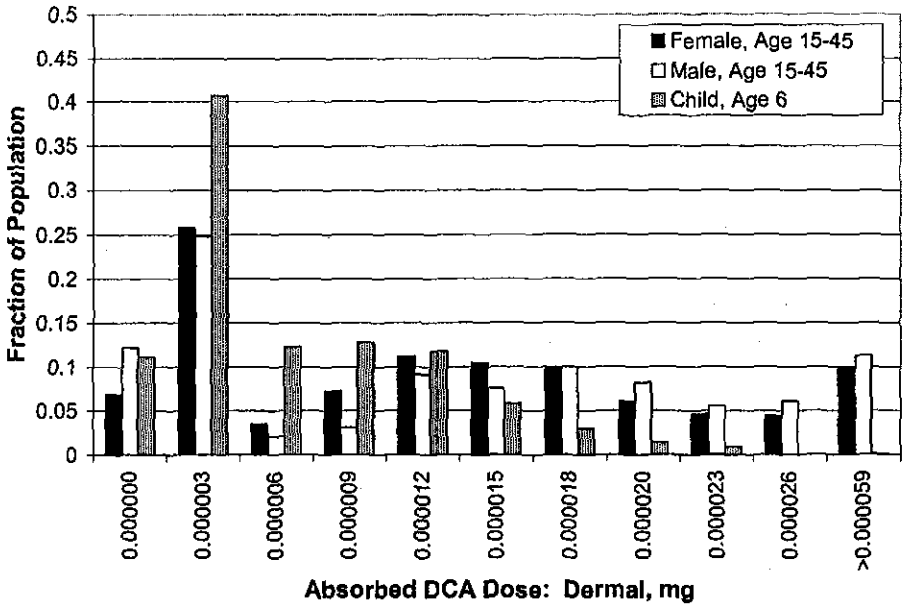


Figure 32. Histogram for Absorbed Dermal DCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

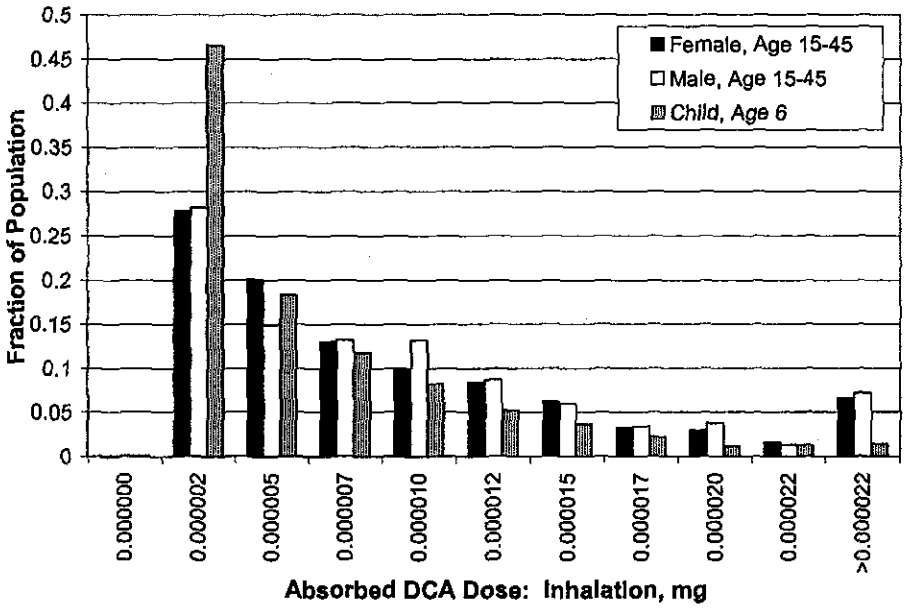
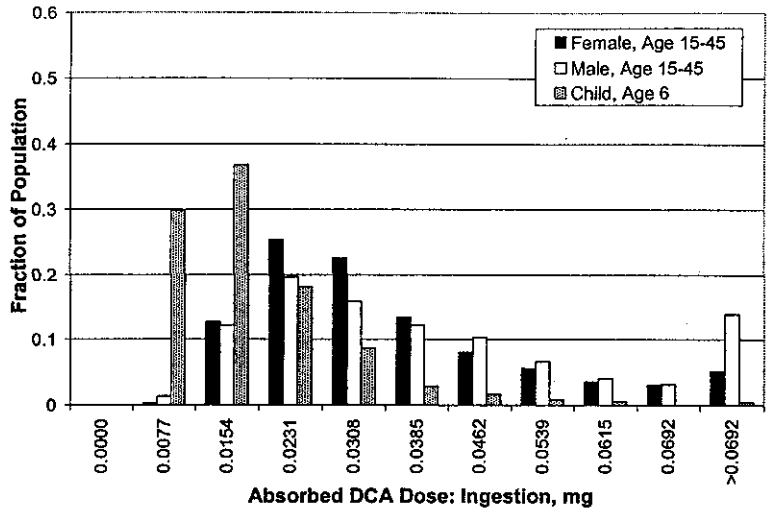
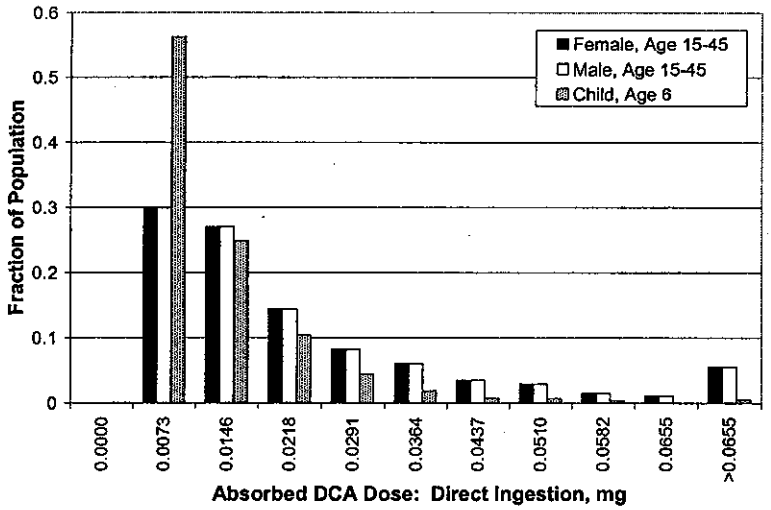


Figure 33. Histogram for Absorbed Inhalation DCA Dose for Females, Males and Children.





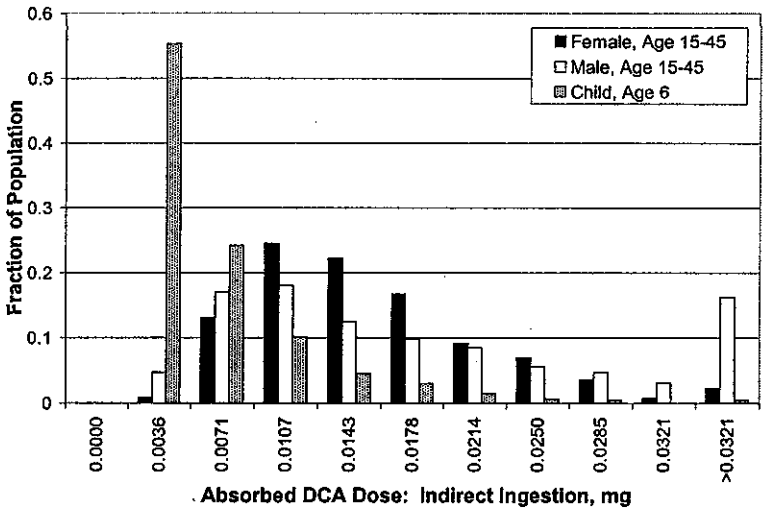


Figure 34. Histograms for the Absorbed DCA Ingestion Dose for Females, Males and Children.

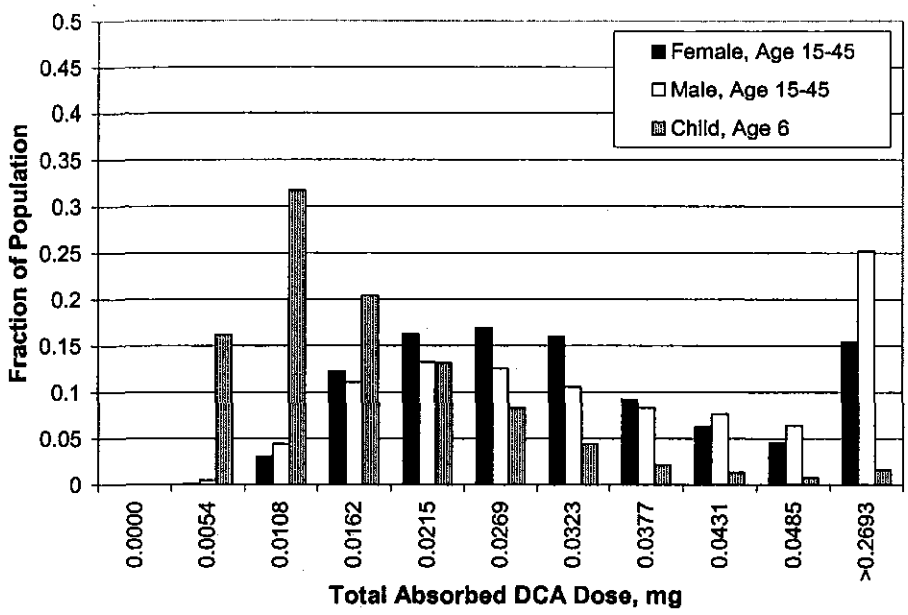


Figure 35. Histogram for the Total Absorbed DCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.7 Uptake Results for TCA

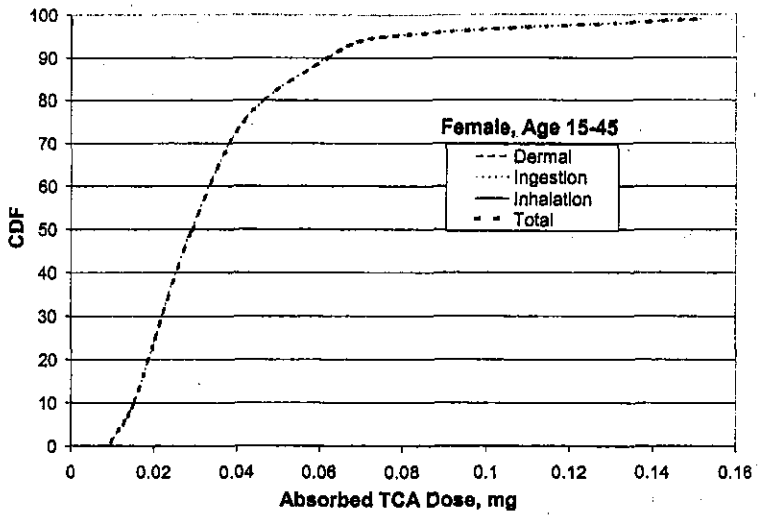
The following Table 61 presents the resultant absorbed dose of TCA from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 36 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of TCA and Figures 37, 38, and 39 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 40 presents the total absorbed TCA dose.

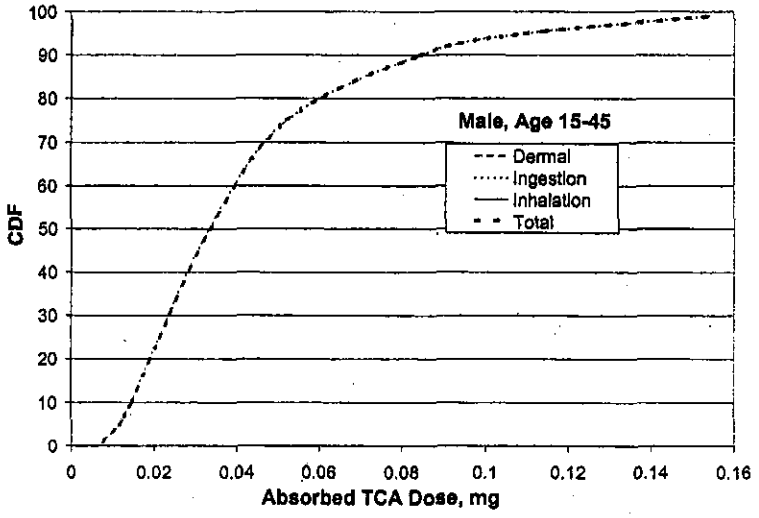
Table 61. TCA Absorbed Dose Results

	TCA Absorbed Dose, mg					
Percentile	**Total [b]**	**Dermal Total**	**Ingestion Direct**	**Ingestion Indirect**	**Ingestion Total**	**Inhalation Total**
Female, Age 15-45						
1	9.65E-03	0 [a]	1.70E-03	4.21E-03	9.48E-03	1.52E-08
5	1.25E-02	0 [a]	3.01E-03	5.92E-03	1.25E-02	2.77E-07
10	1.52E-02	1.21E-06	4.03E-03	6.88E-03	1.51E-02	1.03E-06
25	2.03E-02	2.88E-06	6.89E-03	9.61E-03	2.03E-02	3.90E-06
50	2.90E-02	1.71E-05	1.27E-02	1.32E-02	2.89E-02	9.47E-06
75	4.15E-02	2.87E-05	2.48E-02	1.84E-02	4.15E-02	1.93E-05
90	6.16E-02	4.20E-05	4.53E-02	2.48E-02	6.16E-02	3.24E-05
95	7.48E-02	4.96E-05	5.75E-02	2.77E-02	7.47E-02	4.44E-05
99	1.51E-01	6.58E-05	1.39E-01	3.90E-02	1.51E-01	2.76E-04
Male, Age 15-45						
1	7.55E-03	0 [a]	1.26E-03	2.13E-03	7.52E-03	1.67E-08
5	1.15E-02	0 [a]	2.54E-03	3.91E-03	1.15E-02	3.02E-07
10	1.46E-02	0 [a]	3.51E-03	5.07E-03	1.45E-02	8.17E-07
25	2.14E-02	2.41E-06	6.67E-03	8.12E-03	2.13E-02	3.57E-06
50	3.34E-02	1.88E-05	1.31E-02	1.43E-02	3.33E-02	1.09E-05
75	5.22E-02	3.19E-05	2.55E-02	2.58E-02	5.21E-02	1.99E-05
90	8.45E-02	4.43E-05	4.78E-02	4.42E-02	8.44E-02	3.33E-05
95	1.10E-01	5.44E-05	7.08E-02	6.11E-02	1.10E-01	5.05E-05
99	1.55E-01	7.19E-05	1.17E-01	1.01E-01	1.55E-01	2.34E-04
Child, Age 6						
1	2.30E-03	0 [a]	7.65E-04	3.38E-04	2.28E-03	8.58E-09
5	3.84E-03	0 [a]	1.42E-03	7.01E-04	3.84E-03	1.46E-07
10	4.68E-03	0 [a]	1.91E-03	9.82E-04	4.67E-03	4.01E-07
25	7.12E-03	7.15E-07	3.40E-03	1.86E-03	7.12E-03	1.47E-06
50	1.19E-02	2.06E-06	6.61E-03	3.28E-03	1.19E-02	5.22E-06
75	1.96E-02	1.33E-05	1.26E-02	6.65E-03	1.96E-02	1.21E-05
90	2.90E-02	2.01E-05	2.16E-02	1.16E-02	2.90E-02	2.16E-05
95	3.60E-02	2.46E-05	2.88E-02	1.65E-02	3.59E-02	2.84E-05
99	5.83E-02	3.26E-05	5.34E-02	2.46E-02	5.83E-02	4.35E-05

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.





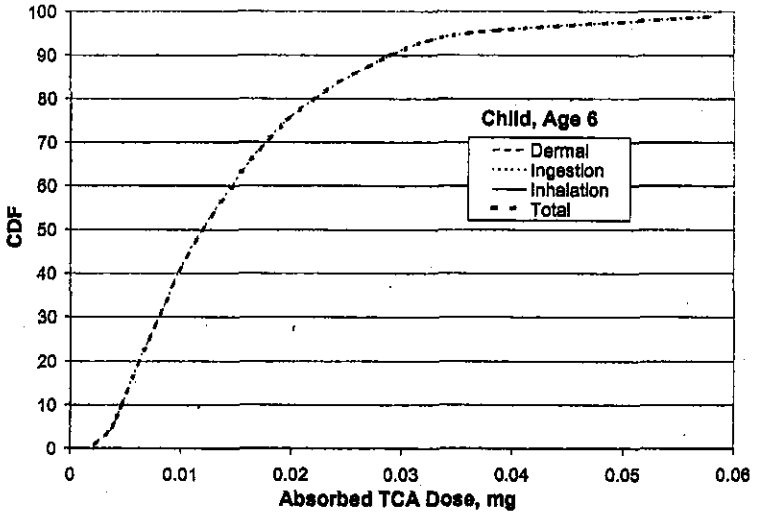


Figure 36. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed TCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

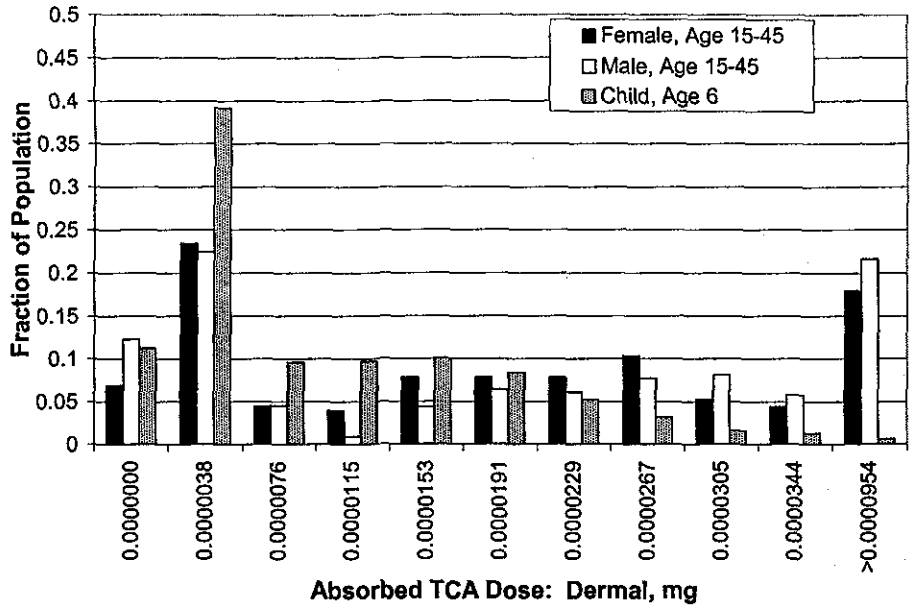


Figure 37. Histogram for Absorbed Dermal TCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

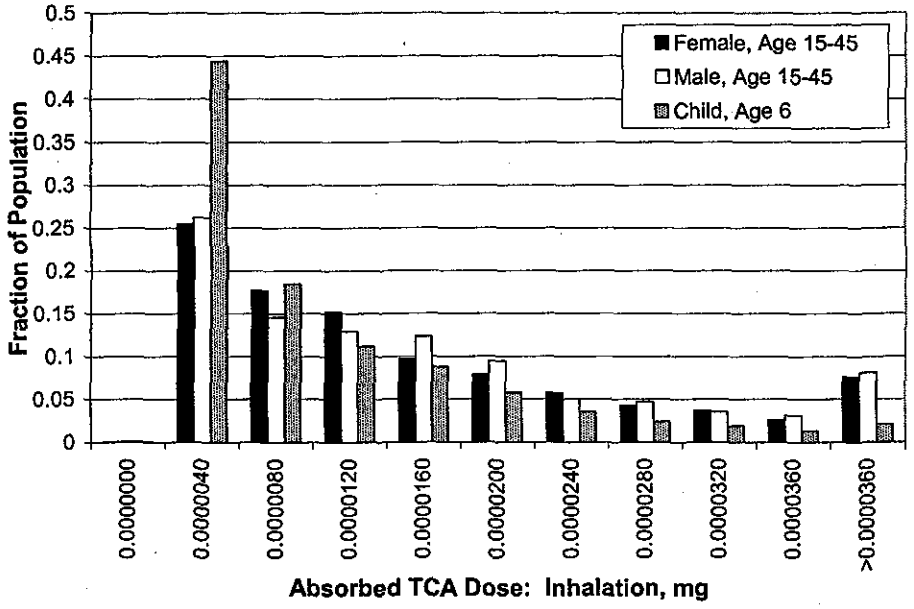


Figure 38. Histogram for Absorbed Inhalation TCA Dose for Females, Males and Children.

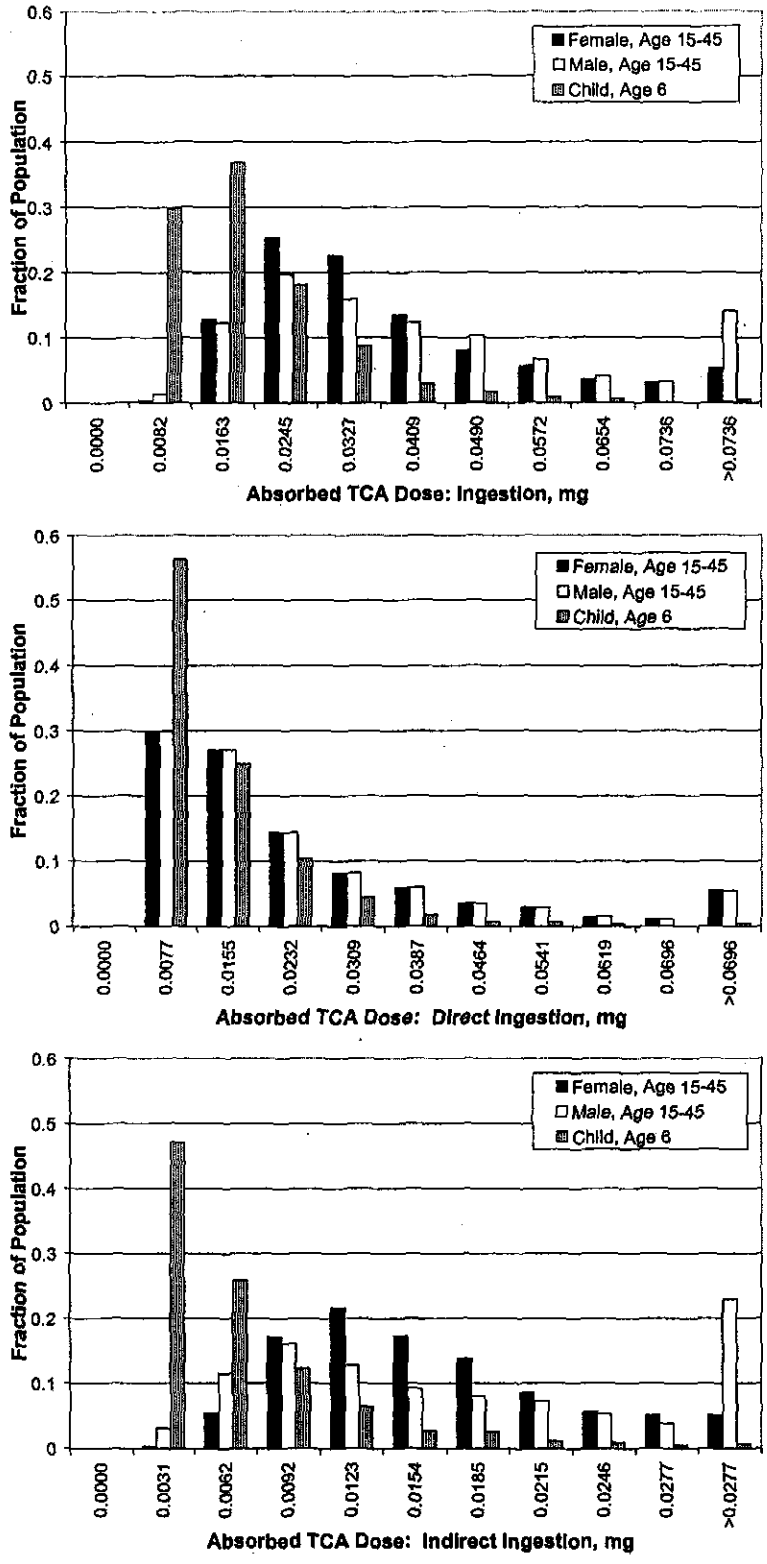


Figure 39. Histograms for the Absorbed TCA Ingestion Dose for Females, Males and Children.

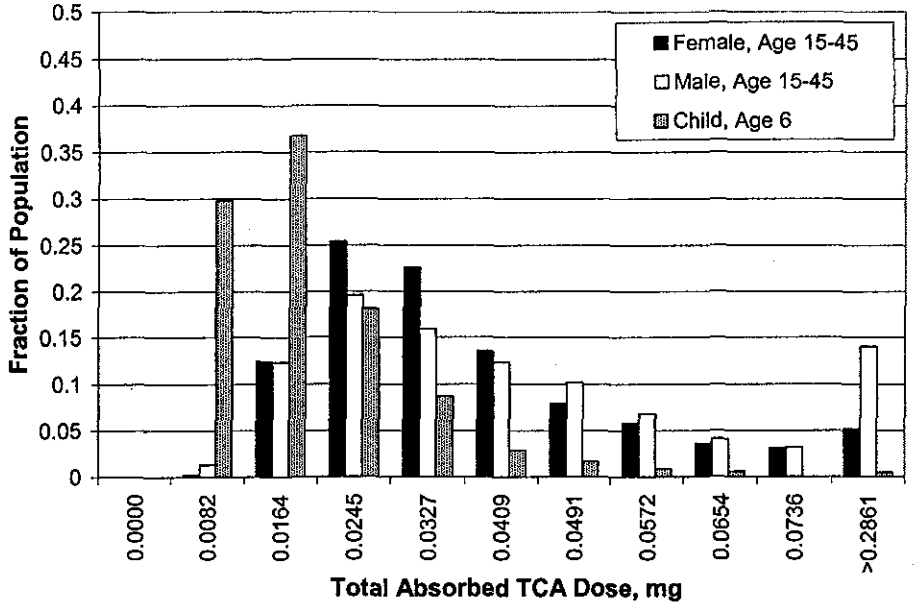


Figure 40. Histogram for the Total Absorbed TCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.8 Uptake Results for MBA

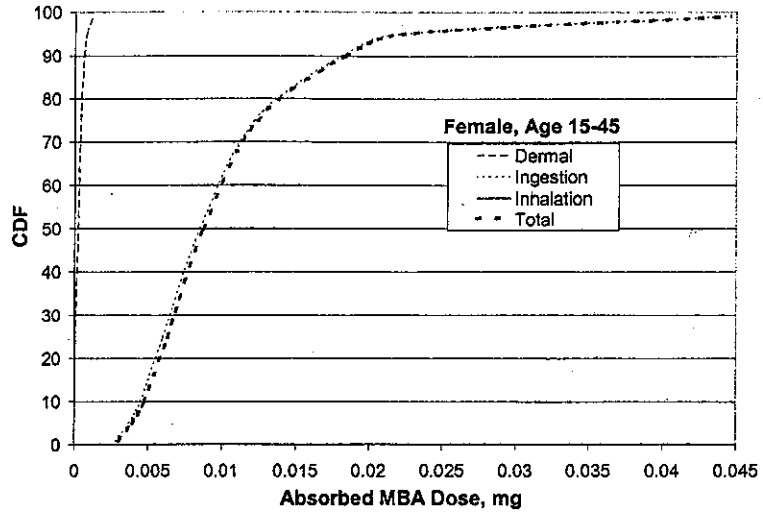
The following Table 62 presents the resultant absorbed dose of MBA from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 41 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of MBA and Figures 42, 43, and 44 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 45 presents the total absorbed MBA dose.

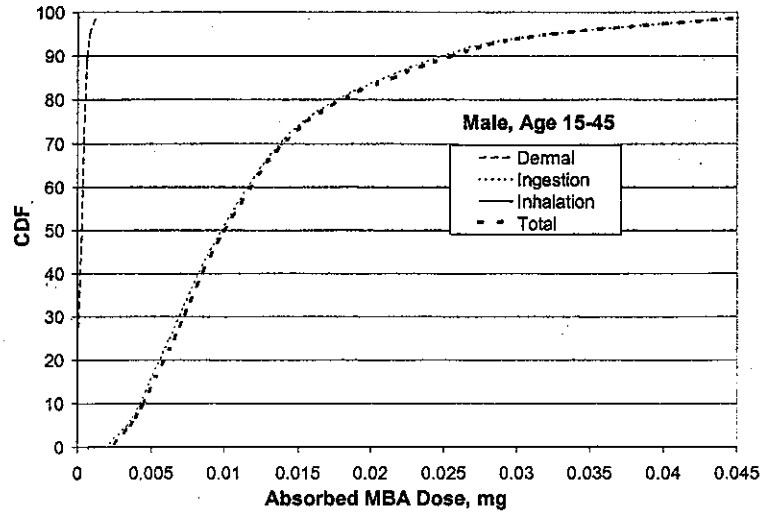
Table 62. MBA Absorbed Dose Results

	MBA Absorbed Dose, mg					
Percentile	**Total [b]**	**Dermal Total**	**Ingestion Direct**	**Ingestion Indirect**	**Ingestion Total**	**Inhalation Total**
Female, Age 15-45						
1	2.97E-03	0[a]	4.99E-04	1.24E-03	2.79E-03	2.90E-09
5	3.91E-03	0[a]	8.85E-04	1.74E-03	3.68E-03	5.65E-08
10	4.70E-03	1.59E-05	1.19E-03	2.02E-03	4.45E-03	2.09E-07
25	6.30E-03	3.78E-05	2.03E-03	2.83E-03	5.98E-03	7.57E-07
50	8.73E-03	2.32E-04	3.74E-03	3.89E-03	8.51E-03	1.79E-06
75	1.24E-02	3.97E-04	7.30E-03	5.41E-03	1.22E-02	3.45E-06
90	1.84E-02	6.31E-04	1.33E-02	7.28E-03	1.81E-02	5.60E-06
95	2.22E-02	7.86E-04	1.69E-02	8.16E-03	2.20E-02	7.85E-06
99	4.45E-02	1.17E-03	4.10E-02	1.15E-02	4.45E-02	4.72E-05
Male, Age 15-45						
1	2.50E-03	0[a]	3.69E-04	6.26E-04	2.21E-03	3.17E-09
5	3.60E-03	0[a]	7.48E-04	1.15E-03	3.38E-03	5.85E-08
10	4.45E-03	0[a]	1.03E-03	1.49E-03	4.27E-03	1.59E-07
25	6.58E-03	3.16E-05	1.96E-03	2.39E-03	6.26E-03	7.41E-07
50	9.97E-03	2.50E-04	3.86E-03	4.20E-03	9.81E-03	1.99E-06
75	1.55E-02	4.41E-04	7.49E-03	7.59E-03	1.53E-02	3.51E-06
90	2.55E-02	6.28E-04	1.41E-02	1.30E-02	2.48E-02	5.75E-06
95	3.25E-02	7.87E-04	2.08E-02	1.80E-02	3.22E-02	8.77E-06
99	4.57E-02	1.17E-03	3.45E-02	2.96E-02	4.55E-02	4.04E-05
Child, Age 6						
1	8.28E-04	0[a]	2.25E-04	9.93E-05	6.69E-04	1.67E-09
5	1.22E-03	0[a]	4.19E-04	2.06E-04	1.13E-03	2.82E-08
10	1.51E-03	0[a]	5.63E-04	2.89E-04	1.37E-03	8.16E-08
25	2.23E-03	9.37E-06	1.00E-03	5.46E-04	2.09E-03	3.09E-07
50	3.61E-03	2.70E-05	1.95E-03	9.64E-04	3.50E-03	1.01E-06
75	5.86E-03	1.91E-04	3.71E-03	1.96E-03	5.76E-03	2.24E-06
90	8.61E-03	2.99E-04	6.36E-03	3.40E-03	8.53E-03	3.79E-06
95	1.08E-02	3.74E-04	8.46E-03	4.84E-03	1.06E-02	5.04E-06
99	1.72E-02	5.15E-04	1.57E-02	7.25E-03	1.72E-02	7.41E-06

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.





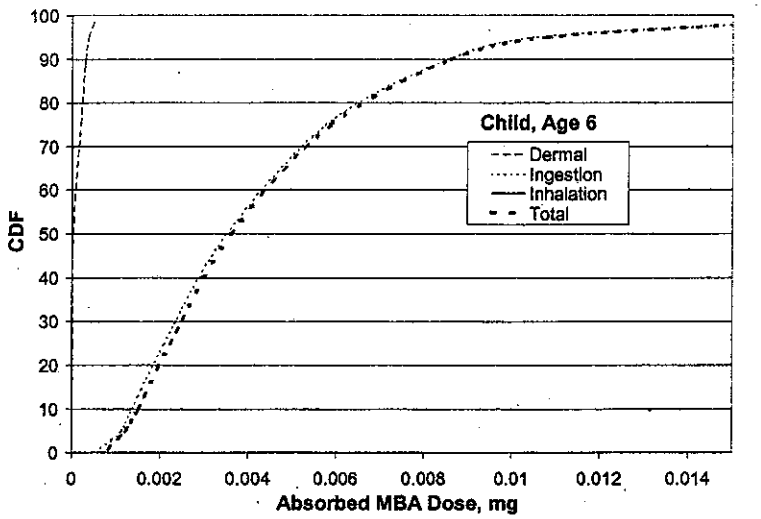


Figure 41. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed MBA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

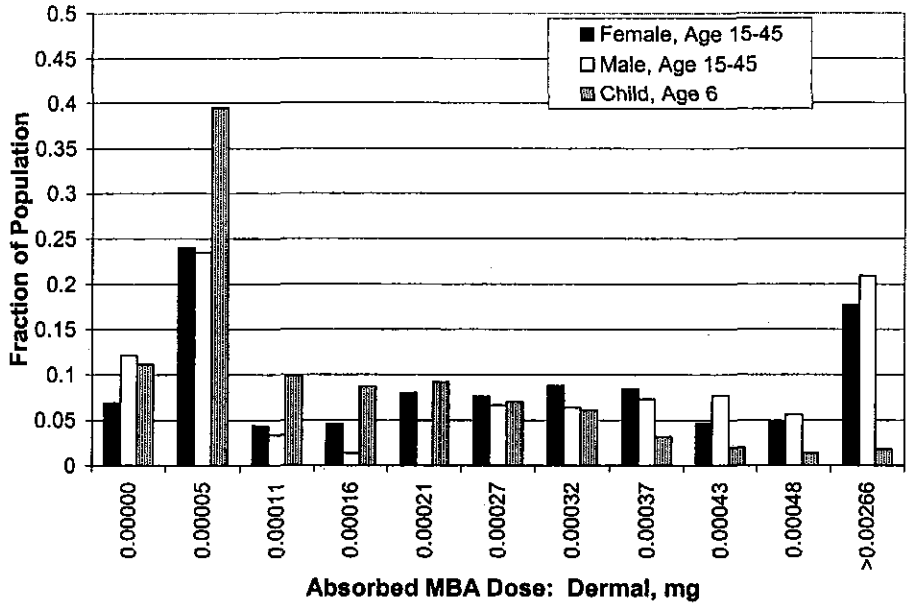


Figure 42. Histogram for Absorbed Dermal MBA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

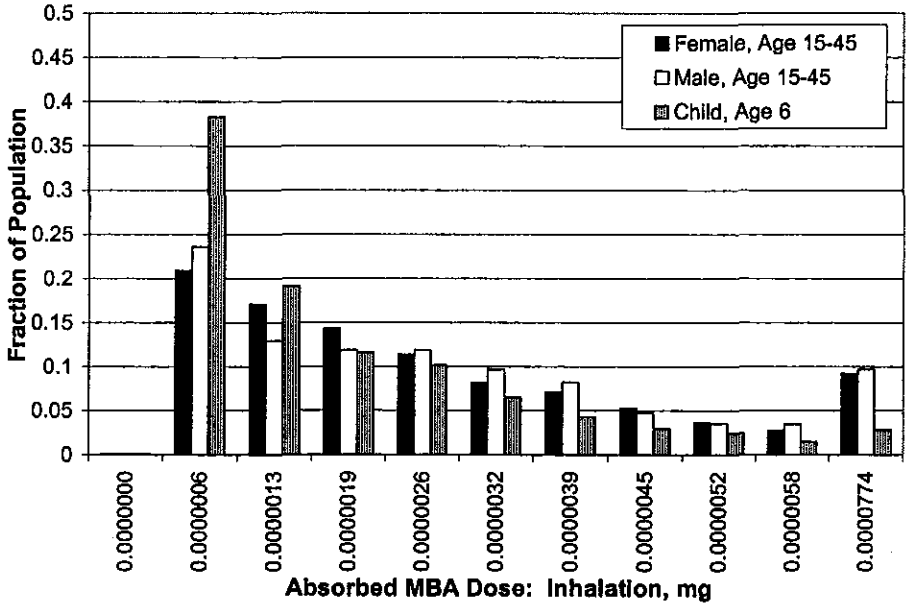


Figure 43. Histogram for Absorbed Inhalation MBA Dose for Females, Males and Children.

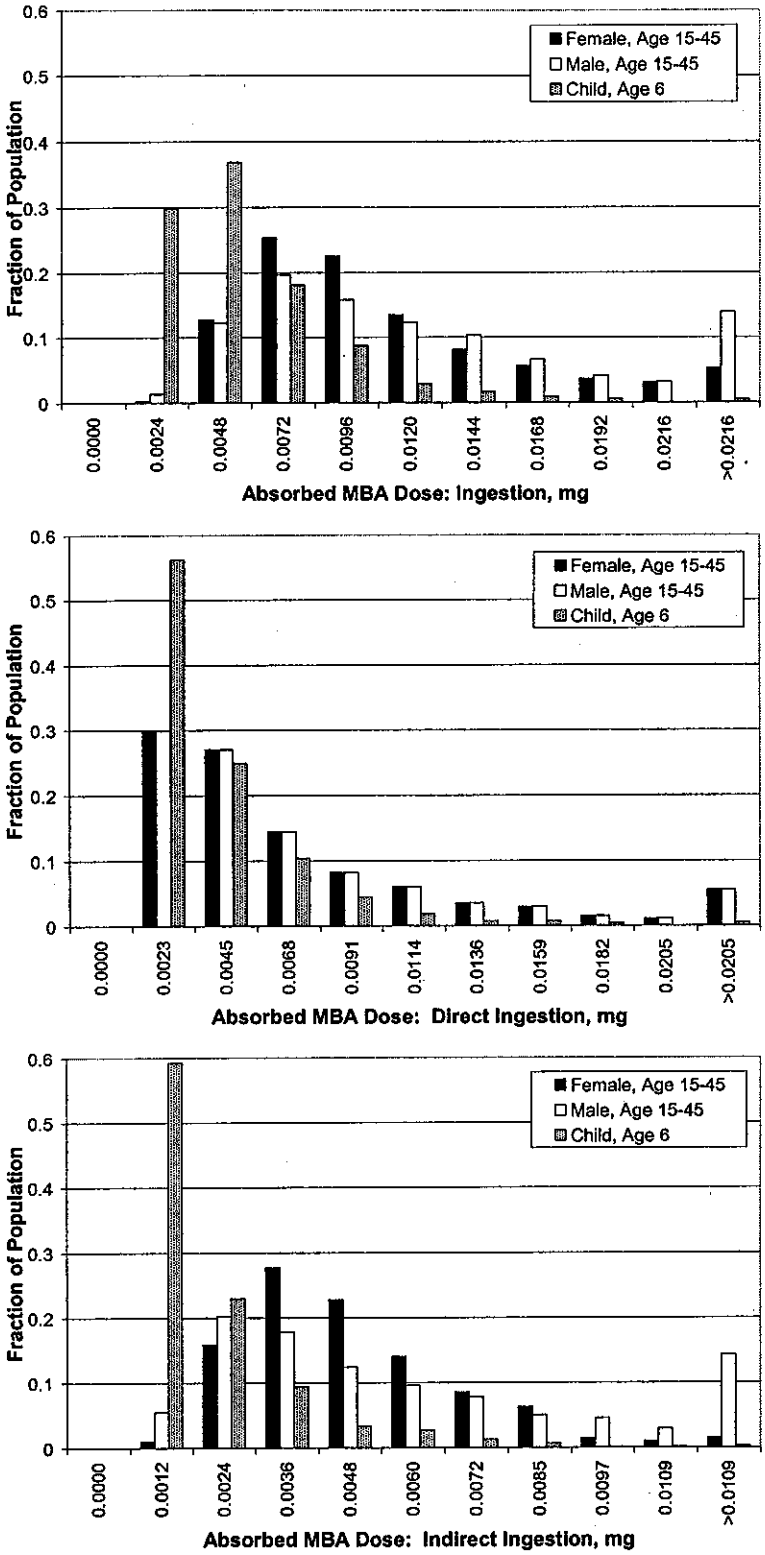


Figure 44. Histograms for the Absorbed MBA Ingestion Dose for Females, Males and Children.

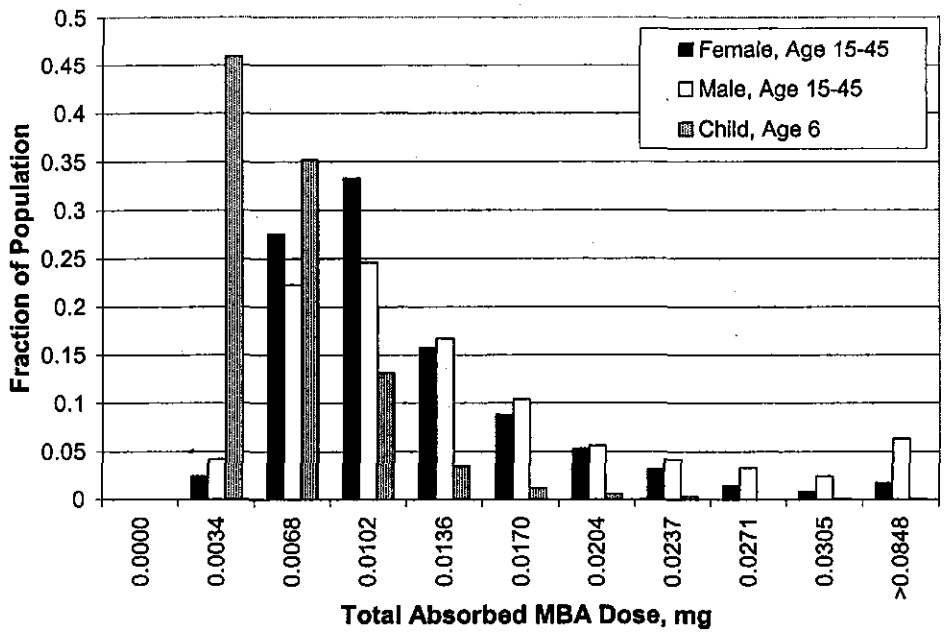


Figure 45. Histogram for the Total Absorbed MBA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.9 Uptake Results for DBA

The following Table 63 presents the resultant absorbed dose of DBA from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 46 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of DBA and Figures 47, 48, and 49 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 50 presents the total absorbed DBA dose.

Table 63. DBA Absorbed Dose Results

	DBA Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	1.28E-03	0[a]	2.15E-04	5.32E-04	1.20E-03	6.58E-10
5	1.69E-03	0[a]	3.81E-04	7.49E-04	1.58E-03	1.26E-08
10	2.02E-03	7.20E-06	5.10E-04	8.70E-04	1.91E-03	4.44E-08
25	2.71E-03	1.72E-05	8.72E-04	1.22E-03	2.57E-03	1.77E-07
50	3.76E-03	1.06E-04	1.61E-03	1.67E-03	3.66E-03	4.33E-07
75	5.33E-03	1.82E-04	3.14E-03	2.33E-03	5.25E-03	8.74E-07
90	7.91E-03	2.92E-04	5.73E-03	3.13E-03	7.79E-03	1.44E-06
95	9.54E-03	3.66E-04	7.27E-03	3.51E-03	9.45E-03	1.97E-06
99	1.92E-02	5.43E-04	1.76E-02	4.93E-03	1.91E-02	1.24E-05
Male, Age 15-45						
1	1.08E-03	0[a]	1.59E-04	2.69E-04	9.51E-04	7.96E-10
5	1.55E-03	0[a]	3.22E-04	4.95E-04	1.45E-03	1.29E-08
10	1.93E-03	0[a]	4.44E-04	6.41E-04	1.84E-03	3.50E-08
25	2.84E-03	1.44E-05	8.43E-04	1.03E-03	2.69E-03	1.65E-07
50	4.29E-03	1.14E-04	1.66E-03	1.81E-03	4.22E-03	5.04E-07
75	6.69E-03	2.03E-04	3.22E-03	3.26E-03	6.59E-03	9.07E-07
90	1.10E-02	2.86E-04	6.05E-03	5.58E-03	1.07E-02	1.49E-06
95	1.40E-02	3.63E-04	8.96E-03	7.73E-03	1.39E-02	2.23E-06
99	1.97E-02	5.46E-04	1.48E-02	1.27E-02	1.96E-02	1.04E-05
Child, Age 6						
1	3.56E-04	0[a]	9.68E-05	4.27E-05	2.88E-04	3.65E-10
5	5.23E-04	0[a]	1.80E-04	8.87E-05	4.85E-04	6.26E-09
10	6.51E-04	0[a]	2.42E-04	1.24E-04	5.90E-04	1.72E-08
25	9.60E-04	4.26E-06	4.30E-04	2.35E-04	9.01E-04	6.56E-08
50	1.56E-03	1.22E-05	8.36E-04	4.14E-04	1.51E-03	2.37E-07
75	2.52E-03	8.75E-05	1.60E-03	8.41E-04	2.47E-03	5.59E-07
90	3.71E-03	1.37E-04	2.74E-03	1.46E-03	3.67E-03	9.78E-07
95	4.65E-03	1.72E-04	3.64E-03	2.08E-03	4.55E-03	1.28E-06
99	7.38E-03	2.38E-04	6.75E-03	3.12E-03	7.38E-03	2.07E-06

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.

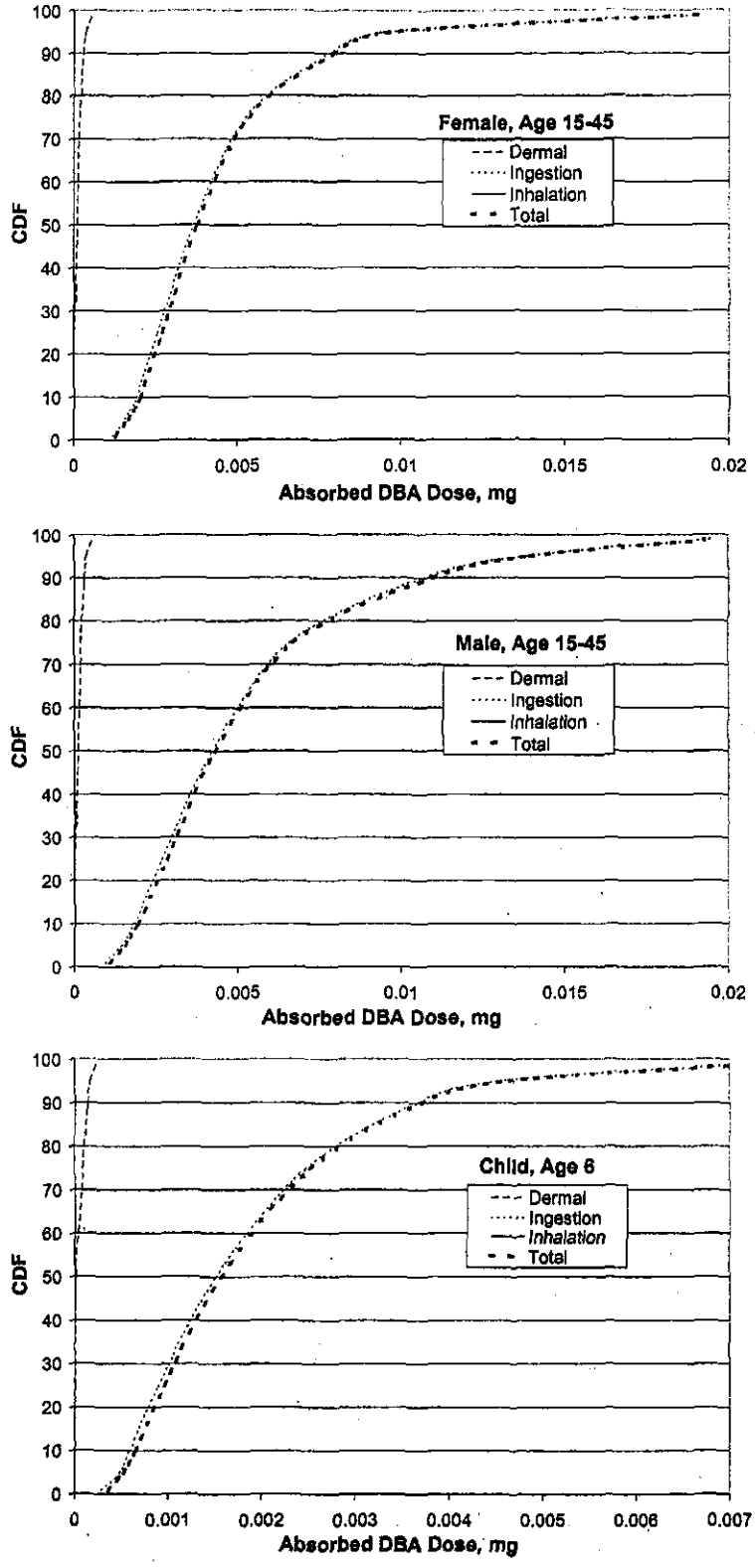


Figure 46. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed DBA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

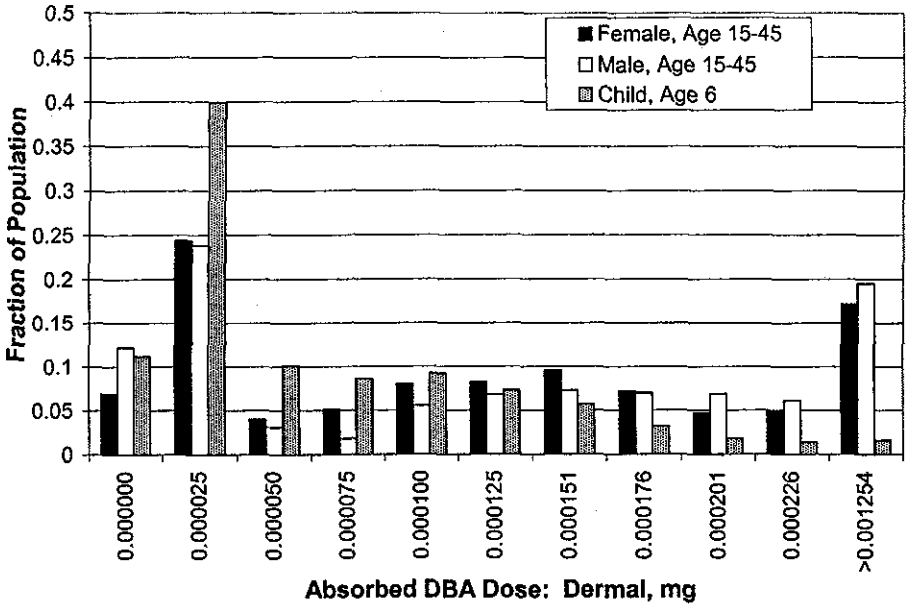


Figure 47. Histogram for Absorbed Dermal DBA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

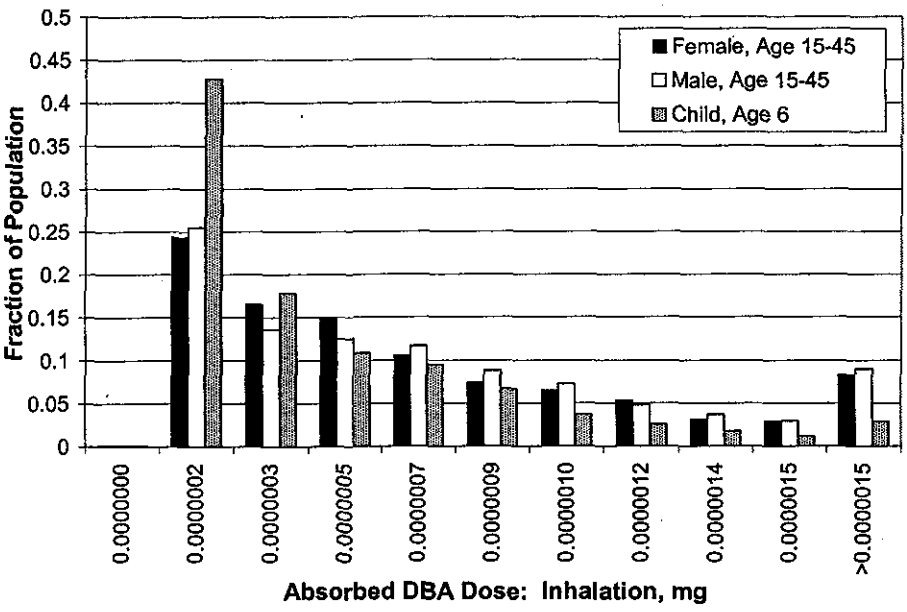
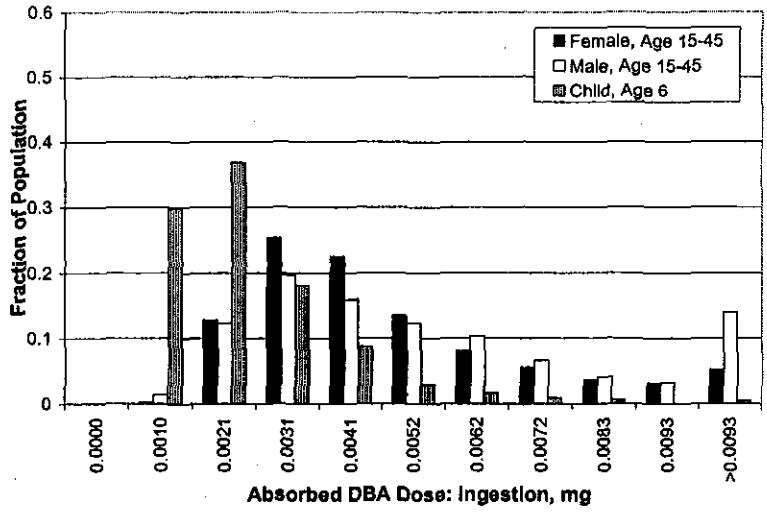
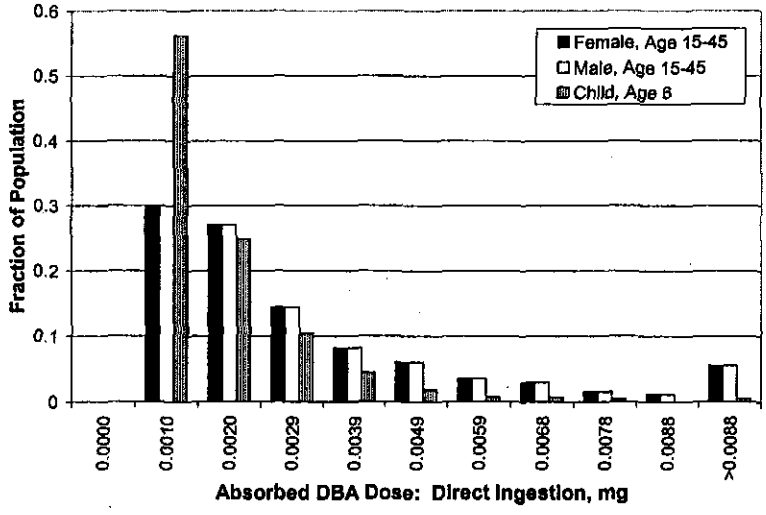


Figure 48. Histogram for Absorbed Inhalation DBA Dose for Females, Males and Children.





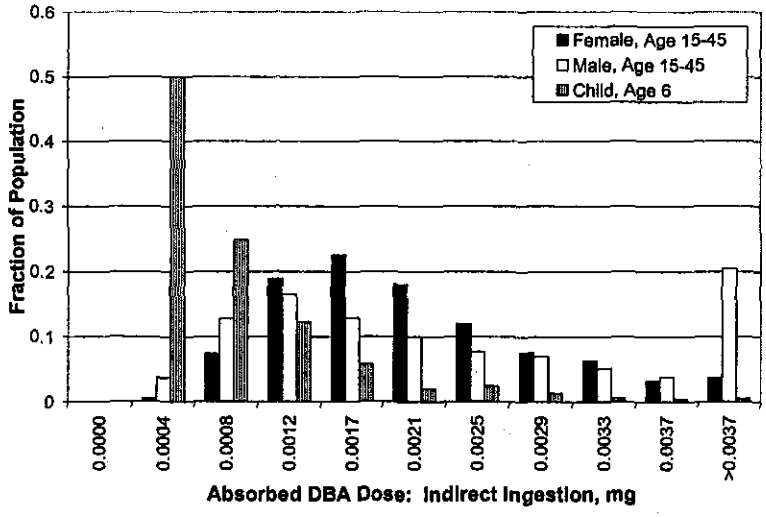


Figure 49. Histograms for the Absorbed DBA Ingestion Dose for Females, Males and Children.

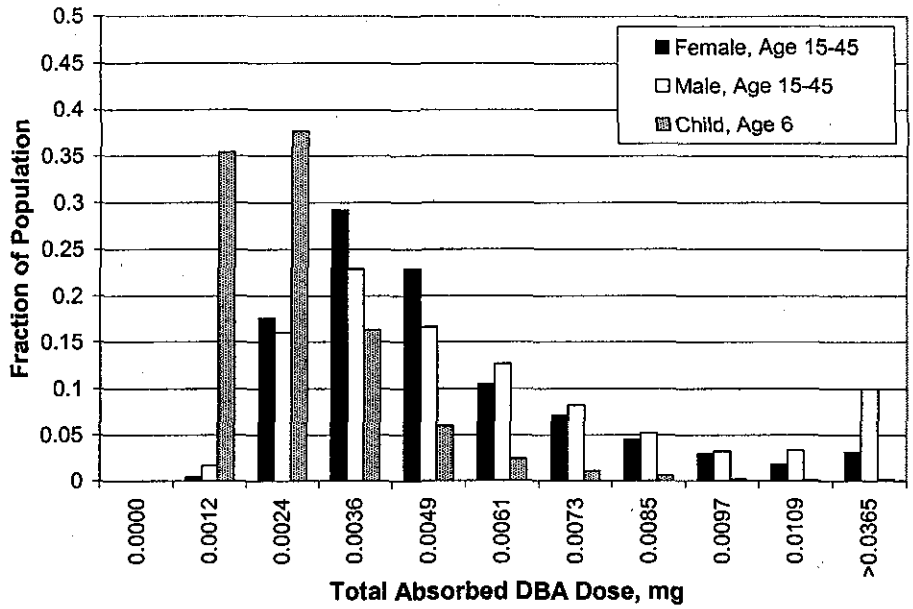


Figure 50. Histogram for the Total Absorbed DBA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.10 Uptake Results for BCA

The following Table 64 presents the resultant absorbed dose of BCA from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 51 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of BCA and Figures 52, 53, and 54 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 55 presents the total absorbed BCA dose.

Table 64. BCA Absorbed Dose Results

	BCA Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	2.71E-03	0[a]	4.54E-04	1.13E-03	2.54E-03	3.93E-09
5	3.56E-03	0[a]	8.06E-04	1.59E-03	3.35E-03	7.29E-08
10	4.28E-03	1.49E-05	1.08E-03	1.84E-03	4.05E-03	2.68E-07
25	5.74E-03	3.54E-05	1.84E-03	2.57E-03	5.44E-03	9.27E-07
50	7.95E-03	2.18E-04	3.40E-03	3.54E-03	7.74E-03	2.09E-06
75	1.13E-02	3.74E-04	6.65E-03	4.92E-03	1.11E-02	4.28E-06
90	1.67E-02	5.97E-04	1.21E-02	6.62E-03	1.65E-02	7.00E-06
95	2.02E-02	7.45E-04	1.54E-02	7.43E-03	2.00E-02	1.04E-05
99	4.05E-02	1.11E-03	3.73E-02	1.04E-02	4.05E-02	6.61E-05
Male, Age 15-45						
1	2.28E-03	0[a]	3.36E-04	5.69E-04	2.01E-03	4.31E-09
5	3.28E-03	0[a]	6.81E-04	1.05E-03	3.08E-03	7.89E-08
10	4.07E-03	0[a]	9.39E-04	1.36E-03	3.89E-03	2.04E-07
25	6.00E-03	2.97E-05	1.78E-03	2.17E-03	5.70E-03	8.32E-07
50	9.08E-03	2.35E-04	3.51E-03	3.82E-03	8.93E-03	2.35E-06
75	1.41E-02	4.16E-04	6.82E-03	6.90E-03	1.39E-02	4.31E-06
90	2.32E-02	5.89E-04	1.28E-02	1.18E-02	2.26E-02	7.42E-06
95	2.95E-02	7.44E-04	1.90E-02	1.63E-02	2.93E-02	1.16E-05
99	4.16E-02	1.11E-03	3.14E-02	2.69E-02	4.14E-02	5.20E-05
Child, Age 6						
1	7.54E-04	0[a]	2.05E-04	9.04E-05	6.09E-04	2.26E-09
5	1.11E-03	0[a]	3.81E-04	1.88E-04	1.03E-03	3.55E-08
10	1.38E-03	0[a]	5.13E-04	2.63E-04	1.25E-03	1.03E-07
25	2.03E-03	8.79E-06	9.10E-04	4.97E-04	1.91E-03	3.94E-07
50	3.29E-03	2.53E-05	1.77E-03	8.77E-04	3.19E-03	1.26E-06
75	5.34E-03	1.80E-04	3.38E-03	1.78E-03	5.24E-03	2.97E-06
90	7.84E-03	2.82E-04	5.79E-03	3.09E-03	7.76E-03	5.27E-06
95	9.85E-03	3.53E-04	7.70E-03	4.41E-03	9.62E-03	6.89E-06
99	1.56E-02	4.88E-04	1.43E-02	6.59E-03	1.56E-02	1.04E-05

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.

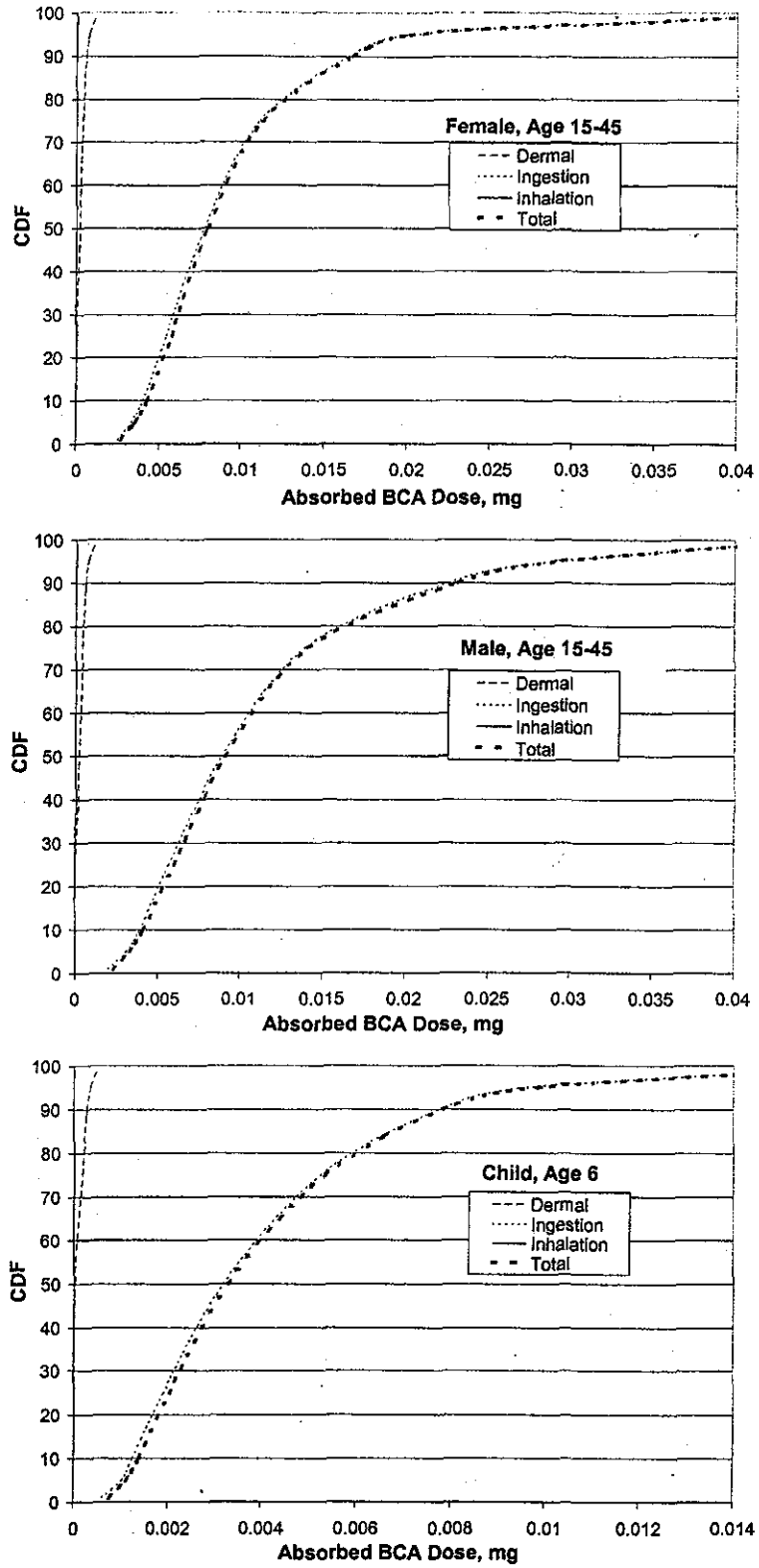


Figure 51. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed BCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

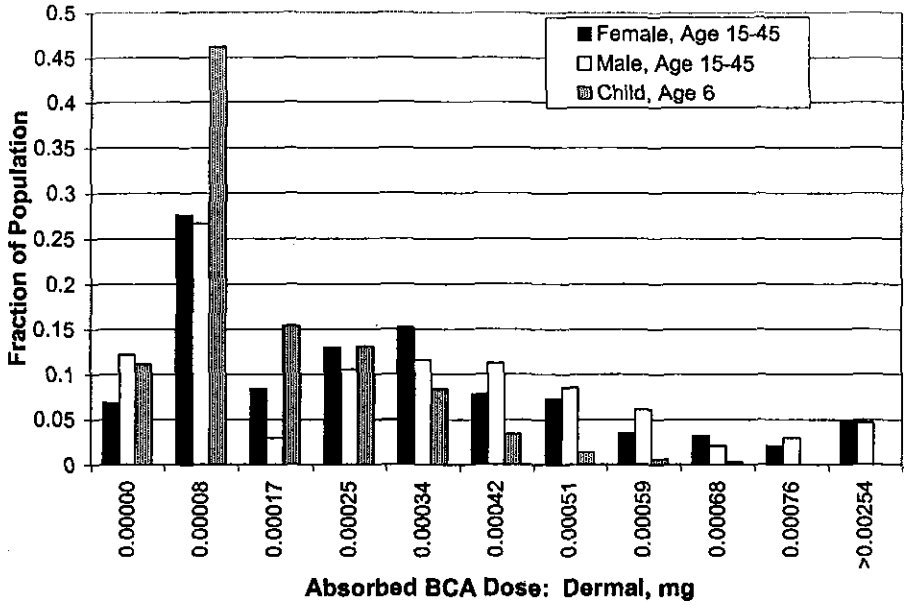


Figure 52. Histogram for Absorbed Dermal BCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

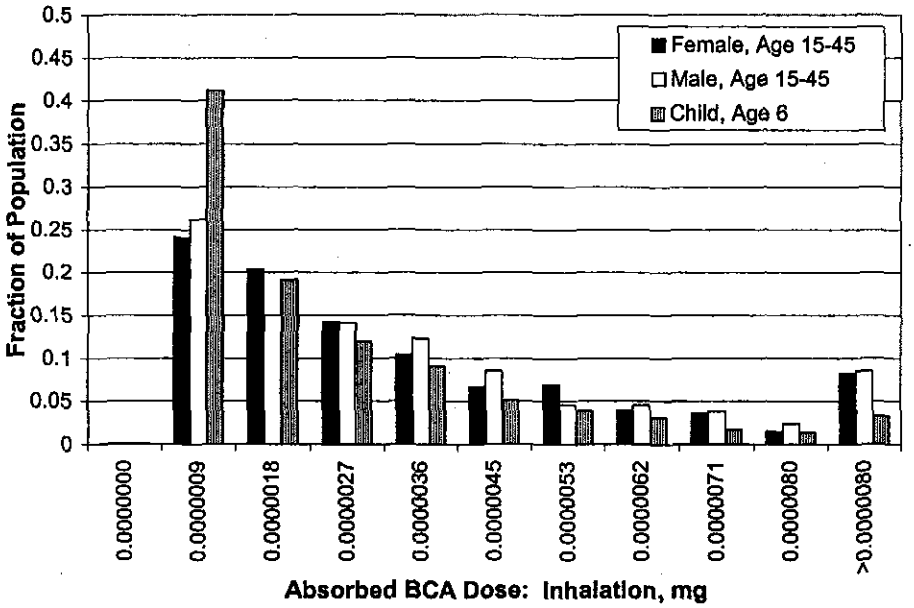


Figure 53. Histogram for Absorbed Inhalation BCA Dose for Females, Males and Children.

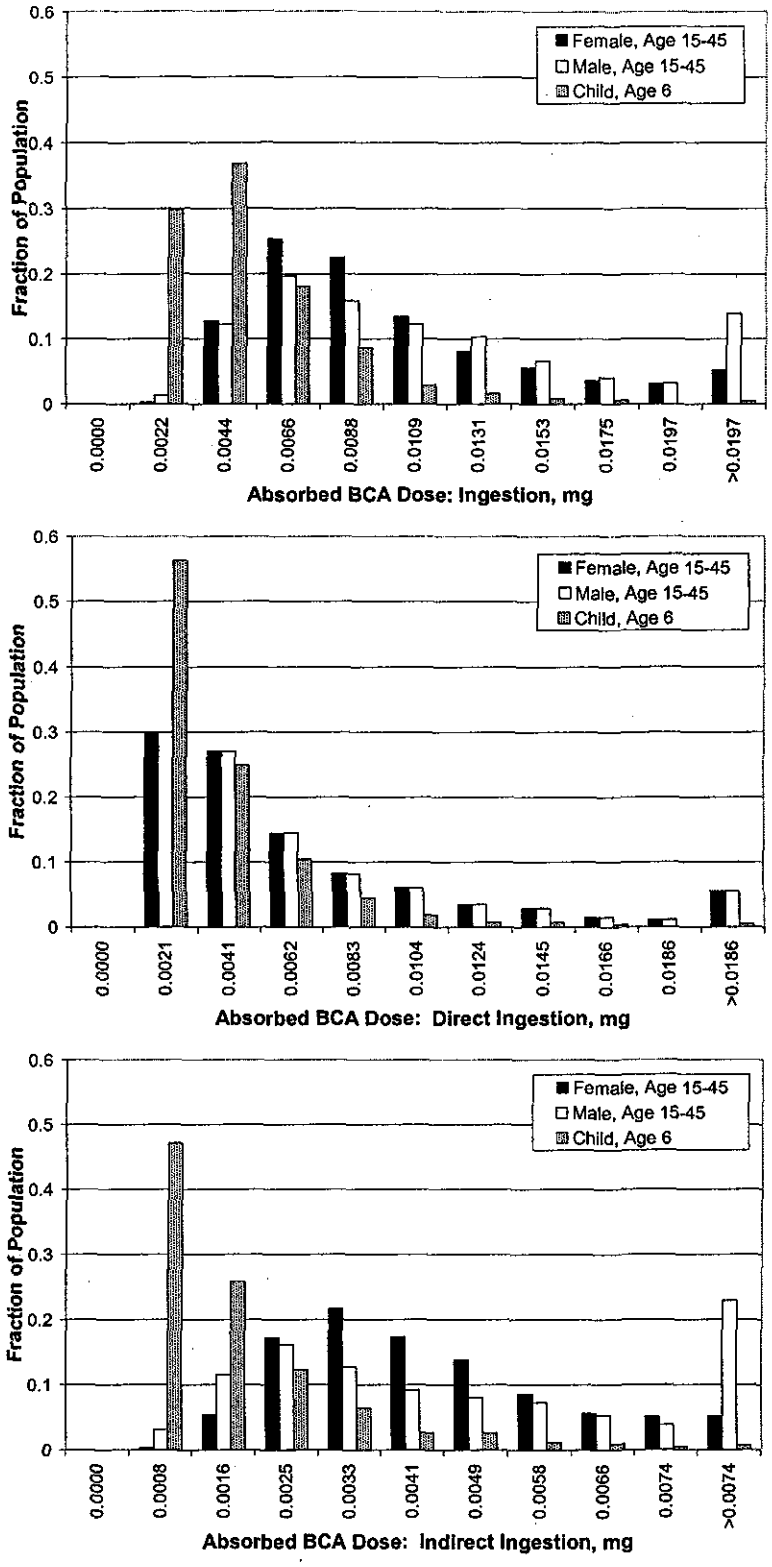


Figure 54. Histograms for the Absorbed BCA Ingestion Dose for Females, Males and Children.

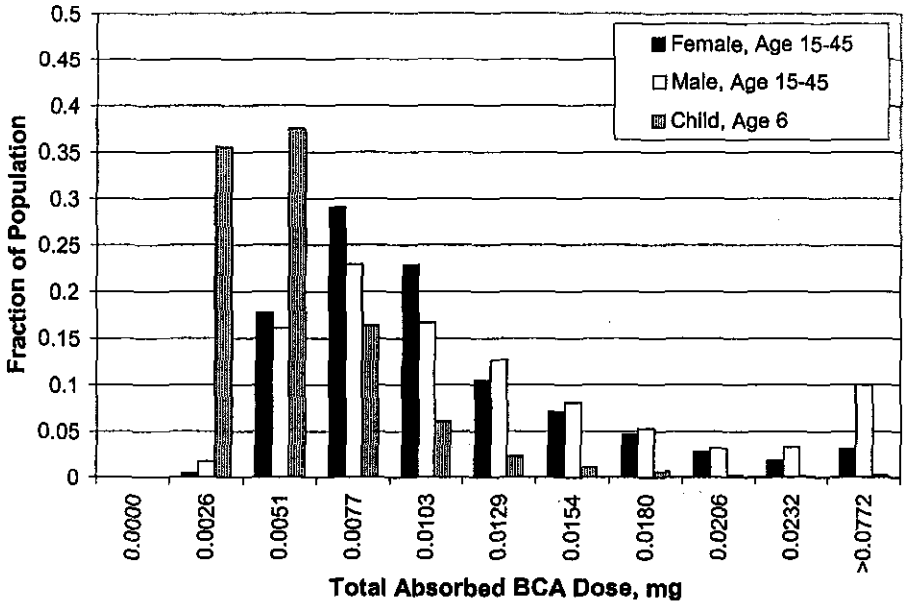


Figure 55. Histogram for the Total Absorbed BCA Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.11 Uptake Results for DCAN

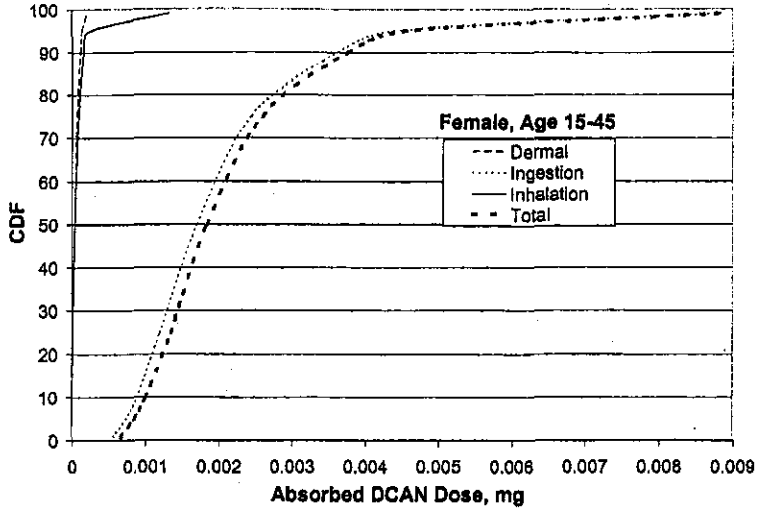
The following Table 65 presents the resultant absorbed dose of DCAN from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 56 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of DCAN and Figures 57, 58, and 59 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 60 presents the total absorbed DCAN dose.

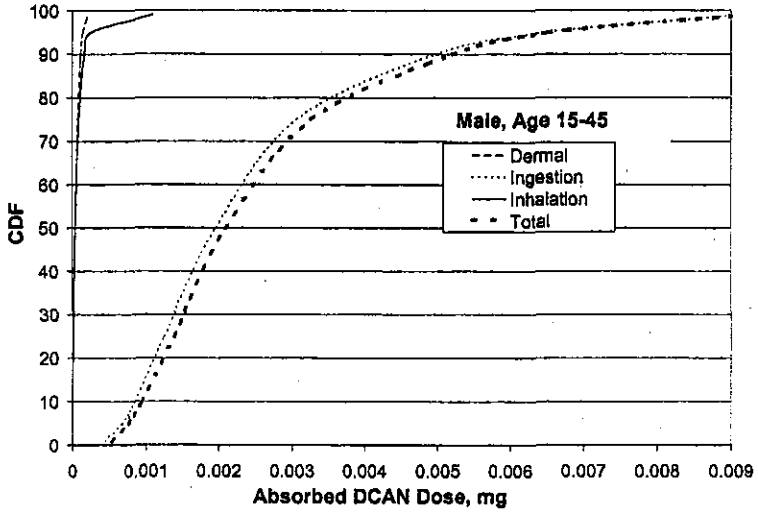
Table 65. DCAN Absorbed Dose Results

	DCAN Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	6.56E-04	0[a]	9.98E-05	2.47E-04	5.58E-04	1.07E-07
5	8.52E-04	0[a]	1.77E-04	3.48E-04	7.36E-04	2.32E-06
10	1.00E-03	2.85E-06	2.37E-04	4.05E-04	8.91E-04	6.86E-06
25	1.34E-03	6.78E-06	4.05E-04	5.65E-04	1.20E-03	1.81E-05
50	1.83E-03	4.08E-05	7.48E-04	7.79E-04	1.70E-03	4.39E-05
75	2.59E-03	7.07E-05	1.46E-03	1.08E-03	2.44E-03	9.00E-05
90	3.76E-03	1.10E-04	2.66E-03	1.46E-03	3.62E-03	1.58E-04
95	4.53E-03	1.37E-04	3.38E-03	1.63E-03	4.40E-03	2.48E-04
99	8.91E-03	1.99E-04	8.20E-03	2.29E-03	8.91E-03	1.32E-03
Male, Age 15-45						
1	5.31E-04	0[a]	7.38E-05	1.25E-04	4.42E-04	9.34E-08
5	7.61E-04	0[a]	1.50E-04	2.30E-04	6.76E-04	2.26E-06
10	9.47E-04	0[a]	2.06E-04	2.98E-04	8.54E-04	5.22E-06
25	1.38E-03	5.68E-06	3.92E-04	4.78E-04	1.25E-03	1.51E-05
50	2.09E-03	4.46E-05	7.72E-04	8.41E-04	1.96E-03	4.26E-05
75	3.26E-03	7.75E-05	1.50E-03	1.52E-03	3.07E-03	9.25E-05
90	5.20E-03	1.11E-04	2.81E-03	2.60E-03	4.97E-03	1.62E-04
95	6.51E-03	1.38E-04	4.17E-03	3.59E-03	6.45E-03	2.49E-04
99	9.15E-03	2.02E-04	6.90E-03	5.92E-03	9.10E-03	1.09E-03
Child, Age 6						
1	1.93E-04	0[a]	4.50E-05	1.99E-05	1.34E-04	6.30E-08
5	2.75E-04	0[a]	8.37E-05	4.13E-05	2.26E-04	9.64E-07
10	3.38E-04	0[a]	1.13E-04	5.78E-05	2.74E-04	2.40E-06
25	4.91E-04	1.68E-06	2.00E-04	1.09E-04	4.19E-04	9.20E-06
50	7.72E-04	4.84E-06	3.89E-04	1.93E-04	7.01E-04	2.57E-05
75	1.22E-03	3.36E-05	7.42E-04	3.91E-04	1.15E-03	6.42E-05
90	1.77E-03	5.18E-05	1.27E-03	6.80E-04	1.71E-03	1.25E-04
95	2.26E-03	6.47E-05	1.69E-03	9.69E-04	2.11E-03	1.63E-04
99	3.52E-03	8.88E-05	3.14E-03	1.45E-03	3.43E-03	2.55E-04

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.





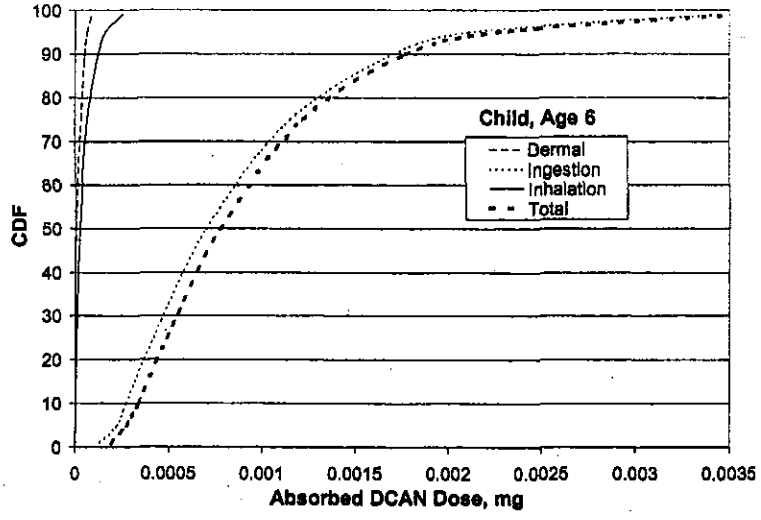


Figure 56. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed DCAN Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

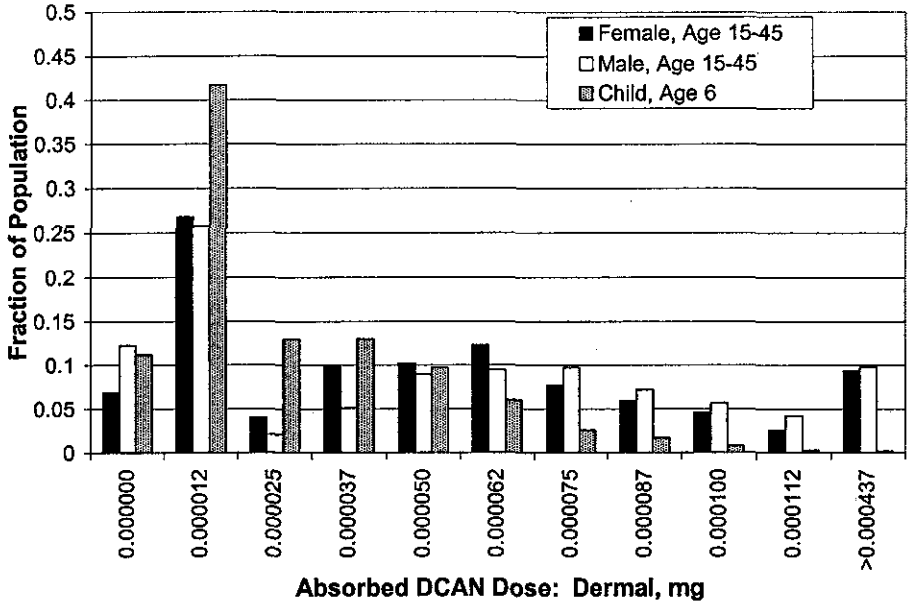


Figure 57. Histogram for Absorbed Dermal DCAN Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

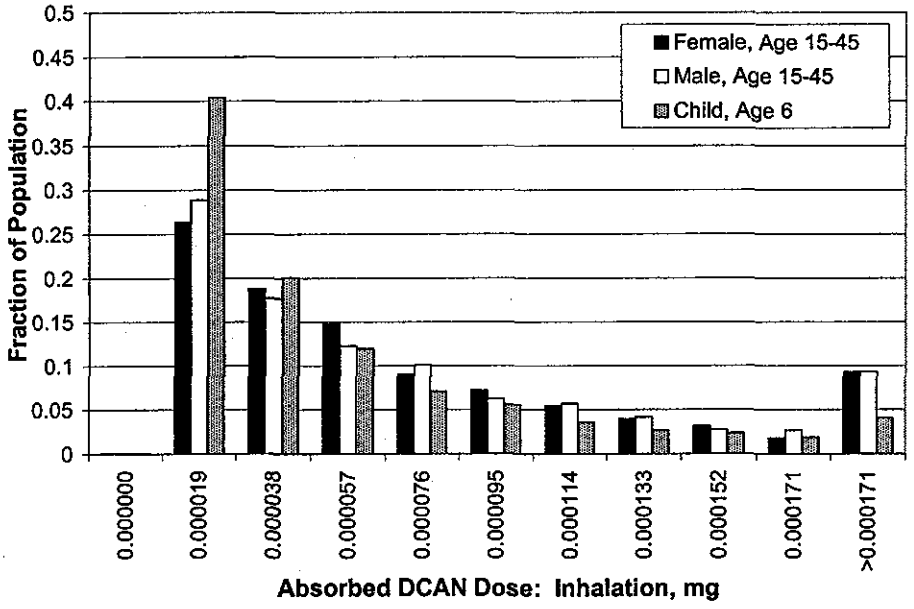
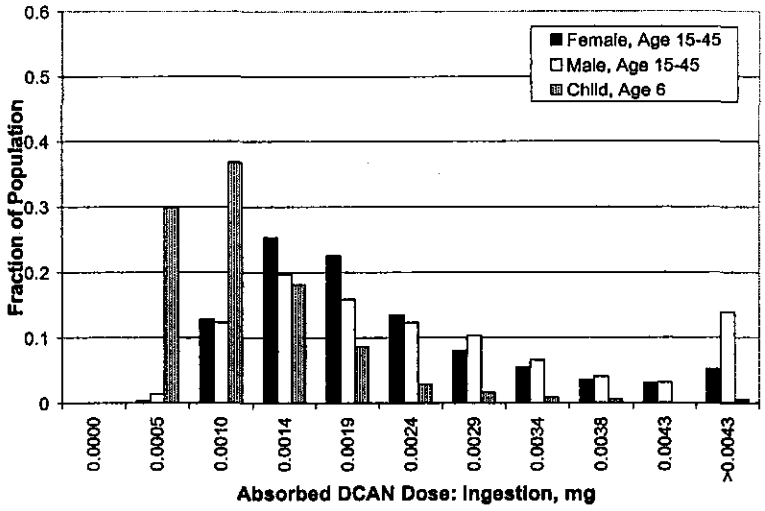
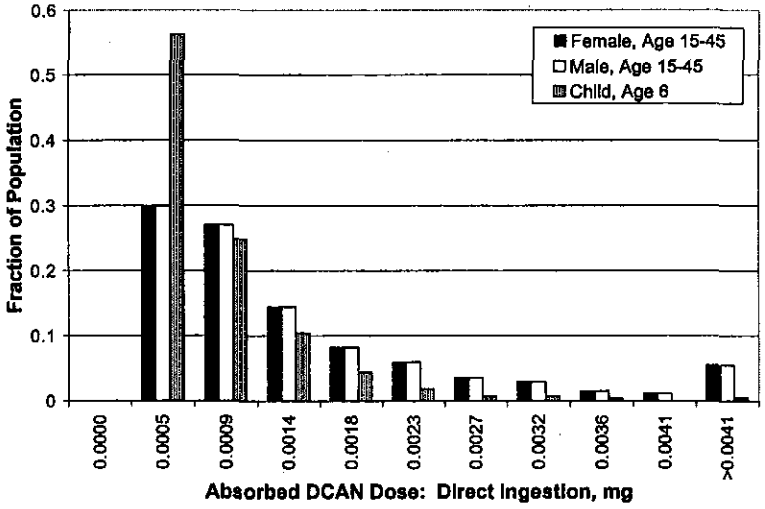


Figure 58. Histogram for Absorbed Inhalation DCAN Dose for Females, Males and Children.





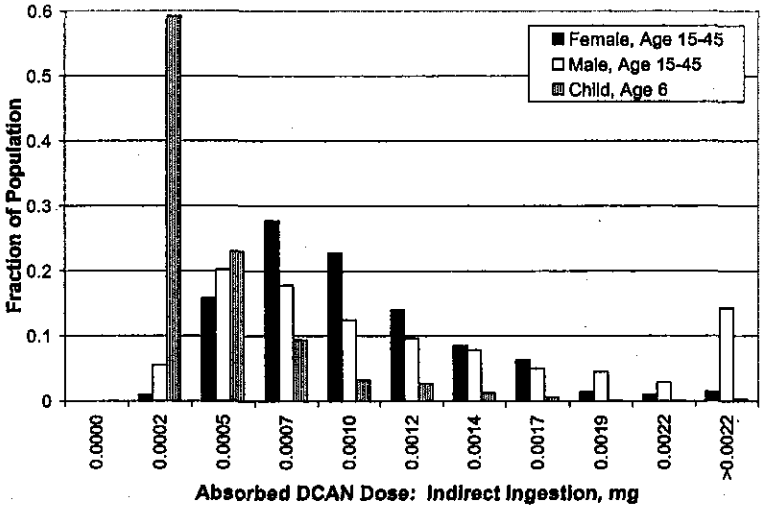


Figure 59. Histograms for the Absorbed DCAN Ingestion Dose for Females, Males and Children.

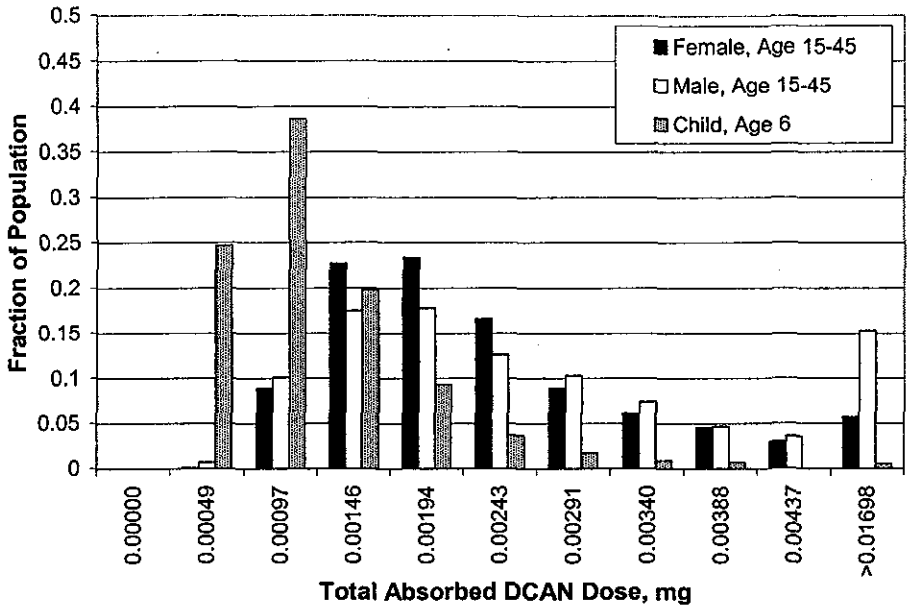


Figure 60. Histogram for the Total Absorbed DCAN Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.12 Uptake Results for TCAN

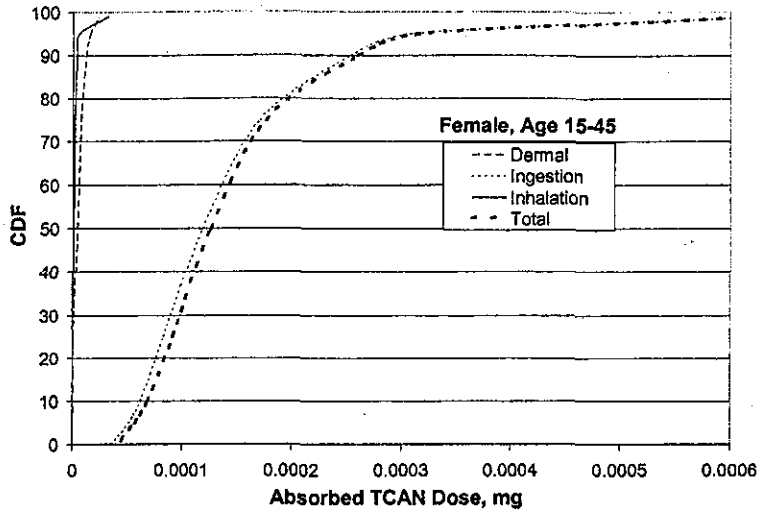
The following Table 66 presents the resultant absorbed dose of TCAN from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 61 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of TCAN and Figures 62, 63, and 64 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 65 presents the total absorbed TCAN dose.

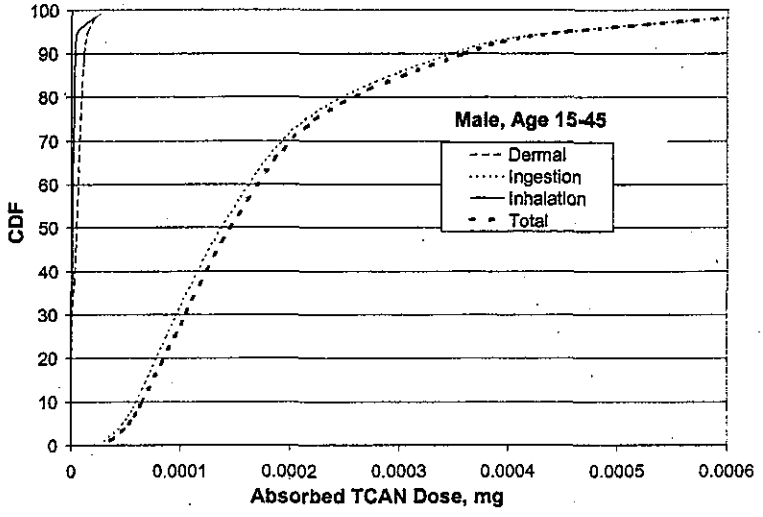
Table 66. TCAN Absorbed Dose Results

	TCAN Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	4.43E-05	0[a]	6.99E-06	1.73E-05	3.90E-05	2.50E-09
5	5.71E-05	0[a]	1.24E-05	2.44E-05	5.15E-05	4.73E-08
10	6.89E-05	2.80E-07	1.66E-05	2.83E-05	6.23E-05	1.48E-07
25	9.19E-05	6.66E-07	2.84E-05	3.96E-05	8.37E-05	4.01E-07
50	1.26E-04	4.18E-06	5.23E-05	5.45E-05	1.19E-04	9.73E-07
75	1.76E-04	7.30E-06	1.02E-04	7.57E-05	1.71E-04	2.00E-06
90	2.60E-04	1.18E-05	1.86E-04	1.02E-04	2.54E-04	3.65E-06
95	3.13E-04	1.50E-05	2.37E-04	1.14E-04	3.08E-04	5.49E-06
99	6.24E-04	2.28E-05	5.74E-04	1.60E-04	6.23E-04	3.17E-05
Male, Age 15-45						
1	3.63E-05	0[a]	5.17E-06	8.76E-06	3.10E-05	2.09E-09
5	5.27E-05	0[a]	1.05E-05	1.61E-05	4.73E-05	4.67E-08
10	6.48E-05	0[a]	1.45E-05	2.09E-05	5.98E-05	1.13E-07
25	9.54E-05	5.58E-07	2.74E-05	3.35E-05	8.76E-05	3.34E-07
50	1.45E-04	4.47E-06	5.40E-05	5.88E-05	1.37E-04	1.00E-06
75	2.23E-04	8.17E-06	1.05E-04	1.06E-04	2.15E-04	2.16E-06
90	3.59E-04	1.16E-05	1.97E-04	1.82E-04	3.48E-04	3.74E-06
95	4.55E-04	1.49E-05	2.92E-04	2.52E-04	4.51E-04	5.69E-06
99	6.41E-04	2.27E-05	4.83E-04	4.14E-04	6.37E-04	2.54E-05
Child, Age 6						
1	1.28E-05	0[a]	3.15E-06	1.39E-06	9.37E-06	1.51E-09
5	1.82E-05	0[a]	5.86E-06	2.89E-06	1.58E-05	1.97E-08
10	2.26E-05	0[a]	7.88E-06	4.04E-06	1.92E-05	5.51E-08
25	3.25E-05	1.65E-07	1.40E-05	7.65E-06	2.93E-05	1.91E-07
50	5.20E-05	4.76E-07	2.72E-05	1.35E-05	4.91E-05	5.57E-07
75	8.39E-05	3.55E-06	5.20E-05	2.74E-05	8.06E-05	1.41E-06
90	1.22E-04	5.68E-06	8.91E-05	4.76E-05	1.19E-04	2.76E-06
95	1.54E-04	7.13E-06	1.18E-04	6.78E-05	1.48E-04	3.55E-06
99	2.42E-04	9.87E-06	2.20E-04	1.01E-04	2.40E-04	5.53E-06

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.





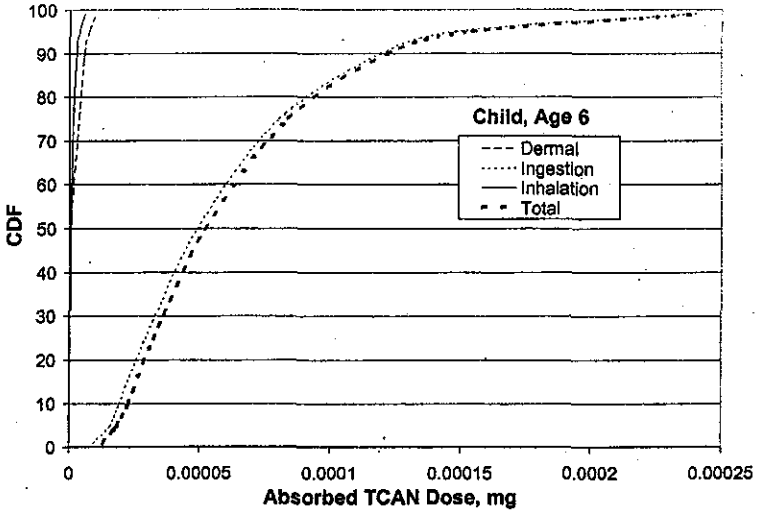


Figure 61. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed TCAN Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

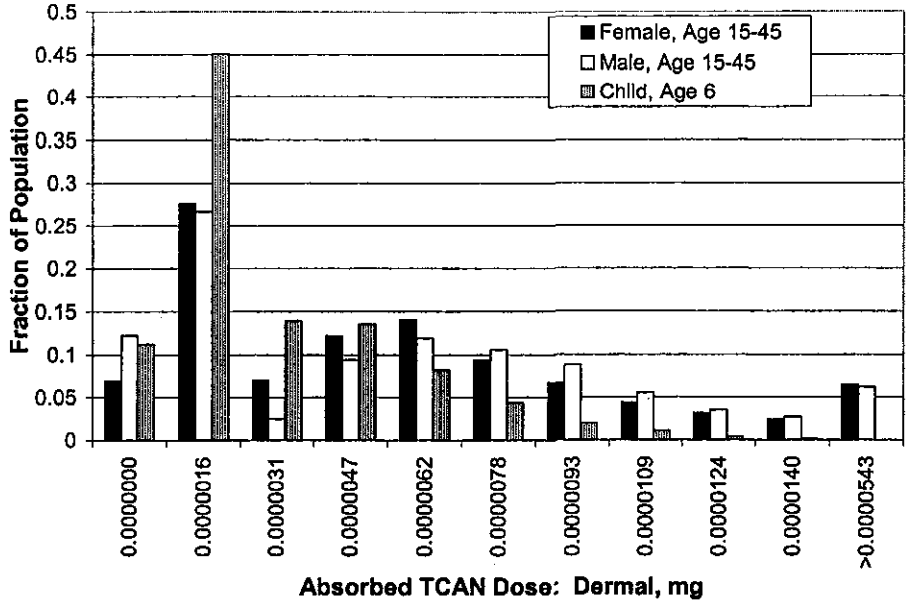


Figure 62. Histogram for Absorbed Dermal TCAN Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

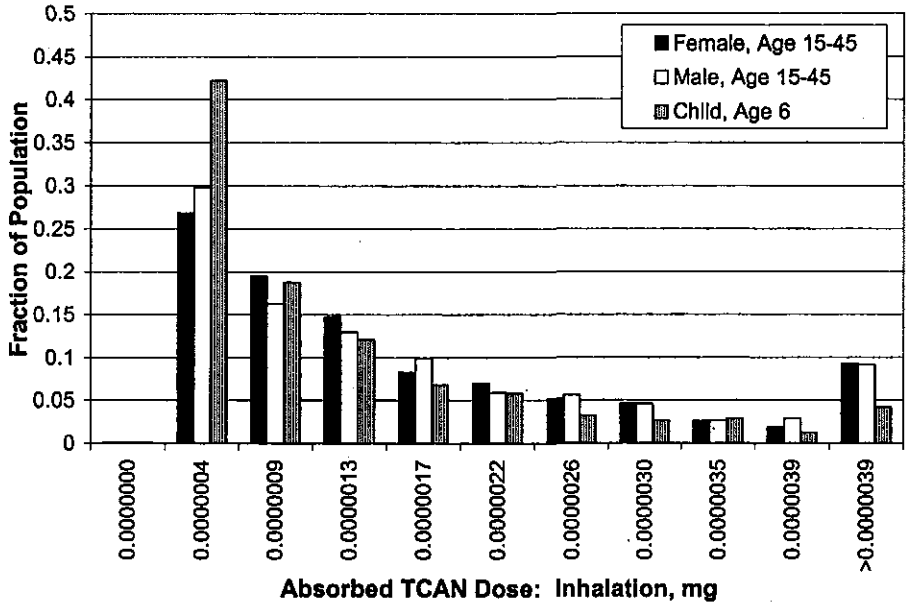


Figure 63. Histogram for Absorbed Inhalation TCAN Dose for Females, Males and Children.

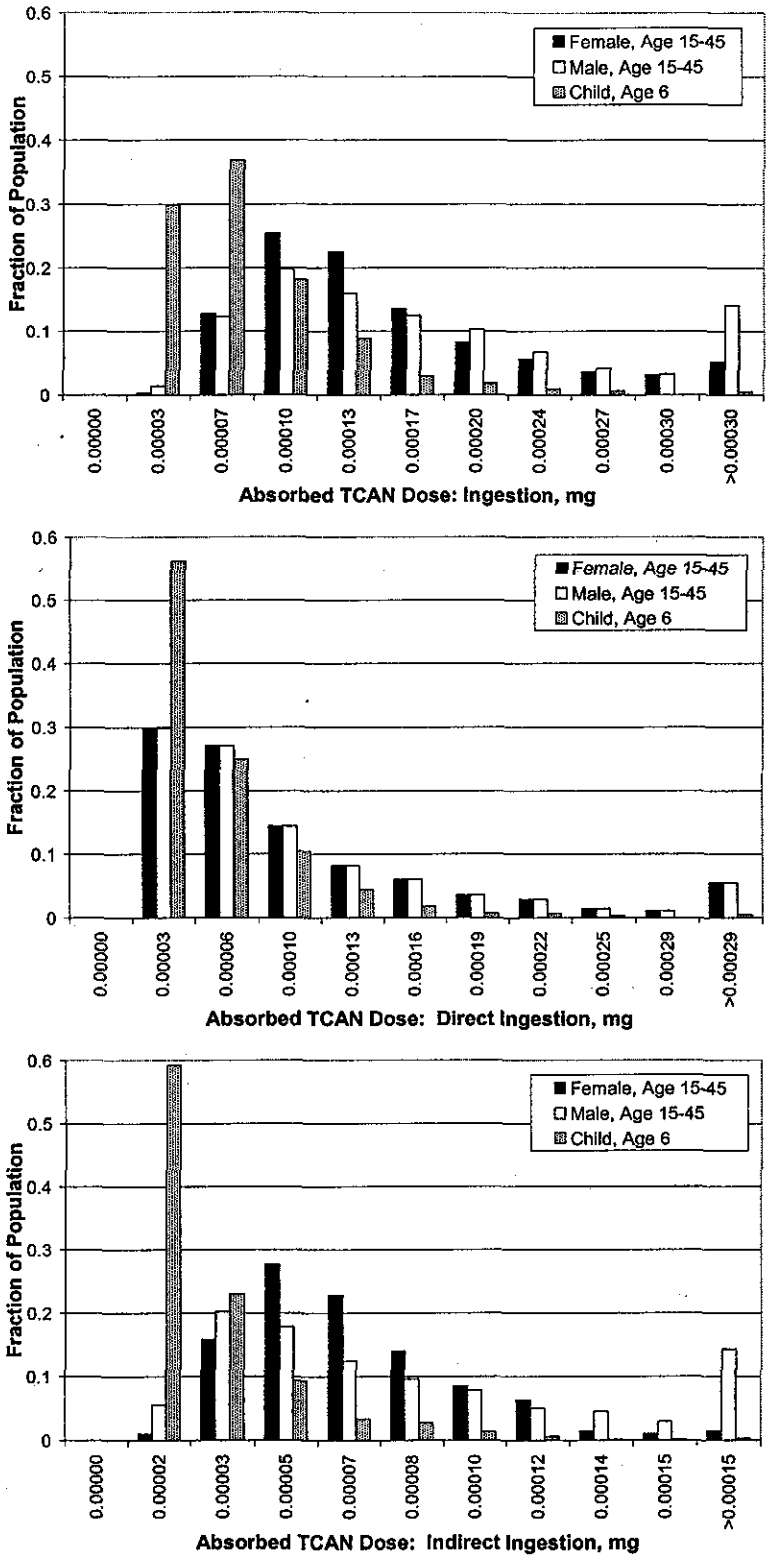


Figure 64. Histograms for the Absorbed TCAN Ingestion Dose for Females, Males and Children.

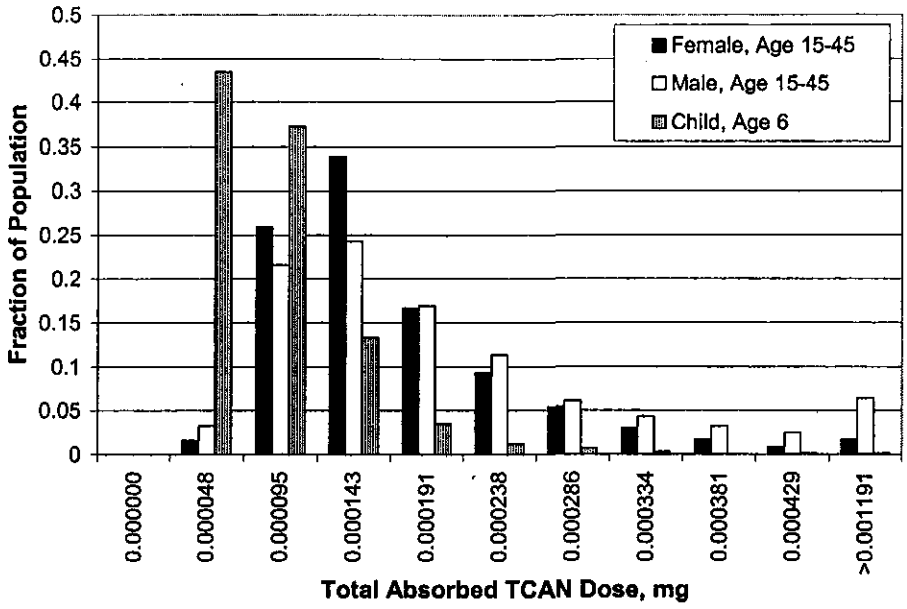


Figure 65. Histogram for the Total Absorbed TCAN Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.2.13 Uptake Results for DBAN

The following Table 67 presents the resultant absorbed dose of DBAN from the analysis of the dermal, ingestion and inhalation exposure routes for each of the population groups: female age 15-45, male age 15-45, and child age 6. Figure 66 presents the resultant cumulative distribution function plots for the analysis of absorbed dose of DBAN and Figures 67, 68, and 69 present the histograms for absorbed dermal dose, inhalation dose, and ingestion dose, respectively, for the female, male and child populations. Figure 70 presents the total absorbed DBAN dose.

Table 67. DBAN Absorbed Dose Results

	DBAN Absorbed Dose, mg					
Percentile	Total [b]	Dermal Total	Ingestion Direct	Ingestion Indirect	Ingestion Total	Inhalation Total
Female, Age 15-45						
1	2.45E-04	0 [a]	4.04E-05	1.00E-04	2.26E-04	4.37E-09
5	3.18E-04	0 [a]	7.17E-05	1.41E-04	2.98E-04	8.41E-08
10	3.82E-04	1.23E-06	9.61E-05	1.64E-04	3.61E-04	2.73E-07
25	5.11E-04	2.94E-06	1.64E-04	2.29E-04	4.84E-04	7.88E-07
50	7.09E-04	1.79E-05	3.03E-04	3.15E-04	6.89E-04	1.88E-06
75	1.00E-03	3.07E-05	5.92E-04	4.38E-04	9.89E-04	3.92E-06
90	1.49E-03	4.86E-05	1.08E-03	5.90E-04	1.47E-03	6.72E-06
95	1.80E-03	6.06E-05	1.37E-03	6.61E-04	1.78E-03	1.01E-05
99	3.61E-03	8.90E-05	3.32E-03	9.28E-04	3.61E-03	6.20E-05
Male, Age 15-45						
1	2.05E-04	0 [a]	2.99E-05	5.07E-05	1.79E-04	4.03E-09
5	2.92E-04	0 [a]	6.06E-05	9.32E-05	2.74E-04	8.56E-08
10	3.65E-04	0 [a]	8.36E-05	1.21E-04	3.46E-04	2.15E-07
25	5.36E-04	2.46E-06	1.59E-04	1.94E-04	5.07E-04	6.75E-07
50	8.13E-04	1.94E-05	3.12E-04	3.40E-04	7.94E-04	1.99E-06
75	1.26E-03	3.40E-05	6.07E-04	6.14E-04	1.24E-03	4.07E-06
90	2.06E-03	4.86E-05	1.14E-03	1.05E-03	2.01E-03	7.09E-06
95	2.63E-03	6.07E-05	1.69E-03	1.46E-03	2.61E-03	1.10E-05
99	3.70E-03	8.99E-05	2.80E-03	2.40E-03	3.69E-03	4.95E-05
Child, Age 6						
1	6.89E-05	0 [a]	1.82E-05	8.05E-06	5.42E-05	2.63E-09
5	9.94E-05	0 [a]	3.39E-05	1.67E-05	9.14E-05	3.50E-08
10	1.23E-04	0 [a]	4.56E-05	2.34E-05	1.11E-04	1.06E-07
25	1.82E-04	7.29E-07	8.10E-05	4.43E-05	1.70E-04	3.62E-07
50	2.94E-04	2.10E-06	1.58E-04	7.81E-05	2.84E-04	1.07E-06
75	4.76E-04	1.47E-05	3.01E-04	1.58E-04	4.66E-04	2.64E-06
90	6.97E-04	2.30E-05	5.15E-04	2.75E-04	6.91E-04	5.09E-06
95	8.76E-04	2.88E-05	6.85E-04	3.92E-04	8.56E-04	6.66E-06
99	1.39E-03	3.94E-05	1.27E-03	5.87E-04	1.39E-03	1.02E-05

a. The zeroes entered in the dermal category represent the portion of the population that has no dermal contact with the water supply during the simulated day. For the female (age 15-45) population group, 6.9% had no dermal contact. For the male (age 15-45) population group, 6.9% had no dermal contact. For the child (age 6) population group, 11.2% had no dermal contact.

b. The "Total" column gives the absorbed dose for the given percentile of the population for the sum of the three routes. It is not the sum of the totals for the three routes.

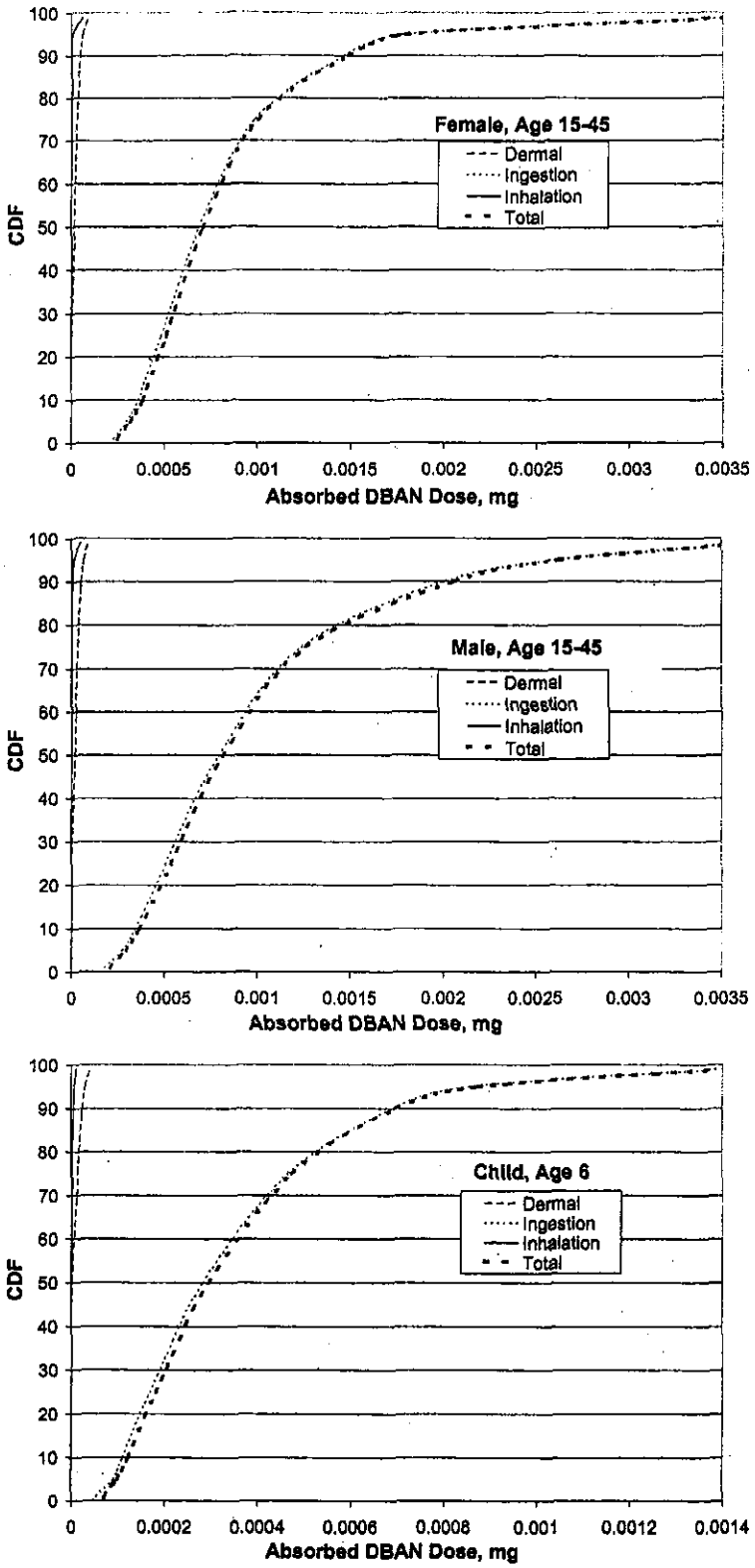


Figure 66. Cumulative Distribution Function for the Dermal, Ingestion, Inhalation, and Total Absorbed DBAN Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

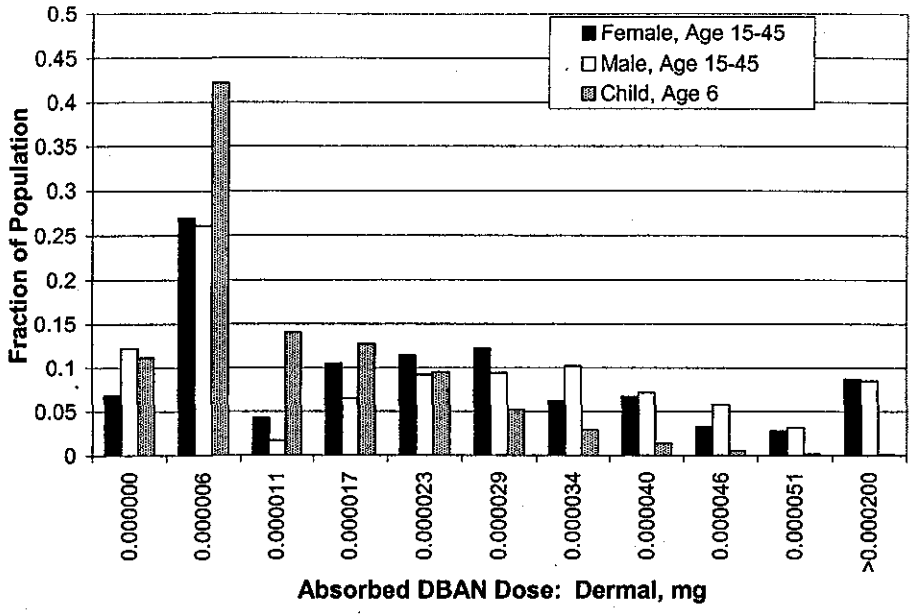


Figure 67. Histogram for Absorbed Dermal DBAN Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

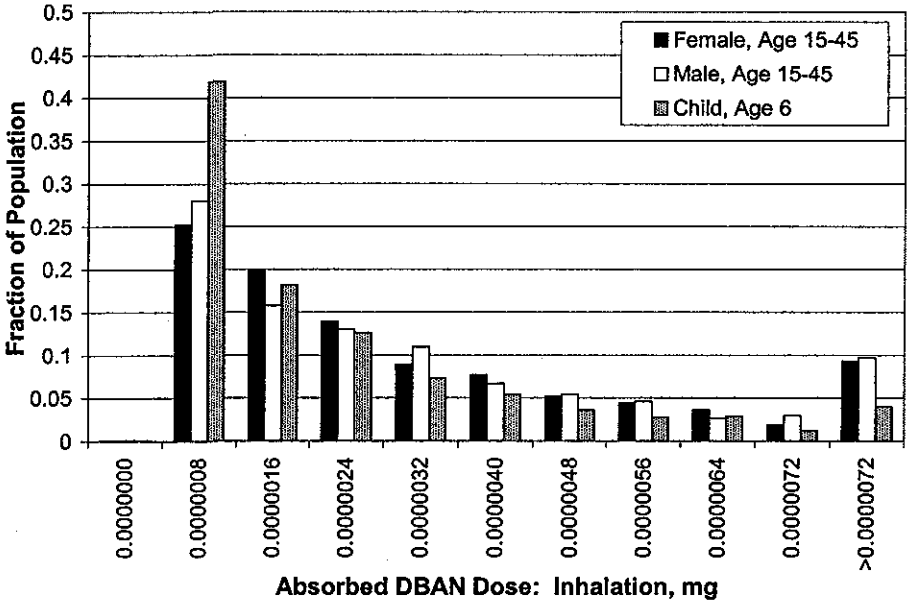
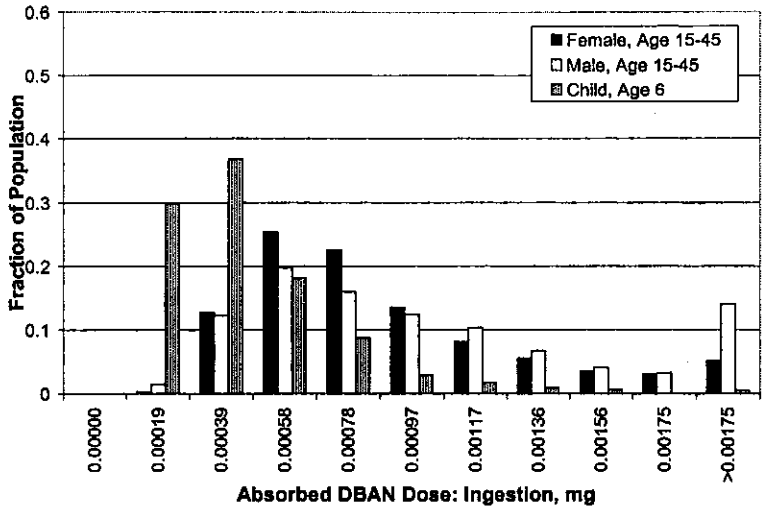
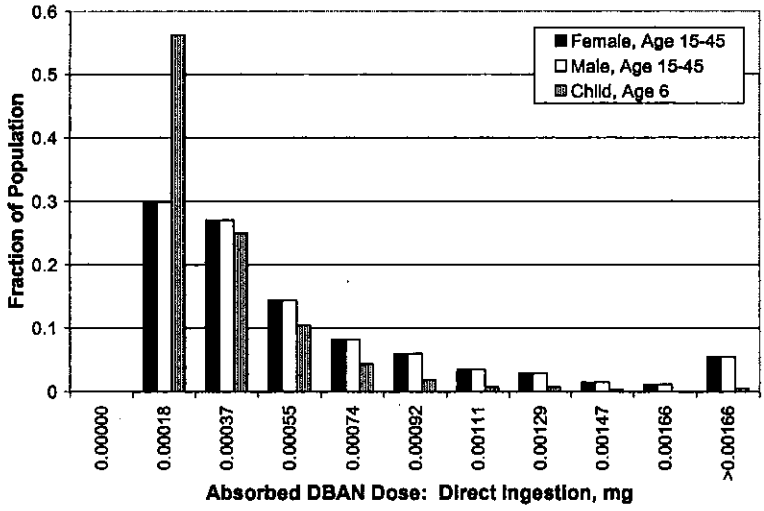


Figure 68. Histogram for Absorbed Inhalation DBAN Dose for Females, Males and Children.





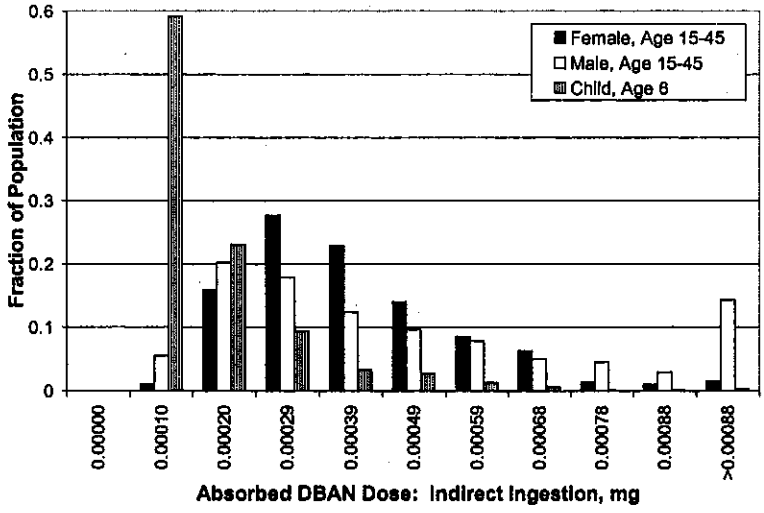


Figure 69. Histograms for the Absorbed DBAN Ingestion Dose for Females, Males and Children.

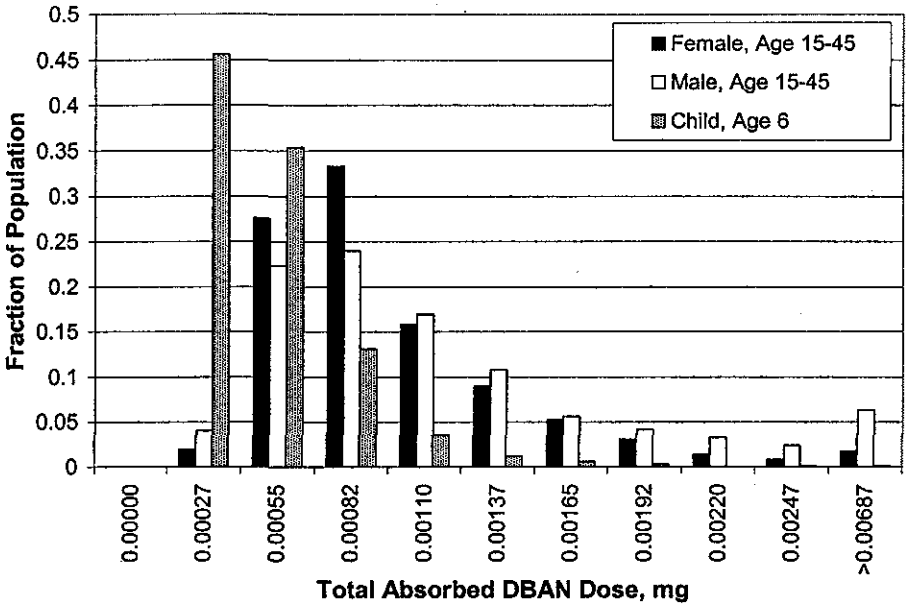


Figure 70. Histogram for the Total Absorbed DBAN Dose for Females, Males and Children.

(The skin permeability coefficient to the dermal model for this compound is very uncertain. The possible range for the skin permeability coefficient crosses an order of magnitude. Therefore these results are uncertain and should be used with caution.)

4.2.3 Analysis of the Impact of the Uncertainty in the Dermal Parameters

The skin permeability rates, given in Table 46, are generally poorly quantified. The values presented in the table are estimated based on correlation with other chemical properties, and there are few measured values for this parameter to serve as a validation. As a result, the uncertainty in this parameter is quite large. The range presented in the table represents an educated guess based on both the estimates and the general lack of measured values. The impact of this uncertainty is examined by calculating the dermal uptake at the minimum and maximum values of the identified range. Figures 71, 72, and 73 compare and contrast the uptake for the three population groups for three of the chemicals: Chloroform, DCA, and TCA. As shown in the figures, the resulting calculated dermal uptake is significantly different at the extremes of the range. The mean estimated dermal uptake for each of population groups and chemicals is between approximately 6 and 75 times higher at the upper end of the range as compared to the lower end of the range. This large range of uncertainty makes it difficult to compare the dermal route to the inhalation and ingestion routes.

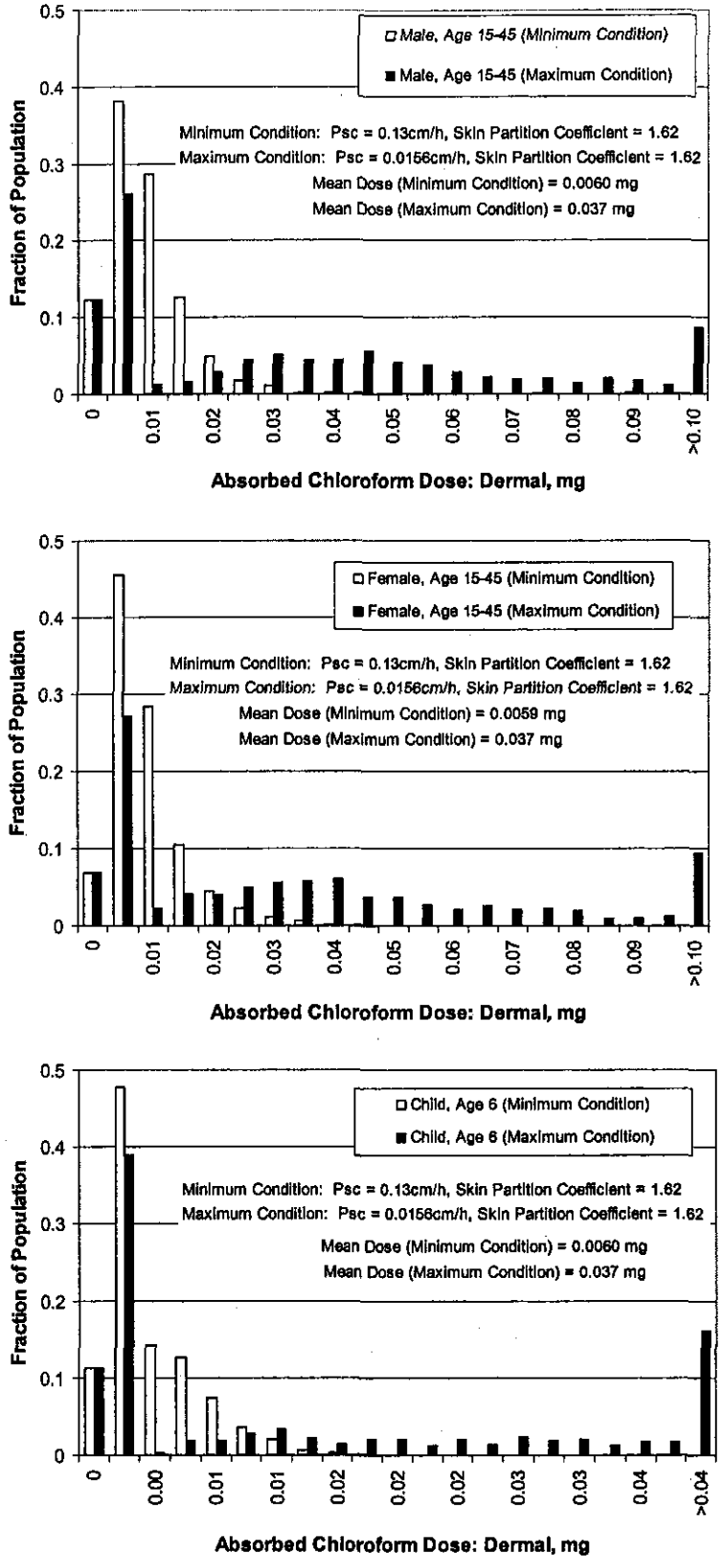
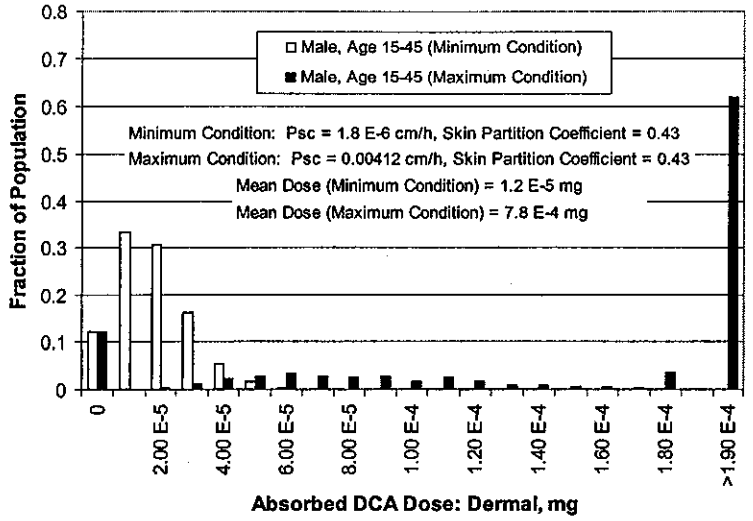
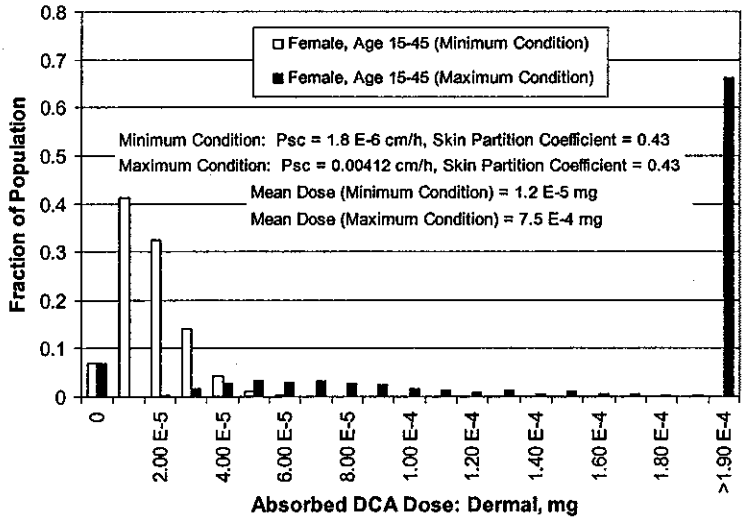


Figure 71. Comparison of Estimated Dermal Absorbed Chloroform Dose Across the Range of Uncertainty in the Permeability Coefficient





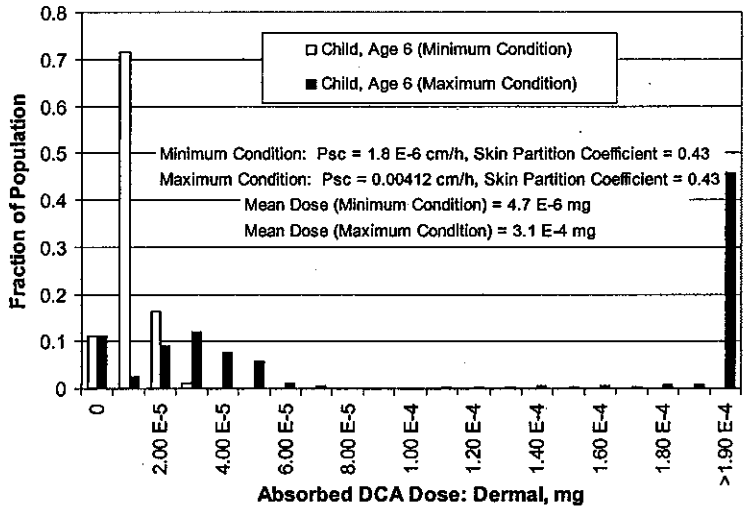
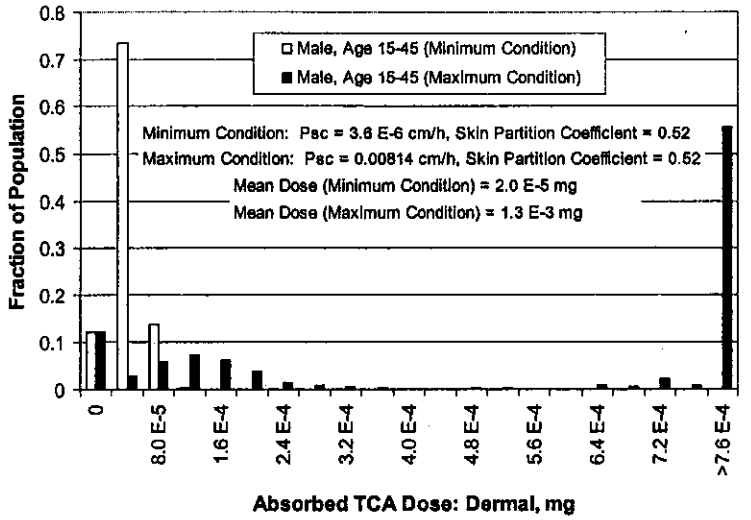
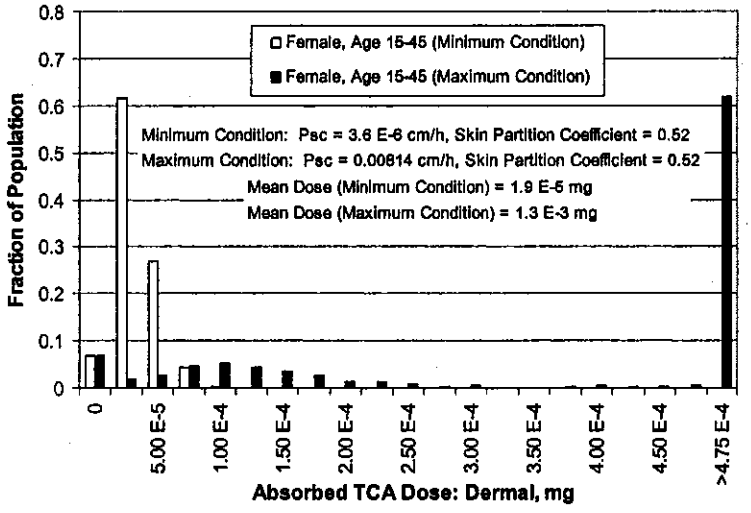


Figure 72. Comparison of Estimated Dermal Absorbed DCA Dose Across the Range of Uncertainty in the Permeability Coefficient





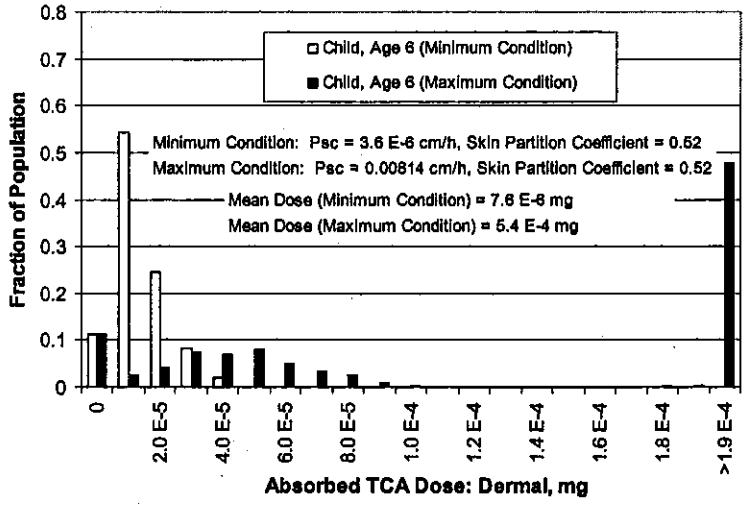


Figure 73. Comparison of Estimated Dermal Absorbed TCA Dose Across the Range of Uncertainty in the Permeability Coefficient

4.2.4 Discussion of Uptake Modeling Results

The results of the uptake modeling provides a massive amount of information for comparing and contrasting the uptake as a function of chemical, the population group and behavior, and the route of exposure. These results are summarized in the figures and tables in Section 4.2.2. General conclusions about the importance of each route can be made by comparing the histograms of uptake for each route. However, specific conclusions can be problematic due to large uncertainties in some of the model parameters, most notably the dermal permeability coefficient as described in the above section.

The route-specific values presented in the absorbed dose results tables for each chemical provide a general understanding of the relative contribution of each route. However, this comparison can be misleading because, as discussed earlier, for a given percentile, the member of the population is likely to be different for each route (e.g., the person who has the 50th percentile absorbed dose by the inhalation route is not the same person as has the 50th percentile dermal absorbed dose).

Many factors influence the uptake by each route. In addition to volatility, the inhalation is influenced by the blood:air partition coefficient, which is inversely related to the Henry's law constant. For example, while chloroform is more volatile that BDCM, the blood:air partition coefficient is significantly higher for BDCM (6.11) than for chloroform. These values indicate that for equal concentrations in the inspired air, the blood will absorb approximately 55% more BDCM than chloroform. Similar relationships exist for the dermal route, where uptake is influenced by the dermal permeability and partition coefficients.

The THMs are the most volatile class of chemicals in this study, and the inhalation route clearly dominates the absorbed dose. The contribution of the ingestion and dermal routes are similar, and given the uncertainty of the parameters, it is unclear which route provides the larger dose. The HAAs and HANs are much less volatile, and therefore the inhalation route has the least contribution to the absorbed dose. Given the large uncertainty in the dermal parameters, it is unclear whether ingestion or dermal is the largest contributor to the total absorbed dose. The results shown in plots are based on calculations using a midpoint estimate for the skin permeability coefficient, as shown in Table 46. However as shown in section 4.2.3, if the value is actually at the high end of the uncertainty range, in some cases, the dermal component becomes a significant contributor to the total absorbed dose. In general for lower volatility compounds, dermal absorption is less than ingestion, but is within an order of magnitude.

The contribution of the dose by route of exposure/uptake is presented for each chemical for the 50th and 95th percentiles of each population group. This summary further illustrates the role of the route as a function of the chemical, particularly with respect to the chemical's volatility. In addition, this summary further underscores the importance of understanding the uncertainties associated with the dominant route. In the case of the dermal route, the summary also shows the importance of understanding this uncertainty to identify the importance of the dermal route. Given the large uncertainty in the dermal parameters, the dermal route cannot be dismissed as not important even though the results indicate it is of lesser importance.

Table 68. Summary of Absorbed Dose by Route for the 50th Percentile of the Population

Chemical	Contribution to Total by Route		
	Dermal	Ingestion	Inhalation
Female, Age 15-45			
Chloroform	9%	9%	81%
BDCM	4%	13%	83%
DBCM	5%	15%	80%
Bromoform	7%	27%	67%
MCA	3%	97%	0%
DCA	0%	100%	0%
TCA	0%	100%	0%
MBA	3%	97%	0%
DBA	3%	97%	0%
BCA	3%	97%	0%
DCAN	2%	95%	2%
TCAN	3%	96%	1%
DBAN	3%	97%	0%
Male, Age 15-45			
Chloroform	10%	11%	80%
BDCM	4%	15%	81%
DBCM	5%	17%	78%
Bromoform	7%	29%	64%
MCA	2%	98%	0%
DCA	0%	100%	0%
TCA	0%	100%	0%
MBA	2%	97%	0%
DBA	3%	97%	0%
BCA	3%	97%	0%
DCAN	2%	96%	2%
TCAN	3%	96%	1%
DBAN	2%	97%	0%
Child, Age 6			
Chloroform	1%	9%	89%
BDCM	1%	15%	84%
DBCM	1%	16%	83%
Bromoform	1%	23%	75%
MCA	1%	99%	0%
DCA	0%	100%	0%
TCA	0%	100%	0%
MBA	1%	99%	0%
DBA	1%	99%	0%
BCA	1%	99%	0%
DCAN	1%	96%	4%
TCAN	1%	98%	1%
DBAN	1%	99%	0%

Table 69. Summary of Absorbed Dose by Route for the 95th Percentile of the Population

Chemical	Contribution to Total by Route		
	Dermal	Ingestion	Inhalation
Female, Age 15-45			
Chloroform	8%	6%	86%
BDCM	3%	8%	89%
DBCM	4%	10%	87%
Bromoform	5%	14%	81%
MCA	3%	97%	0%
DCA	0%	100%	0%
TCA	0%	100%	0%
MBA	3%	97%	0%
DBA	4%	96%	0%
BCA	4%	96%	0%
DCAN	3%	92%	5%
TCAN	5%	94%	2%
DBAN	3%	96%	1%
Male, Age 15-45			
Chloroform	7%	7%	86%
BDCM	2%	10%	88%
DBCM	3%	11%	85%
Bromoform	4%	18%	78%
MCA	2%	98%	0%
DCA	0%	100%	0%
TCA	0%	100%	0%
MBA	2%	98%	0%
DBA	3%	97%	0%
BCA	2%	97%	0%
DCAN	2%	94%	4%
TCAN	3%	96%	1%
DBAN	2%	97%	0%
Child, Age 6			
Chloroform	7%	5%	88%
BDCM	2%	8%	90%
DBCM	3%	8%	89%
Bromoform	4%	12%	84%
MCA	3%	97%	0%
DCA	0%	100%	0%
TCA	0%	100%	0%
MBA	3%	97%	0%
DBA	4%	96%	0%
BCA	4%	96%	0%
DCAN	3%	90%	7%
TCAN	4%	93%	2%
DBAN	3%	96%	1%

Other analyses not conducted as a part of this study could have benefits. A very intensive evaluation of the results would allow an understanding of the impact of each activity and the range of behavior across a population. An analysis of the relationship between water-use behavior and resultant exposure and dose would be useful in identifying and potentially modifying exposure related behaviors. In addition, the impact of a multitude of other factors, such as air exchange rates, water use rates, and water temperature, could be evaluated.

As is clearly described in Section 3.0 Model Parameters, a large number of parameters are required to properly represent exposure to water-borne contaminants. Each of these parameters has an associated uncertainty. The overall uncertainty of the estimated absorbed dose is unclear, and is examined in Section 5 of this report.

4.3 Pharmacokinetic Modeling Results

The TEM model was run to generate 250 time histories for use in PBPK model simulations. They were generated for four chemicals and three demographic groups. The chemicals modeled are a subset of the original 15 proposed for this study. Chloroform ($CHCl_3$), bromodichloromethane (BDCM), dichloroacetic acid (DCA), and trichloroacetic acid (TCA) were modeled for the Adult male and female aged 15-45, and the male child age 6-10. The PBPK parameters for the child were chosen for age 6.

The exposure time histories from TEM were generated for a 24-hour period. They were then repeated for another 24 hours. They were run through the ERDEM model and percentile curves were generated for Liver, Kidney, Venous Blood, and Ovaries or Testes. In addition, percentile curves were generated for exhaled air, chemical in the urine, and the total absorbed dose (Appendix A). Tables of the percentiles at the end of the 48-hour period simulated were generated for AUC and absorbed dose (Tables 70 - 73). Some analysis of the results are presented in Table 74.

4.3.1 Meaning of Exposure Time Histories

Exposure time histories represent measurements of environmental conditions at a particular location. This location could be around a person or a measuring device located on a pole. The chemical in air or in water results in different forms of exposure. A person might be hypothesized to be at the site of emission, or calculations could be performed to determine probable exposure at a more likely location for an exposure. Chemical in air can be absorbed through the skin, but depending on the chemical the greatest exposure would be through inhalation. On the other hand, chemical in water could volatilize into the air, and be inhaled, could be absorbed through the skin, or even absorbed through drinking the water. A person could be exposed to many chemicals through many exposure routes at the same time. The ERDEM model is designed to be able to have multiple exposure time histories, each for a different chemical.

The time histories for inhalation, oral, and dermal exposures input to ERDEM have specific input formats, but special subroutines can be written to convert from other formats as long as all required information is available. The inhalation exposure time history consists of time and the concentration of chemical in the inhaled air. For the oral exposure time and the amount of chemical per unit time (concentration of the chemical in the food times the flow rate) being ingested are required. The dermal exposure requires the time and the concentration of the chemical in the fluid on the skin. In this case the area of the affected skin and the permeation coefficient for the chemical are needed.

The 250 exposure time histories from TEM for each of the four chemicals and three demographic groups were run through ERDEM and the resulting 250 time histories for a given dose metric variable (see Section 4.3.2) were combined to determine the 10th, 50th and 90th percentiles at each time step. This results in a set of three curves for each percentile. This was performed for the concentration and AUC for the Kidney, Liver, Venous Blood, and the Ovaries or Testes. Similarly, curves were determined for the total absorbed dose, the total amount in the urine (for DCA and TCA), and the concentration in exhaled air for BDCM and Chloroform). These plots are given in Appendix A.

4.3.2 Choosing Dose Metrics

Dose metrics may be any measure of chemical at a location and usually time in the body. The dose metric is associated with a site where experimental measurements are available, or a site where there is potential risk to the subject. Total amount of a chemical in the urine at given times, concentration of chemical in exhaled air, peak concentration of chemical in the blood, liver, kidneys, etc., AUC (Area Under the Concentration curve) at a given time are all examples of dose metrics. When a time history for a dose metric is determined, it is called a dose metric variable.

4.3.3 *Variability of PBPK Model Results Due to Variability of Exposure Time Histories*

The time histories from TEM are determined from random choice of subjects who perform various activities. These activities have stochastic components. The simulation results in Tables 70 - 73 show, for each chemical and demographic group, the percentiles at 48 hours for the total absorbed dose and the AUC in the Kidney, Liver, Venous Blood, and Ovaries or Testes. Table 74 includes notes on each chemical and demographic group. Appendix A has the time histories described above.

Table 70. Analysis of PBPK Model Results for Bromodichloromethane for the Adult Male, Adult Female, and Male Child

Demographic Group	Average	Standard Deviation	Skewness	Max	Min	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
Adult Male										
AUC Kidney (mg/L*hr)	0.00230	0.00681	9.98	0.0919	8.56E-06	6.72E-05	9.58E-05	0.000884	0.00386	0.00643
AUC Testes (mg/L*hr)	0.00450	0.0134	9.98	0.180	1.68E-05	0.000132	0.000188	0.00173	0.00757	0.0126
Absorbed Dose (mg)	0.455	1.31	10.0	17.7	0.00730	0.0201	0.0340	0.184	0.732	1.25
AUC Liver (mg/L*hr)	0.00043	0.00119	9.95	0.0161	1.11E-05	2.73E-05	4.26E-05	0.000188	0.000714	0.00114
AUC Venous Blood (mg/L*hr)	0.00176	0.00517	9.96	0.0698	9.04E-06	5.52E-05	8.11E-05	0.000682	0.00294	0.00490
Adult Female										
AUC Kidney (mg/L*hr)	0.00269	0.00721	6.23	0.0640	1.02E-05	5.36E-05	0.00013	0.00103	0.00424	0.00723
AUC Ovaries (mg/L*hr)	0.00372	0.00995	6.22	0.0883	1.4E-05	7.39E-05	0.00018	0.00142	0.00584	0.00994
Absorbed Dose (mg)	0.457	1.20	6.24	10.6	0.00793	0.0206	0.0328	0.177	0.703	1.22
AUC Liver (mg/L*hr)	0.000525	0.00133	6.23	0.0118	1.51E-05	3.33E-05	4.41E-05	0.000217	0.000794	0.00135
AUC Venous Blood (mg/L*hr)	0.00203	0.00540	6.22	0.0479	1.11E-05	4.85E-05	0.000107	0.000778	0.00319	0.00539
Child Male										
AUC Kidney (mg/L*hr)	0.00132	0.00149	2.18	0.00899	3.86E-06	4.85E-05	0.000142	0.000815	0.00342	0.00440
AUC Testes (mg/L*hr)	0.00258	0.00291	2.18	0.0176	7.57E-06	9.52E-05	0.000279	0.00160	0.00670	0.00864
Absorbed Dose (mg)	0.175	0.190	2.19	1.16	0.00174	0.0126	0.0232	0.113	0.437	0.567
AUC Liver (mg/L*hr)	0.000377	0.000392	2.20	0.00244	6.51E-06	4.3E-05	5.94E-05	0.000251	0.000921	0.00118
AUC Venous Blood (mg/L*hr)	0.00104	0.00117	2.19	0.00710	4.38E-06	4.54E-05	0.000119	0.000653	0.00268	0.00345

Table 71. Statistics for Chloroform Simulations for the Adult Male, Adult Female, and Male Child

Demographic Group	Average	Standard Deviation	Skewness	Max	Min	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
Adult Male										
AUC Kidney (mg/L*hr)	0.01118	0.0319	9.70	0.426	1.68E-05	0.000251	0.000552	0.00445	0.0187	0.0316
AUC Testes (mg/L*hr)	0.0141	0.0407	9.70	0.544	2.14E-05	0.000321	0.000704	0.00568	0.0239	0.0403
Absorbed Dose (mg)	1.57	4.43	9.74	59.2	0.0175	0.0650	0.1070	0.658	2.560	4.61
AUC Liver (mg/L*hr)	0.00120	0.00331	9.71	0.0443	2.24E-05	6.32E-05	0.000106	0.000522	0.00194	0.00339
AUC Venous Blood (mg/L*hr)	0.00576	0.0163	9.67	0.218	1.07E-05	0.000142	0.000325	0.00234	0.00960	0.0164
Adult Female										
AUC Kidney (mg/L*hr)	0.0117	0.0311	6.16	0.275	1.39E-05	0.000194	0.000532	0.00448	0.0183	0.0314
AUC Ovaries (mg/L*hr)	0.0114	0.0302	6.16	0.267	1.35E-05	0.000189	0.000519	0.00436	0.0178	0.0305
Absorbed Dose (mg)	1.58	4.10	6.18	36.4	0.0214	0.0622	0.104	0.609	2.45	4.24
AUC Liver (mg/L*hr)	0.001428	0.00362	6.17	0.0321	3.17E-05	7.74E-05	0.000116	0.000585	0.00219	0.00366
AUC Venous Blood (mg/L*hr)	0.00629	0.0164	6.15	0.145	1.119E-05	0.000117	0.000311	0.00241	0.00980	0.0166
Child Male										
AUC Kidney (mg/L*hr)	0.00586	0.00666	2.23	0.0422	5.19E-06	0.000137	0.000622	0.00364	0.0152	0.0201
AUC Testes (mg/L*hr)	0.00772	0.00878	2.23	0.0556	6.84E-06	0.000180	0.000821	0.00480	0.0201	0.0265
Absorbed Dose (mg)	0.601	0.657	2.24	4.20	0.00466	0.0354	0.0796	0.391	1.5	1.99
AUC Liver (mg/L*hr)	0.0010	0.00117	2.26	0.00758	1.43E-05	9.92E-05	0.000165	0.000738	0.00272	0.00354
AUC Venous Blood (mg/L*hr)	0.00319	0.00358	2.24	0.0229	4.19E-06	9.23E-05	0.000347	0.00198	0.00823	0.0108

Table 72. Statistics for Dichloroacetic Acid Simulations for the Adult Male, Adult Female, and Male Child

Demographic Group	Average	*Standard* Deviation	Skewness	Max	Min	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
Adult Male										
AUC Kidney (mg/L*hr)	0.00399	0.00318	3.54	0.0310	0.000392	0.00123	0.00141	0.00317	0.00733	0.00983
AUC Testes (mg/L*hr)	0.00493	0.00393	3.54	0.0384	0.000485	0.00152	0.00174	0.00392	0.00907	0.0122
Absorbed Dose (mg)	0.0693	0.0542	3.26	0.509	0.00633	0.0217	0.0242	0.0544	0.127	0.175
AUC Liver (mg/L*hr)	0.00404	0.00322	3.52	0.0313	0.000396	0.001248	0.001426	0.00321	0.00743	0.00997
AUC Venous Blood (mg/L*hr)	0.00498	0.00397	3.54	0.0388	0.00049	0.00154	0.00176	0.00396	0.00917	0.0123
Adult Female										
AUC Kidney (mg/L*hr)	0.00221	0.00227	4.30	0.0215	0.000284	0.00048	0.000612	0.00159	0.00449	0.00547
AUC Ovaries (mg/L*hr)	0.00262	0.00270	4.30	0.0255	0.000337	0.000569	0.000726	0.00189	0.00533	0.00649
Absorbed Dose (mg)	0.0339	0.0347	4.22	0.325	0.00422	0.00726	0.00934	0.0243	0.0675	0.0848
AUC Liver (mg/L*hr)	0.00224	0.00232	4.31	0.0218	0.000288	0.000486	0.000620	0.00162	0.00456	0.00557
AUC Venous Blood (mg/L*hr)	0.00272	0.00281	4.30	0.0265	0.000351	0.000592	0.000755	0.00196	0.00555	0.00675
Child Male										
AUC Kidney (mg/L*hr)	0.00248	0.00208	2.46	0.0168	0.000195	0.000559	0.000664	0.00185	0.00507	0.00617
AUC Testes (mg/L*hr)	0.00307	0.00257	2.46	0.0208	0.000241	0.000692	0.000821	0.00229	0.00627	0.00763
Absorbed Dose (mg)	0.0161	0.0133	2.46	0.109	0.00133	0.0036	0.00433	0.0121	0.0333	0.0389
AUC Liver (mg/L*hr)	0.00249	0.00208	2.46	0.0169	0.000196	0.000562	0.000667	0.00186	0.00510	0.00619
AUC Venous Blood (mg/L*hr)	0.00310	0.00259	2.46	0.0211	0.000243	0.000699	0.000830	0.00232	0.00633	0.00771

Table 73. Statistics for Trichloroacetic Acid Simulations for the Adult Male, Adult Female, and Male Child

Demographic Group	Average	Standard Deviation	Skewness	Max	Min	5th Percentile	10th Percentile	50th Percentile	90th Percentile	95th Percentile
Adult Male										
AUC Kidney (mg/L*hr)	0.0201	0.0165	3.86	0.166	0.00216	0.00585	0.00729	0.0160	0.0375	0.0488
AUC Testes (mg/L*hr)	0.0317	0.0260	3.86	0.263	0.00341	0.00923	0.0115	0.0252	0.0592	0.0770
Absorbed Dose (mg)	0.0737	0.0576	3.26	0.541	0.00673	0.0231	0.0257	0.0578	0.135	0.186
AUC Liver (mg/L*hr)	0.0205	0.0167	3.85	0.169	0.00219	0.00597	0.00746	0.0163	0.0382	0.0497
AUC Venous Blood (mg/L*hr)	0.0305	0.0250	3.86	0.253	0.00328	0.00888	0.0111	0.0242	0.0570	0.0740
Adult Female										
AUC Kidney (mg/L*hr)	0.0118	0.0123	4.43	0.117	0.00151	0.00251	0.00330	0.00848	0.0237	0.0293
AUC Ovaries (mg/L*hr)	0.0176	0.0183	4.43	0.174	0.00224	0.00373	0.00489	0.0126	0.0352	0.0435
Absorbed Dose (mg)	0.0360	0.0369	4.22	0.346	0.00449	0.00772	0.00992	0.0258	0.0718	0.0901
AUC Liver (mg/L*hr)	0.0120	0.0126	4.45	0.119	0.00153	0.00255	0.00335	0.00861	0.0242	0.0298
AUC Venous Blood (mg/L*hr)	0.0177	0.0185	4.43	0.175	0.00226	0.00376	0.00494	0.0127	0.0356	0.0439
Child Male										
AUC Kidney (mg/L*hr)	0.0154	0.0131	2.47	0.106	0.0011	0.00344	0.00405	0.0114	0.0308	0.0413
AUC Testes (mg/L*hr)	0.0243	0.0206	2.47	0.166	0.00174	0.00543	0.00638	0.0180	0.0485	0.0652
Absorbed Dose (mg)	0.0171	0.0141	2.46	0.115	0.00142	0.00382	0.00459	0.0129	0.0354	0.0414
AUC Liver (mg/L*hr)	0.0155	0.0131	2.47	0.106	0.00111	0.00347	0.00408	0.0115	0.0310	0.0416
AUC Venous Blood (mg/L*hr)	0.0234	0.0198	2.47	0.160	0.00167	0.00522	0.00614	0.0173	0.0466	0.0627

Table 74. Analysis of ERDEM Model Simulations for Four Chemicals and Three Demographic Groups

Demographic Group	Chemical	Comments on AUC at 90th Percentile	Comments on Absorbed Dose at 90th Percentile after 48 Hours
Adult Male	$CHCl_3$ 0.070mg/L	AUC in the Kidney is about 50% higher than would be expected from the BDCM/$CHCl_3$ concentration ratios.	Absorbed dose is 2.56 mg. Based on the ratio of concentrations in the water for $CHCl_3$ to BDCM the absorbed dose should be 2.23. There is more volatility of the $CHCl_3$, and greater skin permeation coefficient.
	BDCM 0.023mg/L	AUC in Testes almost twice as much as that in the Kidney. AUC in Liver is 1/10th of AUC in the Testes.	0.732 mg after 48 hours.
	DCA 0.032mg.L	The Kidney AUC is almost twice that for BDCM. The AUC for the Liver is about the same as for the Kidney. . The AUC in Venous Blood is close in value to that for the Testes	DCA has 1/6th of the absorbed dose of BDCM. There is not enough DCA volatilized to model inhalation. The permeation coefficient is very low, 1.84E-6 so much of the absorbed dose is due to chemical in drinking water.
	TCA 0.034mg/L	The AUC in the Liver ratio to that for BDCM is 53.5. The AUC in Venous Blood ratio to that for BDCM is 19.4. The AUC for the TESTES is about 8 times that for BDCM This is due to the slow clearance of TCA from the system.	The absorbed dose is 0.135277 mg. This is less than 1/5th of the absorbed dose for BDCM.
Adult Female	$CHCl_3$ 0.070mg/L	Very small differences with the Adult Male. The AUC in the Ovaries is about 25% less than for the Adult Male Testes.	Absorbed Dose is 2.45 mg. Very close to that of the Adult Male.
	BDCM 0.023mg/L	AUC in the Kidney is about 30% less than AUC in the Ovaries. Liver AUC is slightly higher than for Adult Male.	Absorbed dose is 0.703, a little less than for the Adult Male.
	DCA 0.032mg/L	The AUC for the Liver is about the same as for the Kidney. . The AUC in Venous Blood is close in value to that for the Ovaries.	The absorbed dose is less than 1/10th of that for BDCM. It is approximately half of that for the Adult Male. They were very close in value for $CHCl_3$ and BDCM.
	TCA 0.034mg/L	The AUC in the Liver ratio to that for BDCM is 30.4. The AUC in Venous Blood ratio to that for BDCM is 11.2. The AUC in the Ovaries is about 6 times that for BDCM	The absorbed dose is very close to 1/10th of that for BDCM. It is approximately half of that for the Adult Male.
Male Child	$CHCl_3$ 0.070mg/L	The Male Child AUCs are with in 20% of the values for the Adult Male and Female.	The absorbed dose is 1.51 mg. Based on the water concentration ratios the absorbed dose would be 1.33 mg. See discussion for the Adult Male.
	BDCM 0.023mg/L	Kidney and Testes AUCs are a little less than for the Adult Male. The Liver AUC is a little higher than for the Adult Male	The absorbed dose is 60% of that for the Adult Male – 0.437 mg.
	DCA 0.032mg/L	The AUC for the Liver is about the same as for the Kidney. The AUC in Venous Blood is close in value to that for the Testes.	Absorbed dose is 1/13th of that for BDCM
	TCA 0.034mg/L	The AUC in the Liver ratio to that for BDCM is 33.7. The AUC in Venous Blood ratio to that for BDCM is 17.3. The AUC in the Testes is 7.2 times that for BDCM	The absorbed dose is about 1/12th of that for BDCM. It is approximately 1/4th of that for the Adult Male.

Table 75 shows the largest values for the 90th percentile of the concentration (mg/Liter) in the Liver, and the Testicles or Ovaries for chloroform and bromodichloromethane. They are taken from the sets of Figures in Appendix A, A-2, A-6, A-10 for BDCM, and Figures A-14, A-18, and A-22 for chloroform. The values show that the concentrations for the BDCM are a little more than half of the corresponding values for chloroform for the Adult Male. For the Adult Female, the BDCM values are about two-Thirds of the chloroform values. The BDCM concentrations for the Male Child .are a little less than half of those for chloroform (similar to the Adult Male). The activities for each subject are different and the peaks occur at different times. These concentrations are not the peaks, but represent the 90th percentile of the frequency distribution at each time step and the table values are the largest values over the full 48 hours of the exposure.

Table 75. Largest 90th Percentile Concentrations for Chloroform and Bromodichloromethane for Three Demographic Groups

Demographic Group	Largest 90th Percentiles of Chloroform Concentrations (mg/Liter)		Largest 90th Percentiles of Bromodichloromethane Concentrations (mg/Liter)	
	Liver	Testes/Ovaries	Liver	Testes/Ovaries
Adult Male	0.00011	0.0012	0.00006	0.0007
Adult Female	0.000112	0.00105	0.00008	0.0006
Male Child	0.000105	0.00098	0.00005	0.0004

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5.0 Sensitivity Analysis

5.1 Overview

The values of the parameters that define the modeling problem ultimately determine the predicted exposures and doses. The uncertainty in the estimated parameter values provided in this report varies depending upon the parameter. For example, many estimated parameter values, such as water flowrate, water volume, house and room volumes, etc. are known within a reasonable and somewhat definable range of uncertainty. Other parameter estimates, such as those for skin permeability coefficients and various behavioral parameters may have uncertainties of an order of magnitude or higher.

When conducting this analysis, both sensitivity and uncertainty analyses were considered. Uncertainty may be evaluated by framing a stochastic model simulation (i.e., Monte Carlo type simulation of model inputs) and evaluating the impact of the uncertainty in each parameter on the selected model outputs. However, due to the difficulty of separating uncertainty and variability in many of the behavioral parameters, it was concluded that it would be more meaningful to conduct a screening-level sensitivity analysis to identify the parameters having the most significant impact (EPA, 1997). Therefore, neither Monte Carlo simulation nor uncertainty analyses are provided in this section, however the results of sensitivity analysis are invaluable as a means of characterizing the importance of each parameter, and allow a qualitative judgment of the importance of a parameter's uncertainty.

The overall purpose of this section is to evaluate the model sensitivity to a selected set of the parameters. In conducting this sensitivity analysis, it is recognized that due to the sheer number of model parameters and the large uncertainty in some of the parameter values, the results of this analysis may be used as guidance in selecting the set of important parameters, but a more refined study may be necessary as the parameter estimates are refined. In addition, the sensitivity of the various parameters is expected to be similar for each of the three modeled subjects. For this reason, the analysis will focus on the adult male. Some results will also be presented for the adult female and the child to demonstrate this similarity.

This study combines exposure and uptake modeling with pharmacokinetic modeling (PBPK) to yield an estimate of population-based exposure and absorbed dose to 15 DBPs. The exposure and uptake model is the Total Exposure Model (TEM), developed by Wilkes Technologies. The PBPK model is the Exposure Related Dose Estimating Model (ERDEM, formerly DEEM) developed by Anteon Corporation in collaboration with the Human Exposure Research Branch of the National Environmental Research Laboratory of the USEPA in Las Vegas, Nevada. The detailed discussions on TEM and ERDEM are presented in Section 2 of this report.

This combination provides both benefits and challenges. One significant benefit is the ability to evaluate target tissue dose as a function of a variety of behaviors, environmental factors, and other exposure related parameters. However, due to logistical constraints and the large number of parameters affecting the outcome, it is not reasonable to attempt a comprehensive sensitivity analysis. Therefore, the sensitivity analysis has been limited to a subset of the available conditions. This sensitivity analysis is performed for two disinfection byproducts, chloroform ($CHCl_3$) and dichloroacetic acid (DCA). The sensitivity analysis will evaluate the two modeling components separately: (1) the exposure and uptake model components, and (2) the physiological model components.

The impact of the parameters affecting each of the three exposure routes (inhalation, dermal exposure, and ingestion) are evaluated. The sensitivity analysis is conducted for a 24-hour scenario during which the male individual is exposed to a single disinfection byproduct via household water usage. The two chemicals of interest are chloroform and DCA (separately). The sensitivity analysis is performed to determine the impact of the various parameters on the resultant uptake and dose. It was expected that the uptake and dose of these two chemicals would be impacted by a different set of parameters, due to the fact that chloroform is highly volatile and DCA is not. The following sections describe the methods and results of the sensitivity analysis.

5.2 Methods

The sensitivity analysis is conducted by first establishing a base-case scenario, consisting of a base-case set of activities and model parameters. To evaluate the sensitivity of a particular parameter, the value of that parameter is varied by 10% (±10%) from its base-case value. The impact of this change is then evaluated by comparing the relative change in the chosen dose metrics.

In analyzing the exposure and uptake parameter sensitivities, the base-case scenario consists of the same three-person household as in the exposure modeling study in Sections 1 through 4 (male age 15-45, female age 15-45, and child age 6) and was chosen from the set of simulations derived under the modeling study. The chosen simulation was selected primarily because it contained most of the "typical" water uses. This "base-case" scenario is chosen because it represents plausible activity pattern, and is not necessarily representative the mean behavior and exposure of the population. The water uses were modified slightly from those simulated by inserting additional water uses to provide a set of water uses consistent with the average behavior of each population group as defined in Section 3.0. The activities and locations for the base-case scenario are presented in Tables 76 – 78, with the resultant water uses summarized in Table 79 and the base-case consumption behavior given in Table 80. The residence assumed for the base-case scenario is shown in Figure 74. The values of zone volumes, interzonal air flows, and whole house air exchange rate are those sampled for the chosen simulation, and are well within the range of "typical" values for US housing. The water concentrations for chloroform and DCA were assumed to be 0.07 mg/L and 0.032 mg/L, respectively, consistent with the above exposure and uptake modeling calculations.

In analyzing the physiological parameter sensitivities, only the adult male (age 15-45) is analyzed. He is assumed to have a mean alveolar ventilation rate of 540 liters/hour (L/h) at rest and 600 L/h during sedentary activity, and a mean body volume of 77.6 kg (1 kg ~ 1 L).

Each model run is a simulation of activities and processes that occur over a 24-hour period. Each 24-hour simulation includes three sequential activity level periods: a period of rest in the morning from midnight to 7:05 am, a sedentary period from 7:05 am to 8:30 pm, and another rest period in the evening from 8:30 pm to midnight.

Chloroform was modeled with metabolism to phosgene and carbon dioxide. The metabolisms of DCA were modeled as elimination in the liver. Inhalation was not modeled for DCA because the volatility of DCA is very low.

5.2.1 Sensitivity Analysis Framework

To study the impact that the various water-use parameters have on the resultant exposure to the individual, a base-case value for each parameter was increased and decreased by 10% to derive upper and lower end values for parameter inputs. The model was run using the upper end value of a single parameter while maintaining all other parameters constant, and then the model was run using the lower end value of the parameter. The difference in the resultant modeled absorbed doses between the case using the upper end value and the case using the lower end value were then evaluated to determine the sensitivity of that parameter on the dose metric.

The sensitivity analysis is conducted by altering each parameter or parameter set while holding the remaining parameters at their baseline value, and executing the model or combined models as required. To observe how changes of model parameters impacted dose metric outputs, we used a measure of relative sensitivity defined by:

$$\textit{Relative Sensitivity} = \frac{(y - y_0)/y_0}{(x - x_0)/x_0} \cdot 100\% \qquad (5.1)$$

where y = the modeled output of dose (given the altered value of the model parameter)
y_0 = the modeled output of dose (given the base values of all model parameters)
x = the altered value of the chosen model parameter
x_0 = the base value of the chosen model parameter

The resulting relative sensitivity is interpreted as the percent change in the output relative to the input. A value of 100% indicates an identical relative change. A negative value indicates the parameter and the output are inversely related.

5.2.2 Model Parameters

The combination of TEM and ERDEM require a large set of input parameters. A subset of model parameters were selected from the available set for inclusion in this sensitivity analysis. The basis and chosen parameters are described in the following sections.

5.2.2.1 Exposure and Uptake Model Parameters

The exposure and model parameters for inclusion in the sensitivity analysis are given in Tables 81–82. These parameters include the majority of parameter values required by the model. However, other less straightforward model issues potentially have a large impact on the estimated dose. These include:

- Impact of occupant location behavior: Occupant behavior is sampled from the NHAPS database. However from other analyses, it is obvious that these reported activity patterns are not always representative, and frequently lack the necessary detail to represent all relevant activities.
- *Impact of family size and demographics: This study assumes a three-person size with an* adult male, adult female and a child. The impact of other family sizes and makeup is not evaluated. (Refer to Section 3.2 for a description of the demographic population groups.)
- Impact of changing household conditions: Conditions such as opening and closing of doors and windows, operation of fans and mechanical equipment (e.g., heating and cooling systems), etc. indirectly have an impact on air concentrations by changing the

ventilation characteristics. Many of these impacts have been studied elsewhere, and are not included in this study.

- Model appropriateness: This sensitivity analysis assumes the applied emission, fate and transport, and exposure models appropriately represent the relevant processes.

Although these issues may have uncertainty, they are difficult to evaluate or are generally outside the scope of this study.

When evaluating the sensitivity of a parameter, that parameter is changed while all other parameters are held constant. However, in the case of household volumes and airflow rates, these parameters are changed as a unit, such that as the household volume increases, all the individual zones in the household increase by the same percentage. A similar approach is used in evaluating the effect of air exchange rate, such that when the rate is increased the interzonal airflows are increased by a proportional amount.

When evaluating parameters that are affected by the activity level (rest or sedentary), the simulations were run such that the resultant breathing rate was increased or decreased by 10% for all activity levels in a given simulation.

5.2.2.2 PBPK Model Parameters

The sensitivity analysis on the PBPK model parameters was conducted on the adult male. There were 39 model input parameters for the chloroform, and 34 for the DCA sensitivity analysis. The upper and lower perturbations were plus 10% and minus 10% of the baseline values. The physiological model parameters evaluated in the sensitivity analysis are the various parameters defining body compartment volumes and blood flows (by activity), alveolar ventilation rates, skin permeability coefficients, gastro-intestinal absorption rates, partition coefficients, metabolism rate constants, and elimination rate constants. The specific parameters are presented in Tables 83-84.

Each sensitivity analysis run spans 24 hours and contains time periods for both the "at rest" and the "sedentary" activities. A compartment blood flow is perturbed for one activity at a time.

The impacts of the activity levels on the alveolar ventilation rate (breathing rate) were adjusted in a manner similar to that described in Section 5.2.2.1. When analyzing the sensitivity of the alveolar ventilation rates, blood flows or cardiac output, these three parameters were changed as a unit due to their interdependency. The cardiac output is calculated as 85.43% of the alveolar ventilation rate, and the blood flow value is determined from the cardiac output. When analyzing the sensitivity of the blood flows, only the blood flow for the current compartment is altered. Cardiac output is the sum of the blood flows to the individual compartments. The percentages of cardiac output at rest or sedentary are 4.8% (for Dermis), 4.8% (Fat), 19.4% (Kidney), 23.7% (Liver), 27% (Rapidly Perfused Tissue), 19% (Slowly Perfused Tissue), and 1.3% (Testes). For example, when the blood flow in the liver decreases, the cardiac output is re-calculated as the new sum of blood flow. The alveolar ventilation rate remains the same. This computational process is applied on each of the activities, because the activity determines the value of alveolar ventilation rate.

The sensitivity analysis for the blood flow in the liver for the adult male is as the follows:

1. The baseline values of the alveolar ventilation rate and cardiac output are defined for rest and sedentary activity levels. The baseline alveolar ventilation rates are as 540 liters/hour for resting and 600 liters/hour for sedentary activity; and the baseline

cardiac outputs are calculated as 461.34 liters/hour for resting, and 512.64 liters/hours for sedentary activity.

2. For the sensitivity analysis, the plus/minus 10% perturbations in blood flow for the liver are calculated from the cardiac output for a given activity. Then the blood flows for all compartments are added to get a new value for the cardiac output (based on the adjusted blood flow to the liver). The blood flow percentages for each compartment are then recalculated and used as input parameters for the particular model run. These calculations are performed for both the resting and sedentary activity levels.

A similar procedure is used for the volume of other compartments in the body, but they do not change with the activity

5.2.3 Dose Metrics in Sensitivity Analysis

The term Dose Metric is used to describe a dose endpoint of interest. It typically describes the amount of a chemical at a location within the body, either at a given time or integrated over a specific time period. Ideally, the dose metric will be highly correlated with the risk associated with an outcome, such as an undesirable health outcome (e.g., cancer risk). Several relevant dose metrics are available as outputs from the exposure model and the PBPK model. From these, a set of dose metrics is chosen for use in evaluating the sensitivity of the selected model parameters for this sensitivity analysis.

5.2.3.1 Exposure and Uptake Model Dose Metrics

The exposure model provides an estimate of exposure, potential dose and absorbed dose as a result of the modeled activities. The exposure and potential dose are generally not good dose metrics because their route-specific values do not account for the processes that occur when the chemical crosses a boundary (i.e., skin, lungs or stomach). Therefore, the absorbed dose (the mass of chemical entering the person's bloodstream) represents the most meaningful metric. Therefore, the absorbed dose, both total and route specific, is used as the primary dose metric for the exposure and uptake models.

5.2.3.2 PBPK Model Dose Metrics

Six dose metrics were selected to study the impact of the various modeling parameters on exposure to the disinfection byproducts of chloroform and DCA. The dose metrics evaluated were: (1) total absorbed dose, (2) area under the concentration-time curve (AUC) at 24 hours in the liver, (3) AUC at 24 hours in the testes, (4) total amount metabolized in the liver at 24 hours, (5) peak concentration in the liver and (6) peak concentration in the testes. The total absorbed dose indicates how much chemical enters the person's body. The AUC provides information on the length of time at various chemical concentration levels in a particular organ or compartment. A high AUC may mean either a very high concentration for a short time, or a low concentration for a very long time. The amount metabolized is an indication of (1) the probable amount of the parent chemical that remained available for clearance, and (2) the amount of metabolites that are available for clearance. Analyzing peak concentrations is valuable when a short-term peak value can cause damage to the tissue in question. The time of the peak helps determine how long a person might have to get a chemical out of their system before damage might occur.

5.3 Results

5.3.1 Results of Sensitivity Analysis Using TEM

The TEM model predicted air concentrations for the base-case are presented in Figures 75 and 76 for chloroform and DCA, respectively. At the top of each figure, a line graph indicates when each water appliance is active. Combining these predicted air concentrations with each occupant's breathing rate and location, the model estimates the potential inhalation dose. Using the uptake models, TEM further calculates the absorbed inhalation dose. The absorbed dermal dose is calculated by the uptake model considering the water use and the skin area in contact with the water. The ingestion dose is calculated by estimating the amount of contaminant remaining in the water at the time of consumption, and assumes 100% absorption. The base-case values for potential and absorbed dose are presented in Tables 85-86 as a function of route and population group. Tables 87 and 88 present the relative sensitivity for the TEM dose metrics, absorbed dose and potential dose. Potential dose is shown only for route specific exposure and not for total dose, since potential dose cannot be meaningfully compared across routes of exposure.

5.3.2 Results of Sensitivity Analysis Using ERDEM

The ERDEM model predicted values for the base-case scenario for the six dose metrics are given in Table 89 for chloroform and DCA. The dose and relative sensitivity are given for the results of the ERDEM model in Tables 90-100 consisting of 6 tables for chloroform and 5 tables for DCA. The results are reported for the six dose metrics described above: Absorbed Dose; AUC for the Liver; AUC for the Testes; Amount Metabolized in the Liver; Peak Concentration in the Liver; and Peak Concentration in the Testes. The Absorbed Dose results for DCA are not provided, since all relative sensitivities are negligible. Figures 77 (a) through (f) for chloroform and Figures 78 (a) through (f) for DCA exhibit dose metric curves over a 24-hour time period for the baseline values of the input model parameters.

5.4 Discussion

The purpose of conducting sensitivity and uncertainty analysis is to identify which assumptions, parameters, and uncertainties significantly impact the conclusions. This sensitivity analysis, referred to as a "screening level" sensitivity analysis is conducted without a reasonable understanding of the uncertainty inherent in many of the parameters. Some parameters, for example skin permeability coefficients and some behavioral characteristics, are uncertain across several orders of magnitude. If the uncertainties were well understood across the set of model parameters, a combined uncertainty and sensitivity analysis would provide the basis for evaluating the relative importance of each parameter. Alternatively, this screening level sensitivity analysis provides a basis for evaluating only the sensitivity of each parameter. If the output is highly sensitive to a given parameter and the parameter value has a high degree of uncertainty relative to the assumed sensitivity range (10% for this study), it is reasonable to conclude that the value of the given parameter is important relative to parameters that are less sensitive. However, if a parameter is both less sensitive and highly uncertain relative to the assumed sensitivity range, the conclusion is less obvious.

The following subsections present discussion about the sensitivity analysis of both TEM and ERDEM.

5.4.1 Discussion on Sensitivity Analysis Using TEM

The exposure model sensitivity analysis identified a number of important results. From the results, it is clear that the conclusions are not consistent across chemicals. Table 101 presents a ranking of the parameters by their absolute value of relative sensitivity. The parameters are ranked in descending order for the adult male with shaded cells for the parameters that are out of order (of different order of ranking) for the female and child. The table provides a clear means for identifying input parameters as well as contrasting changes across activity patterns. For volatile chemicals as represented by chloroform, the parameters influencing the air concentrations have the most significant impact. These parameters include the overall mass transfer coefficients, air exchange rates, zone volumes, water flowrates, and duration of water uses. The air exchange rates and zone volumes are inversely related to the absorbed dose because of their effect of lowering airborne concentrations. The overall mass transfer coefficient is the most sensitive parameter for chloroform, consistent with the inhalation route having the largest dose, causing approximately an 8% change in the absorbed dose for a 10% change in the overall mass transfer coefficient. Although the mass transfer coefficients were examined as a group, it is intuitively obvious that larger inhalation exposure events, such as showering, will be more sensitive to this parameter. For the volatile chemical, chloroform, the model is relatively insensitive to the actual volume of non-flowing type water appliances (e.g., bath volume, dishwasher volume, clothes washer volume, toilet volume, etc.) with less than a 0.2% change in dose for a 10% change in the volume parameter. In addition, the model is relatively insensitive to Henry's law constant (H), yielding a relative change of less than 0.3% for a 10% change in H.

For low volatility chemicals, as represented by DCA, consumption and dermal contact play the most significant roles. Consumption is by far the most sensitive parameter, changing the absorbed dose approximately 10% for a 10% change in the consumption volume. The dermal influence, though much less significant, is evident in the shower duration for the adults (who showered) and in the bath duration for the child (who took a bath). Although the inhalation route's contribution to the absorbed dose is small relative to the other routes, it is interesting to note that, with the exception of Henry's law constant, the sensitivity of the inhalation parameters are in the same sequential order as for chloroform. The increased relative influence of Henry's law constant as compared to the mass transfer coefficient is due to the dynamics of the equilibrium relationship as defined by Henry's law. The concentration in the air is limited to the equilibrium condition, as defined by Henry's law, which is approached in the vicinity of the water appliance during water uses of duration longer than a few minutes, thereby attenuating the mass transfer rate. For this reason, Henry's law constant is the most sensitive parameter for the inhalation route.

Although chloroform is a volatile chemical and DCA is a low volatility chemical, and as such they are generally representative of chemicals with similar chemical properties, many other factors affect the exposure and uptake of a chemical. Factors such as skin permeability are not highly correlated with volatility, and therefore the fractional dermal uptake can be very different for chemicals with similar volatility. Therefore, the conclusions reached based on the sensitivity analysis for the two chemicals considered here would have to consider the effect of the other chemical properties which impact uptake.

5.4.2 Discussion on Sensitivity Analysis Using EDREM

The PBPK model (ERDEM) sensitivity analysis identified a number of highly sensitive parameters, but also identified numerous insensitive parameters. In some cases, the change in the dose metric variables, due to the perturbation of an input variable, was less than the relative error in the integration process. For these cases, the results are not reported.

Tables 92 and 93 contain the relative sensitivities for Liver AUC and Testes AUC dose metrics for chloroform respectively. These tables show that the AUC estimates for the Liver differ by a factor of around 10 from the estimates for the Testes. But, for DCA the values of AUC are very similar for Liver versus Testes. The volumes of the Body, Fat, and the Slowly Perfused Tissue show a high relative sensitivity in the Liver but not in the Testes. Liver Metabolism is sensitive in the Liver, but not in the Testes.

Tables 94 and 95 contain the peak concentration of Liver and Testes dose metrics, respectively, for chloroform. The input parameters that exhibit high relatively sensitivity are: volume of the Body, Alveolar Ventilation Rate, Cardiac Output, the blood flows to the Liver and Slowly Perfused Tissue, and the partition coefficients for the Static Lung/Air and Static Lung/Blood. However, the volumes of the Dermis, Fat, Rapidly Perfused Tissue, and Slowly Perfused Tissue, and the partition coefficient of Rapidly Perfused Tissue/Blood are sensitive in the Liver but not in the Testes. The partition coefficient of Testes/Blood is sensitive in the Testes only. In a similar manner to the results shown for chloroform, Tables 96-100 present the relative sensitivities for each dose metric for DCA (except absorbed dose as mentioned above).

The dose metric – absorbed dose – has negligible relative sensitivity for all 34 input parameters for DCA, while for chloroform the absorbed dose is most sensitive to Alveolar Ventilation rate (relative sensitivity of 89.38%). The absorbed dose for chloroform has negligible relative sensitivity for the rest of the 39 input parameters. (See Table 90)

The relative sensitivity of the most sensitive input parameter for each dose metric is shown in Table 102 for each chemical. Table 103 presents a summary of the highly sensitive input parameters for chloroform. Table 104 presents a summary of the highly sensitive input parameters for DCA. These tables identify the parameters that have the greatest impact on each dose metric for chloroform and DCA. Comments provided in Tables 103 and 104 describe some of the primary reasons these parameters are most sensitive.

5.4.3 Other Model Sensitivity Issues

Several model parameters were not explicitly examined as a part of this study, including the following:

- Location behavior of exposed individual
- Impact of other occupants (family size, behavior of other occupants, etc.)
- Impact of mechanical systems (e.g., the heating/air conditioning system, other fans, etc.)
- Impact of changing physical conditions in the house (e.g., opening and closing of doors and windows)
- Impact of weather
- Water temperature
- Other chemical properties
- Model appropriateness (mass balance model, uptake models, behavioral models, etc.)

Although these parameters were not explicitly studied, the impacts of several of the parameters were indirectly addressed. The impact of changing physical conditions and weather were addressed indirectly by looking at the effect of increasing the whole house air exchange rate and inter-zonal airflows. It is clear that any change that causes ventilation to increase will, in general, lower peak concentrations at the source. However, while opening an interior door will decrease the peak concentration at the source, it will also increase the concentrations at other locations in the home, thereby potentially providing additional exposure to the occupants in those locations. Similarly, the use of a mechanical system will encourage mixing in the house causing lower exposures at the source but potentially higher exposures at other locations. The impact of a local exhaust fan was demonstrated by Wilkes et al. (1992). Wilkes et al. showed that using a bathroom fan to exhaust emissions during a showering event lowered the estimated exposure to trichloroethylene (TCE) by between 23 and 36% for assumed scenarios for 2 adults and a child.

The impact of water temperature and other chemical properties are also indirectly examined by looking at the effect of changing the overall mass transfer coefficient. Water temperature increases the chemical's diffusivity in water, and for chemicals whose volatilization is limited by liquid phase mass transfer, an increased water temperature will increase the overall mass transfer coefficient. The liquid and gas phase diffusivities will have a similar effect subject to the phase that provides the greatest resistance to mass transfer.

The impact of behavioral characteristics of the occupants clearly has the potential for causing the greatest variation. Wilkes et al. (1992) showed that, for TCE, someone taking a second shower immediately following another person's shower would be exposed to much greater air concentrations, and receive a higher dose. For the scenario examined by Wilkes et al., the second shower was estimated to provide approximately a 50% higher dose than the first shower of identical length and conditions due to the elevated air concentrations. Wilkes et al. (1996) showed, for TCE, a high degree of correlation between behavior and predicted dose, with the most important predictors being shower duration, bath duration, time spent in the bathroom, and total household water use. Wilkes et al. (1992) also compared the estimated exposures of single occupant households to two occupant households. The two person households showed a mean increase in the potential inhalation dose of 38% for the male population group and 11% for the female population group.

5.4.4 Conclusions

This sensitivity analysis provides the basis for designing and implementing a more detailed sensitivity and uncertainty analysis of the variables that have been shown to be sensitive. Variables that are identified as being highly uncertain or highly sensitive require a more in-depth analysis. It is clear that identifying the range of uncertainty for each variable and conducting a combined sensitivity and uncertainty analysis will provide additional insight.

As a result of the sensitivity analysis presented in this report, it is clear that additional research into the more sensitive parameters would be beneficial. In addition, characterizing the variability and uncertainty of these parameters as probability distributions would provide the basis for designing and implementing a meaningful uncertainty and sensitivity analysis.

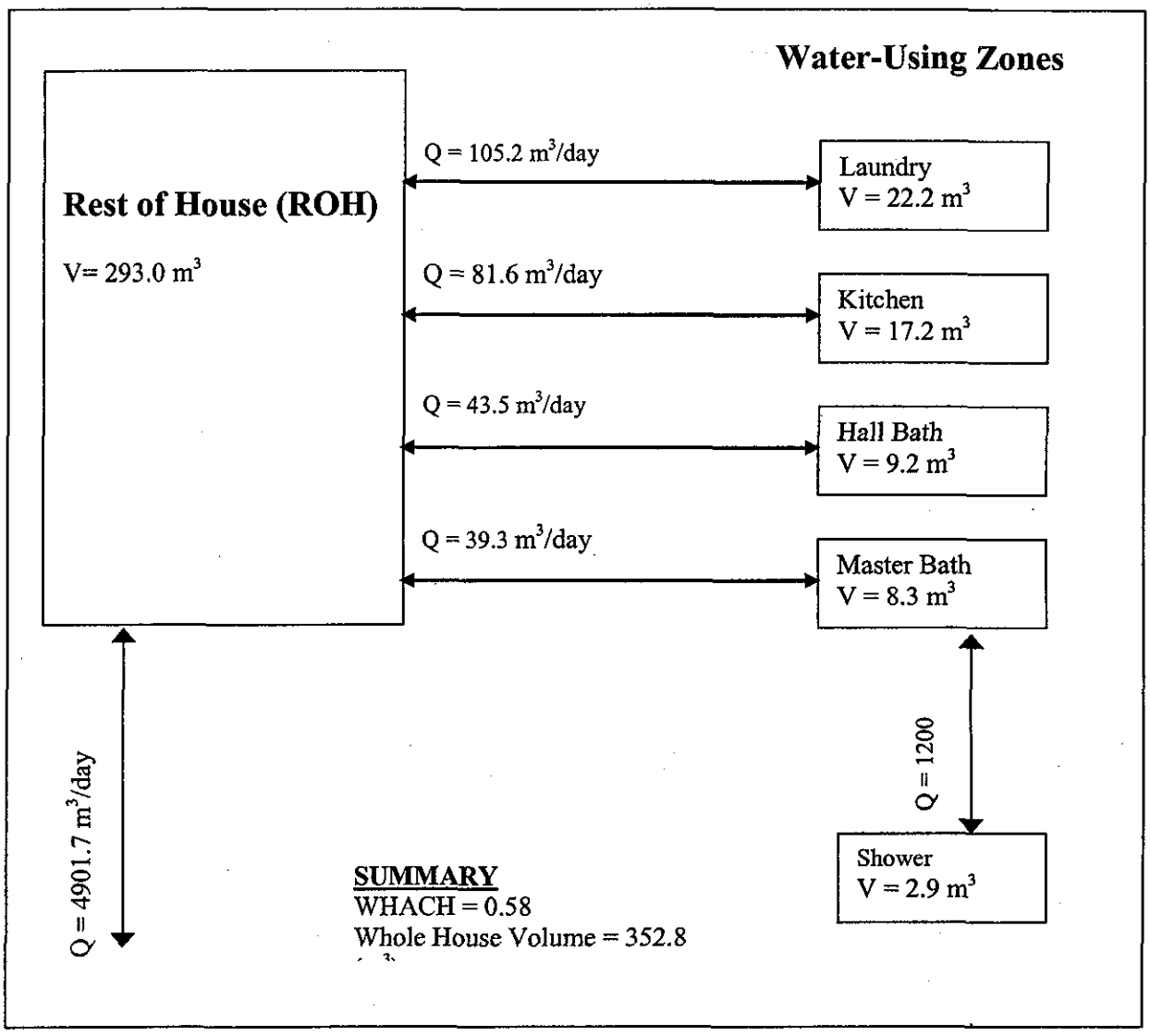


Figure 74. Schematic Representation of House Interzonal Air Flows for the Base-Case Sensitivity Analysis.

Table 76. *Base-Case Activity and Water Use Patterns for Adult Male (Ages 15 – 45) Used in Sensitivity Analysis*

Activity Location	Start Hour	Start Min	End Hr	End Min	Breathing Rate	Water Use	Location	Start Hr	Start Min	End Hr	End Min	Skin Area
Kitchen	7	5.00	7	12.00	14.4	Faucet -- Kitchen	Kitchen	7	5.68	7	6.52	913.74
Kitchen	7	5.00	7	12.00	14.4	Faucet -- Kitchen	Kitchen	7	6.52	7	6.97	913.74
Master Bath	7	12.00	7	13.25	14.4	Toilet	Master Bath	7	12.00	7	12.10	0.00
Master Bath	7	12.00	7	13.25	14.4	Faucet -- Bathroom	Master Bath	7	12.20	7	13.20	913.74
Shower	7	13.25	7	20.40	14.4	Shower	Shower	7	13.25	7	20.40	17460.00
Master Bath	7	20.40	7	30.00	14.4	Toilet	Master Bath	7	20.50	7	20.60	0.00
Master Bath	7	20.40	7	30.00	14.4	Faucet -- Bathroom	Master Bath	7	20.70	7	21.80	913.74
ROH	7	30.00	10	22.00	14.4							
Master Bath	10	22.00	10	24.00	14.4	Toilet	Master Bath	10	22.00	10	22.10	0.00
Master Bath	10	22.00	10	24.00	14.4	Faucet -- Bathroom	Master Bath	10	22.10	10	23.10	913.74
ROH	10	24.00	13	22.00	14.4							
Master Bath	13	22.00	13	24.00	14.4	Toilet	Master Bath	13	22.00	13	22.10	0.00
Master Bath	13	22.00	13	24.00	14.4	Faucet -- Bathroom	Master Bath	13	22.10	13	23.10	913.74
ROH	13	24.00	14	0.00	14.4							
Outdoors	14	0.00	15	0.00	14.4							
ROH	15	0.00	17	0.00	14.4							
Outdoors	17	0.00	19	0.00	14.4							
ROH	19	0.00	20	0.00	14.4							
Kitchen	20	0.00	20	24.00	14.4	Faucet -- Kitchen	Kitchen	20	0.61	20	0.92	913.74
Kitchen	20	0.00	20	24.00	14.4	Faucet -- Kitchen	Kitchen	20	5.07	20	5.65	913.74
Kitchen	20	0.00	20	24.00	14.4	Faucet -- Kitchen	Kitchen	20	8.22	20	9.41	913.74
Kitchen	20	0.00	20	24.00	14.4	Faucet -- Kitchen	Kitchen	20	10.91	20	11.76	913.74
Kitchen	20	0.00	20	24.00	14.4	Faucet -- Kitchen	Kitchen	20	19.99	20	21.08	913.74
Master Bath	20	24.00	20	30.00	14.4	Toilet	Master Bath	20	27.00	20	28.00	0.00
Master Bath	20	24.00	20	30.00	14.4	Faucet -- Bathroom	Master Bath	20	28.00	20	29.30	913.74
ROH	20	30.00	24	0.00	12.96							
Household Water Use Activities												
						Clothes Washer	Laundry	18	0	0	0	0
						Dishwasher	Kitchen	20	11	20	51	0

Table 77. Base-Case Activity and Water Use Patterns for Adult Female (Ages 15 – 45) Used in Sensitivity Analysis

Activity Location	Start Hour	Start Min	End Hr	End Min	Breathing Rate	Water Use	Location	Start Hr	Start Min	End Hr	End Min	Skin Area
Master Bath	5	0.00	5	5.00	11.52	Faucet -- Bathroom	Master Bath	5	2.44	5	4.80	796.93
Master Bath	5	0.00	5	5.00	11.52	Toilet	Master Bath	5	3.40	5	5.52	0.00
ROH	5	5.00	5	10.00	11.52							
Kitchen	5	10.00	5	30.00	11.52	Faucet -- Kitchen	Kitchen	5	12.96	5	13.46	796.93
Kitchen	5	10.00	5	30.00	11.52	Faucet -- Kitchen	Kitchen	5	13.46	5	15.00	796.93
Kitchen	5	10.00	5	30.00	11.52	Faucet -- Kitchen	Kitchen	5	25.52	5	27.79	796.93
Outdoors	5	30.00	18	30.00	11.52							
Master Bath	18	30.00	18	49.90	11.52	Faucet -- Bathroom	Master Bath	18	33.79	18	34.91	796.93
Master Bath	18	30.00	18	49.90	11.52	Toilet	Master Bath	18	35.55	18	37.26	0.00
Master Bath	18	30.00	18	49.90	11.52	Faucet -- Bathroom	Master Bath	18	39.48	18	40.80	796.93
Master Bath	18	30.00	18	49.90	11.52	Faucet -- Bathroom	Master Bath	18	48.34	18	49.90	796.93
Master Bath	18	30.00	18	49.90	11.52	Toilet	Master Bath	18	48.30	18	48.80	0.00
Shower	18	49.90	19	0.00	11.52	Shower	Shower	18	49.90	19	0.00	15228.00
Master Bath	19	0.00	19	2.00	11.52							
ROH	19	0.00	20	0.00	11.52							
Kitchen	20	0.00	20	10.00	11.52	Faucet -- Kitchen	Kitchen	20	0.92	20	1.83	796.93
Kitchen	20	0.00	20	10.00	11.52	Faucet -- Kitchen	Kitchen	20	2.57	20	3.99	796.93
ROH	20	10.00	23	5.00	11.52							
Master Bath	23	5.00	23	15.00	11.52	Faucet -- Bathroom	Master Bath	23	8.00	23	11.00	796.93
ROH	23	15.00	24	0	10.32							
Household Water Use Activities												
						Clothes Washer	Laundry	18	0	0	0	0
						Dishwasher	Kitchen	20	11	20	51	0

Table 78. Base-Case Activity and Water Use Patterns for the Child (Age 6) Used in Sensitivity Analysis

Activity Location	Start Hour	Start Min	End Hr	End Min	Breathing Rate	Water Use	Location	Start Hr	Start Min	End Hr	End Min	Skin Area
Hall Bath	11	0.00	11	40.00	10.44	Hall Bath	Hall Bath	11	3.00	11	25.00	7137.00
Hall Bath	11	0.00	11	40.00	10.44	Hall Toilet	Hall Bath	11	2.50	11	2.80	0.00
Hall Bath	11	0.00	11	40.00	10.44	Hall Faucet	Hall Bath	11	2.70	11	3.00	373.50
Hall Bath	11	0.00	11	40.00	10.44	Hall Toilet	Hall Bath	11	32.26	11	32.62	0.00
Hall Bath	11	0.00	11	40.00	10.44	Hall Toilet	Hall Bath	11	32.62	11	33.66	0.00
Hall Bath	11	0.00	11	40.00	10.44	Hall Faucet	Hall Bath	11	35.49	11	37.79	373.50
Hall Bath	11	0.00	11	40.00	10.44	Hall Faucet	Hall Bath	11	38.60	11	40.00	373.50
Kitchen	11	40.00	12	15.00	10.44	Faucet -- Kitchen	Kitchen	11	43.00	11	45.00	373.50
Outdoors	12	15.00	17	5.00	10.44							
ROH	17	5.00	17	20.00	10.44							
Kitchen	17	20.00	17	45.00	10.44	Faucet -- Kitchen	Kitchen	17	21.00	17	22.50	373.50
Kitchen	17	20.00	17	45.00	10.44	Faucet -- Kitchen	Kitchen	17	40.00	17	41.00	373.50
ROH	17	45.00	19	20.00	10.44							
Hall Bath	19	20.00	19	30.00	10.44	Hall Toilet	Hall Bath	19	24.00	19	25.00	0.00
Hall Bath	19	20.00	19	30.00	10.44	Hall Faucet	Hall Bath	19	26.00	19	29.00	373.50
ROH	19	30.00	24	0	9.84							
Household Water Use Activities												
						Clothes Washer	Laundry	18	0	0	0	0
						Dishwasher	Kitchen	20	11	20	51	0

Table 79. Summary of Base-Case Water Uses Used in Sensitivity Analysis

Water Use Event	Male (15-45 Years)	Female (15-45 Years)	Child (6 years)
Number of Shower Events	1	1	0
Shower Mean Duration, minutes	7.15	10.10	N/A
Number of Bath Events	0	0	1
Bath Mean Duration, minutes	N/A	N/A	22.00
Bath Volume, gallons	N/A	N/A	50.00
Number of Toilet Events	5	4	4
Toilet Volume, gallons/flush	3.50	3.50	3.50
Number of Dishwasher Events	1 (Household Characteristic)		
Dishwasher Mean Duration, minutes	60.00 (Household Characteristic)		
Dishwasher Volume, gallons	8.51 (Household Characteristic)		
Number of Clothes Washer Events	1 (Household Characteristic)		
Clothes Washer Mean Duration, min	24.7 (Household Characteristic)		
Clothes Washer Volume, gal	37.78 (Household Characteristic)		
Number of Kitchen Faucet Events	7	5	3
Kitchen Faucet Mean Duration, min	0.76	1.33	1.50
Number of Bathroom Faucet Events	5	5	4
Bathroom Faucet Mean Duration, min	1.08	1.75	1.75
Consumption Volume, liters	2.46	0.71	1.01

Table 80 Base-Case Consumption Activity Patterns Used in Sensitivity Analysis

Type	Start Time	End Time	Consumption Vol (L)
ADULT MALE			
Direct	5:35:21 AM	5:37:32 AM	0.03
Direct	6:39:20 AM	6:48:20 AM	0.03
Direct	8:24:23 AM	8:28:51 AM	0.01
Direct	10:02:18 AM	10:03:57 AM	0.01
Direct	10:30:57 AM	10:32:10 AM	0.01
Direct	2:18:25 PM	2:18:56 PM	0.03
Direct	3:17:27 PM	3:22:15 PM	0.02
Direct	8:13:59 PM	8:15:20 PM	0.02
Direct	8:36:07 PM	8:39:57 PM	0.02
Direct	9:56:16 PM	9:58:26 PM	0.01
Indirect	7:24:27 AM	7:27:17 AM	0.04
Indirect	7:02:31 PM	7:05:20 PM	0.13
Indirect	7:35:30 PM	7:41:45 PM	0.35
Indirect	7:43:28 PM	7:44:22 PM	0.37
Indirect	8:56:49 PM	9:00:03 PM	0.36
Total Direct			0.19
Total Indirect			1.25
Total			1.44
ADULT FEMALE			
Direct	5:28:41 AM	5:29:04 AM	0.03
Direct	5:31:35 AM	5:32:37 AM	0.03
Direct	7:54:43 AM	7:58:14 AM	0.02
Direct	7:55:03 AM	7:58:48 AM	0.02
Direct	1:23:48 PM	1:35:26 PM	0.02
Direct	2:50:58 PM	2:52:08 PM	0.02
Direct	4:34:08 PM	4:34:43 PM	0.02
Direct	7:41:12 PM	7:53:14 PM	0.02
Direct	8:38:35 PM	8:40:46 PM	0.02
Direct	9:03:31 PM	9:06:25 PM	0.03
Direct	9:31:48 PM	9:33:12 PM	0.03
Indirect	9:54:24 AM	9:54:33 AM	0.10
Indirect	10:00:18 AM	10:04:30 AM	0.20
Indirect	2:54:18 PM	2:54:33 PM	0.11
Indirect	5:09:48 PM	5:26:02 PM	0.12
Total Direct			0.26
Total Indirect			0.53
Total			0.79
CHILD			
Direct	1:41:39 PM	1:42:20 PM	0.09
Direct	3:03:57 PM	3:05:28 PM	0.30
Direct	7:43:03 PM	7:53:00 PM	0.17
Indirect	5:27:43 AM	5:31:12 AM	0.09
Indirect	5:36:43 AM	5:37:39 AM	0.04
Indirect	7:26:12 AM	7:28:14 AM	0.03
Indirect	8:52:10 AM	8:55:16 AM	0.04
Indirect	9:42:27 AM	9:47:26 AM	0.04
Indirect	10:38:35 AM	10:39:26 AM	0.02
Indirect	11:01:36 AM	11:02:38 AM	0.01
Indirect	6:39:31 PM	6:40:57 PM	0.08
Indirect	8:48:03 PM	11:01:32 PM	0.04
Total Direct			0.56
Total Indirect			0.39
Total			**0.95**

Table 81. Master List of Water Use Variables in TEM for Sensitivity Analysis

Parameter	Male (Age 15-45)			Female (Age 15-45)			Child (Age 6)		
	Base-case	- 10%	+ 10%	Base-case	- 10%	+ 10%	Base-case	- 10%	+ 10%
Number of Shower Events	1	1	1	1	1	1	0	0	0
Shower Mean Duration, minutes	7.15	6.44	7.87	10.10	9.09	11.11	N/A	N/A	N/A
Shower Flowrate, gal/min	2.40	2.16	2.64	2.40	2.16	2.64	N/A	N/A	N/A
Number of Bath Events	0	0	0	0	0	0	1	1	1
Bath Mean Duration, minutes	N/A	N/A	N/A	N/A	N/A	N/A	22.00	19.80	24.20
Bath Volume, gallons	N/A	N/A	N/A	N/A	N/A	N/A	50.00	45.00	55.00
Bath Flowrate, gal/min	N/A	N/A	N/A	N/A	N/A	N/A	2.27	2.04	2.50
Number of Toilet Events	5	5	5	4	4	4	4	4	4
Toilet Volume, gallons/flush	3.50	3.15	3.85	3.50	3.15	3.85	3.50	3.15	3.85
Number of Dishwasher Events	1	1	1	(Household Characteristic)					
Dishwasher Mean Duration, min	60.00	54.00	66.00	(Household Characteristic)					
Dishwasher Volume, gallons	8.51	7.66	9.36	(Household Characteristic)					
Number of Clothes Washer Events	1	1	1	(Household Characteristic)					
Clothes Washer Mean Duration, min	24.7	22.23	27.17	(Household Characteristic)					
Clothes Washer Volume, gal	37.78	34.00	41.56	(Household Characteristic)					
Number of Kitchen Faucet Events	7	7	7	5	5	5	3	3	3
Kitchen Faucet Mean Duration, min	0.76	0.68	0.83	1.33	1.19	1.46	1.50	1.35	1.65
Kitchen Faucet Flowrate, gal/min	1.20	1.08	1.32	1.20	1.08	1.32	1.20	1.08	1.32
Number of Bathroom Faucet Events	5	5	5	5	5	5	4	4	4
Bathroom Faucet Mean Duration, min	1.08	0.97	1.19	1.75	1.58	1.93	1.75	1.58	1.93
Bathroom Faucet Flowrate, gal/min	1.20	1.08	1.32	1.20	1.08	1.32	1.20	1.08	1.32
Number of Laundry Faucet Events	0	0	0	0	0	0	0	0	0
Laundry Faucet Mean Duration, min	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Laundry Faucet Flowrate, gal/min	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Consumption Volume, Liters/day	2.46	2.21	2.71	0.71	0.64	0.78	1.01	0.91	1.11
Consumption Volume, Direct, L/day	0.15	0.14	0.17	0.17	0.15	0.19	0.59	0.53	0.65
Consumption Volume, Indirect, L/day	2.31	2.08	2.54	0.54	0.49	0.59	0.42	0.38	0.46

Table 82. Master List of Environmental and Chemical Parameters in TEM for Sensitivity Analysis

Parameter		Value		
		Mean	- 10%	+ 10%
House and Zone Volumes (m^3)	Whole House	352.86	317.58	388.15
	ROH	293.03	263.73	322.34
	Kitchen	17.22	15.50	18.94
	Master Bath	8.30	7.47	9.14
	Hall Bath	9.18	8.26	10.10
	Laundry	22.20	19.98	24.42
	Shower	2.92	2.63	3.22
House Air Exchange Rate (hr^{-1})	ACH	0.58	0.52	0.64
Interzonal Air Flows (m^3/hr)	Kitchen to ROH	3.40	3.06	3.74
	Master Bath to ROH	1.64	1.48	1.80
	Hall Bath to ROH	1.81	1.63	1.99
	Laundry to ROH	4.38	3.94	4.82
	Shower to Master Bath	50.00	45.00	55.00
Henry's Law Constant (Dimensionless) Chloroform	25°C	0.153	0.138	0.168
	30°C	0.195	0.176	0.215
	35°C	0.238	0.214	0.262
	40°C	0.287	0.258	0.316
Henry's Law Constant (Dimensionless) DCA	25°C	3.4E-7	3.1E-07	3.7E-07
	30°C	5.2E-7	4.7E-07	5.7E-07
	35°C	7.9E-7	7.1E-07	8.7E-07
	40°C	1.2E-6	1.1E-06	1.3E-06
Overall Mass Transfer Coefficient (K_{OLA}) Chloroform	Shower	0.432	0.389	0.475
	Bath, Fill	0.243	0.219	0.267
	Bath, Pool	0.078	0.070	0.086
	Clothes Washer, fill	0.317	0.285	0.349
	Clothes Washer, wash	0.113	0.102	0.124
	Clothes Washer, rinse	0.403	0.363	0.443
	Toilet	0.00468	0.00421	0.00515
	Faucets (35°C)	0.128	0.115	0.141
	Faucets (30°C)	0.117	0.105	0.129
Overall Mass Transfer Coefficient (K_{OLA}) DCA	Shower	4.37E-4	3.93E-04	4.81E-04
	Bath, Fill	7.42E-6	6.678E-06	8.16E-06
	Bath, Pool	3.27E-6	2.943E-06	3.60E-06
	Clothes Washer, fill	3.69E-6	3.321E-06	4.06E-06
	Clothes Washer, wash	3.67E-7	3.303E-07	4.04E-07
	Clothes Washer, rinse	1.52E-6	1.368E-06	1.67E-06
	Toilet	1.63E-7	1.467E-07	1.79E-07
	Faucets (35°C)	3.58E-6	3.222E-06	3.94E-06
	Faucets (30°C)	2.32E-6	2.088E-06	2.55E-06

Table 83. List of Gender Specific Physiological Parameters in ERDEM for Sensitivity Analysis

	Male (Age 15 – 45)			Female (Age 15 – 45)			Child (Age 6)		
	Mean	Lower 10%	Upper 10%	Mean	Lower 10%	Upper 10%	Mean	Lower 10%	Upper 10%
Volume of the Body (Kg)	77.6	69.8	85.5	63.8	57.4	70.2	22.5	20.3	24.8
Arterial Blood (%)	6	5.4	6.6	6	5.4	6.6	6	5.4	6.6
Dermis (%)	9	8.1	9.9	9	8.1	9.9	9	8.1	9.9
Fat (%)	17	15.3	18.7	23	20.7	25.3	17	15.3	18.7
Kidney (%)	0.4	0.36	0.44	0.4	0.36	0.44	0.4	0.36	0.44
Liver (%)	2.6	2.34	2.86	2.6	2.34	2.86	2.6	2.34	2.86
Ovaries (%)	n/a			0.0063	0.0057	0.0069	n/a		
Rapidly Perfused Tissue (%)	4.6	4.14	5.06	4.6	4.14	5.06	4.6	4.14	5.06
Slowly Perfused Tissue (%)	56.0	50.4	61.5	50.0	45.0	55.0	56.0	50.4	61.6
Static Lung (%)	1.4	1.26	1.54	1.4	1.26	1.54	1.4	1.26	1.54
Testes (%)	0.046	0.041	0.051	n/a			0.0074	0.0067	0.0081
Venous Blood (%)	3	2.7	3.3	3	2.7	3.3	3	2.7	3.3
Alveolar Ventilation Rates - (L/hr)									
At Rest Activity	540	486	594	430	387	473	410	369	451
Sedentary Activity	600	540	660	480	432	528	435	391.5	478.5
Blood Flows - (L/hr)									
Cardiac Output – "At Rest" (L/hr)	461.3	415.2	507.5	423.6	381.2	465.9	350.3	315.3	385.3
Cardiac Output – "Sedentary" (L/hr)	512.6	461.3	563.9	472.8	425.5	520.1	371.6	334.5	408.8
Dermis (%)	4.8	4.32	5.28	4.8	4.32	5.28	4.8	4.3	5.3
Fat (%)	4.8	4.32	5.28	4.8	4.32	5.28	4.8	4.3	5.3
Kidney (%)	19.4	17.5	21.3	19.6	17.6	21.6	19.6	17.6	21.6
Liver (%)	23.7	21.3	26.1	24	21.6	26.4	24	21.6	26.4
Ovaries (%)	n/a			0.02	0.018	0.022	n/a		
Rapidly Perfused Tissue (%)	27	24.3	29.7	27.6	24.8	30.3	27.4	24.7	30.1
Slowly Perfused Tissue (%)	19	17.1	20.9	19.2	17.28	21.12	19.2	17.3	21.1
Testes (%)	1.3	1.17	1.43	n/a			0.21	0.19	0.23

[a] These variables are scaled to the body weight to the –0.25 power.
[b] Vmax is scaled to the body weight to the +0.7 power.

Table 84. *List of General Physiological Parameters in ERDEM for Sensitivity Analysis*

	All Demographic Groups		
	Mean	Lower 10%	Upper 10%
Chloroform Skin Permeability Coefficient (cm/hr)	0.13	0.117	0.143
DCA Skin Permeability Coefficient (cm/hr)	1.84E-06	1.656E-06	2.024E-06
Chloroform Gastro-Intestinal Absorption Rate Constants			
Stomach to Portal Blood Rate Constant (1/hr)	5	4.5	5.5
Stomach to Intestine Rate Constant (1/hr)	2	1.8	2.2
Intestine to Portal Blood Rate Constant (1/hr)	6	5.4	6.6
DCA Gastro-Intestinal Absorption Rates Constants			
Stomach to Portal Blood Rate Constant (1/hr)	13.65	12.285	15.015
Stomach to Intestine Rate Constant (1/hr)	2.18	1.962	2.398
Intestine to Portal Blood Rate Constant (1/hr)	0.044	0.0396	0.0484
Chloroform Partition Coefficients Used by ERDEM			
Dermis/Blood	1.62	1.458	1.782
Fat/Blood	37.69	33.921	41.459
Kidney/Blood	1.48	1.332	1.628
Liver/Blood	2.29	2.061	2.519
Ovaries/Blood	1.37	1.233	1.507
Rapidly Perfused Tissue/Blood	2.29	2.061	2.519
Slowly Perfused Tissue/Blood	1.62	1.458	1.782
Static Lung/Air	7.43	6.687	8.173
Static Lung/Blood	1	0.9	1.1
Testes/Blood	1.89	1.701	2.079
DCA Partition Coefficients Used by ERDEM			
Dermis/Blood	0.43	0.387	0.473
Fat/Blood	2.8	2.52	3.08
Kidney/Blood	0.8	0.72	0.88
Liver/Blood	0.8	0.72	0.88
Ovaries/Blood	0.95	0.855	1.045
Rapidly Perfused Tissue/Blood	0.8	0.72	0.88
Slowly Perfused Tissue/Blood	0.43	0.387	0.473
Static Lung/Air	n/a		
Static Lung/Blood	0.16	0.144	0.176
Testes/Blood	0.99	0.891	1.089
Chloroform Metabolism Parameters			
Liver Linear Metabolism Rate Constant (1/hr/kg) [a]	0.39917	0.359253	0.439087
Kidney Linear Metabolism Rate Constant (1/hr/kg) [a]	0.001857	0.0016713	0.0020427
Liver Metabolism Vmax (mg/hr/kg) [b]	15.7	14.13	17.27
Kidney Metabolism Ratio of Kidney to Liver Vmax	0.033	0.0297	0.0363
Liver Metabolism Michaelis-Menten Constant (mg/L)	0.448	0.4032	0.4928
Kidney Metabolism Michaelis-Menten Constant (mg/L)	0.448	0.4032	0.4928
DCA Elimination Rate Constants			
Urine Elimination Rate Constant (1/hr/kg) [a]	0.023	0.0207	0.0253
Liver Elimination Rate Constant (1/hr/kg) [a]	20.5	18.45	22.55

[a] These variables are scaled to the body weight to the *–0.25* power.
[b] Vmax is scaled to the body weight to the +0.7 power.

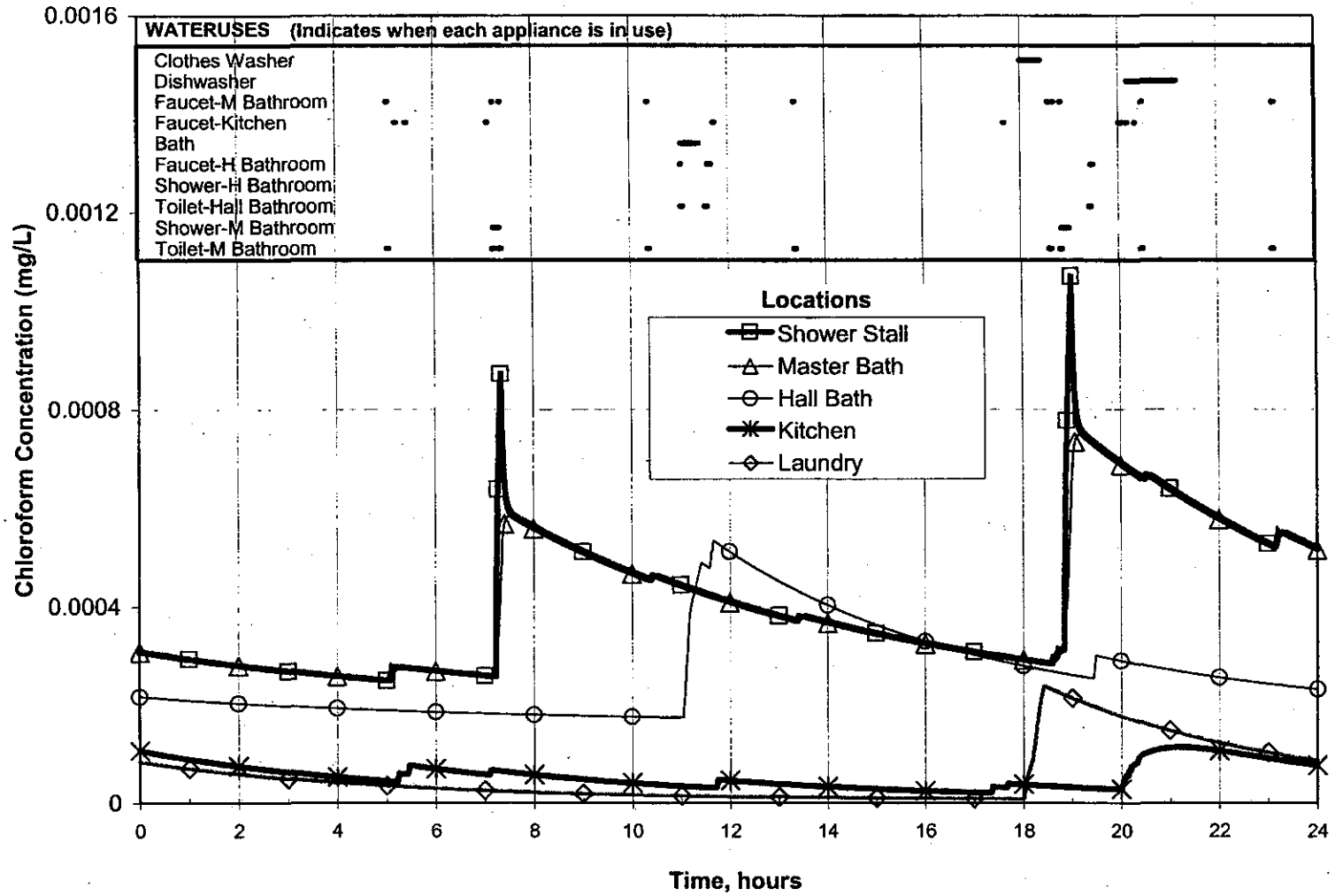


Figure 75. Predicted Chloroform Air Concentrations for the Base-case Scenario
Note: The time when water uses occur are shown in the upper inset.

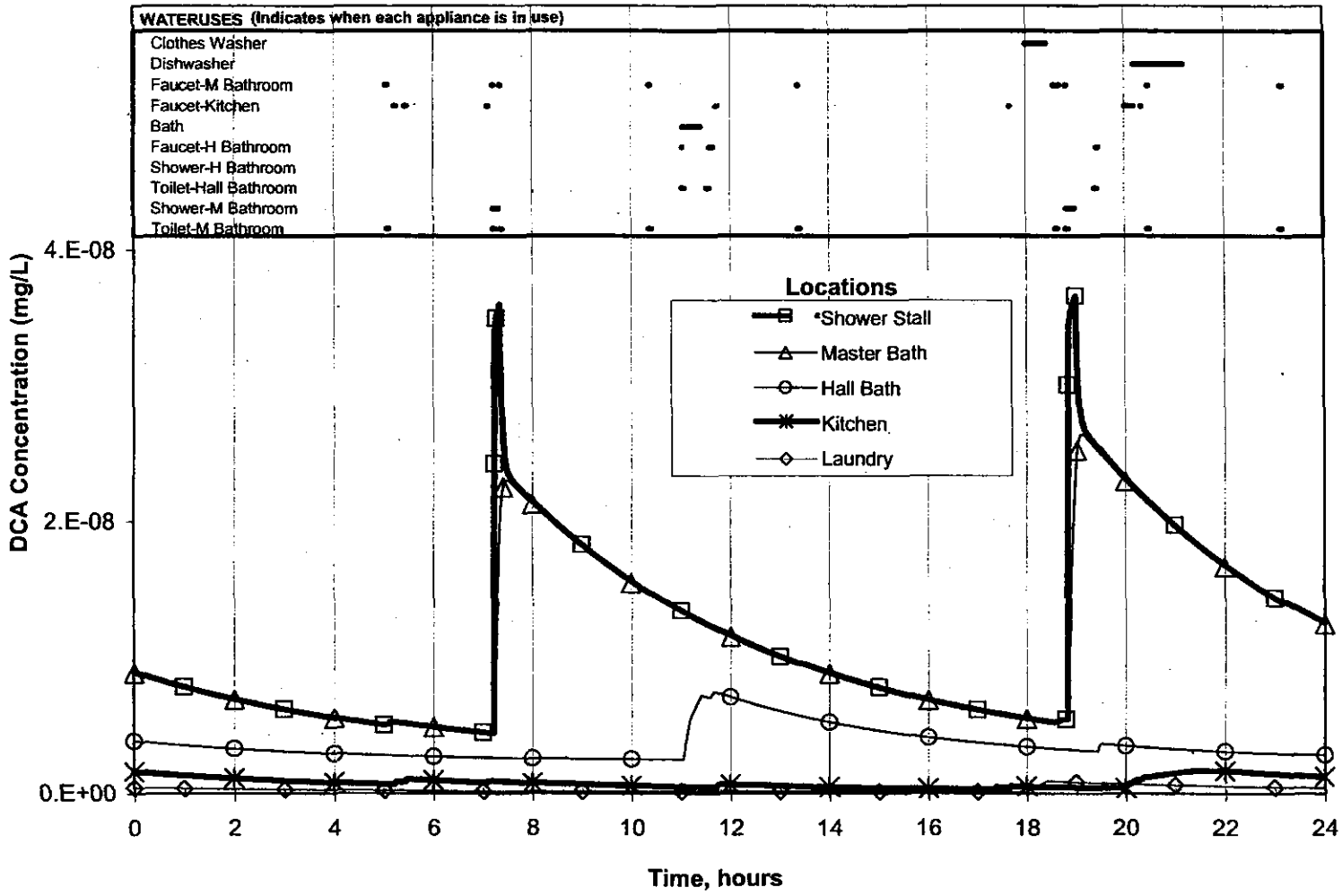
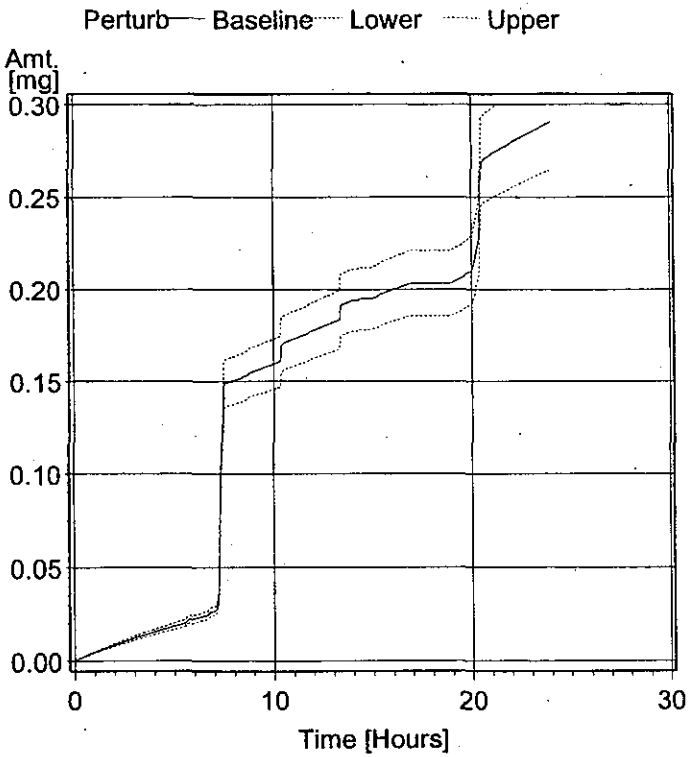
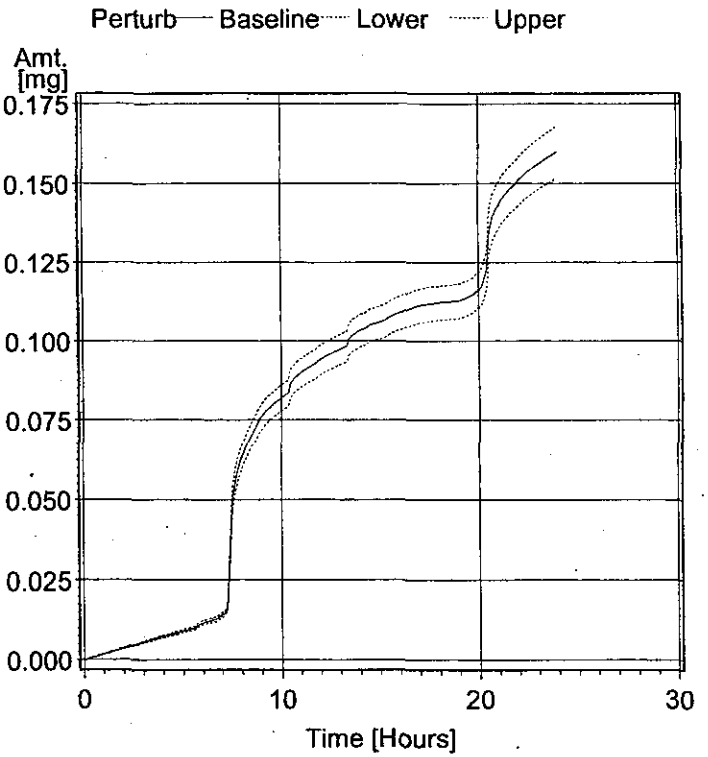


Figure 76. Predicted DCA Air Concentrations for the Base-case Scenario
Note: The time when water uses occur are shown in the upper inset.

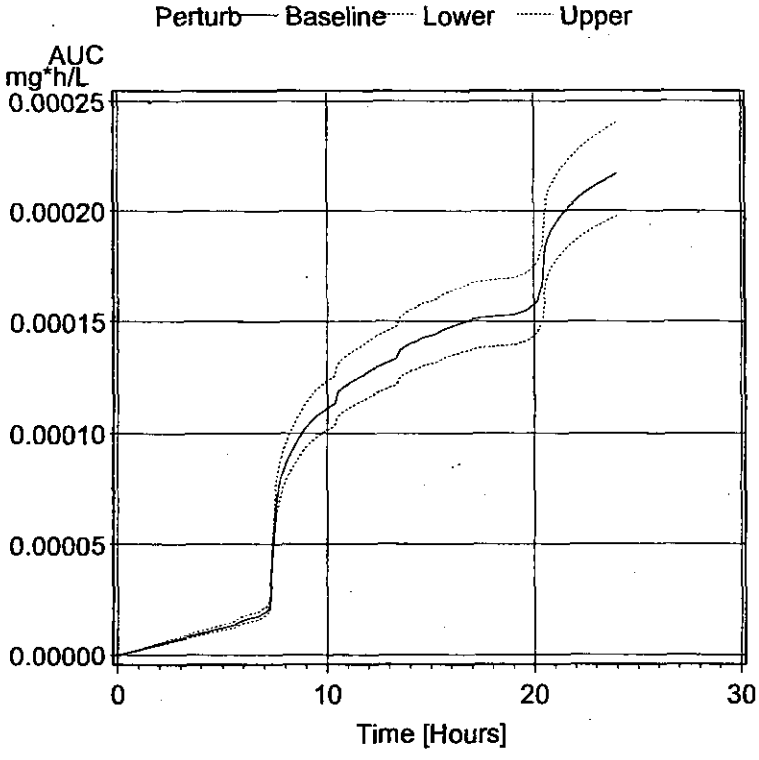


(a) Absorbed Dose Perturbing on Alveolar Ventilation Rate

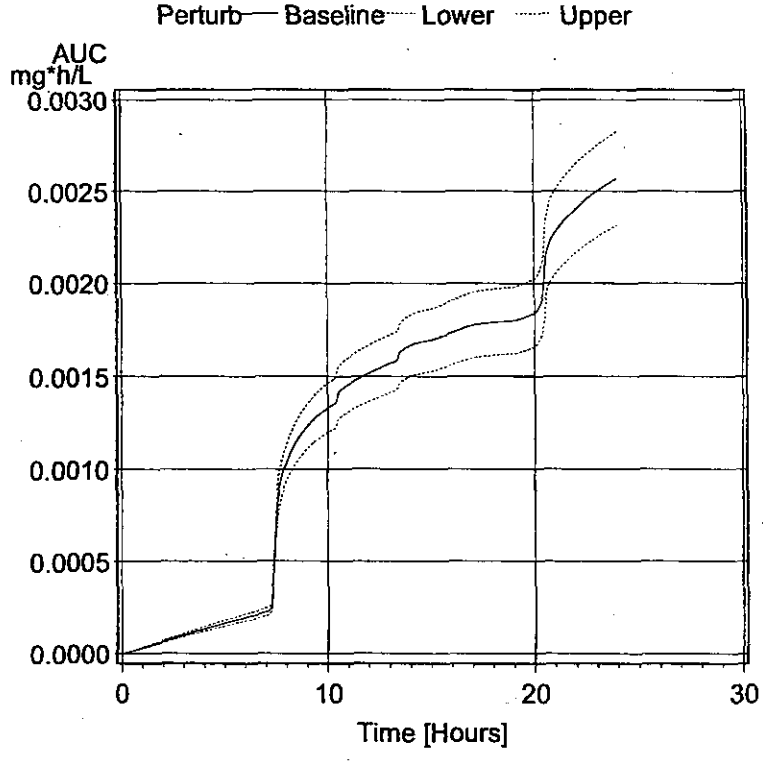


(b) Amount Metabolized in the Liver Perturbing on Alveolar Ventilation Rate

Figures 77a and b. Dose Metric Curves for Chloroform: Absorbed Dose and Amount Metabolized in the Liver

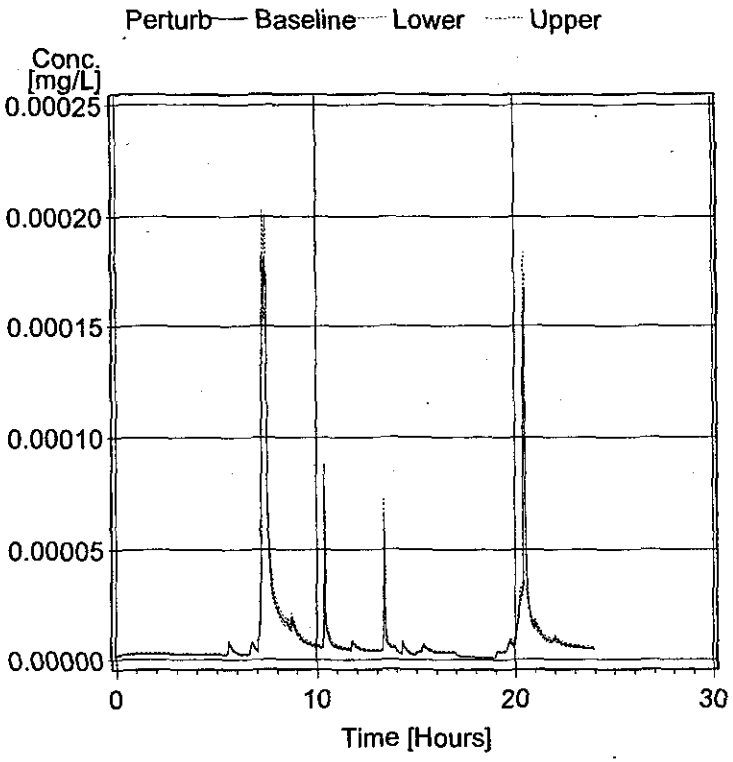


(c) AUC in the Liver Perturbing on Liver Metabolism Vmax

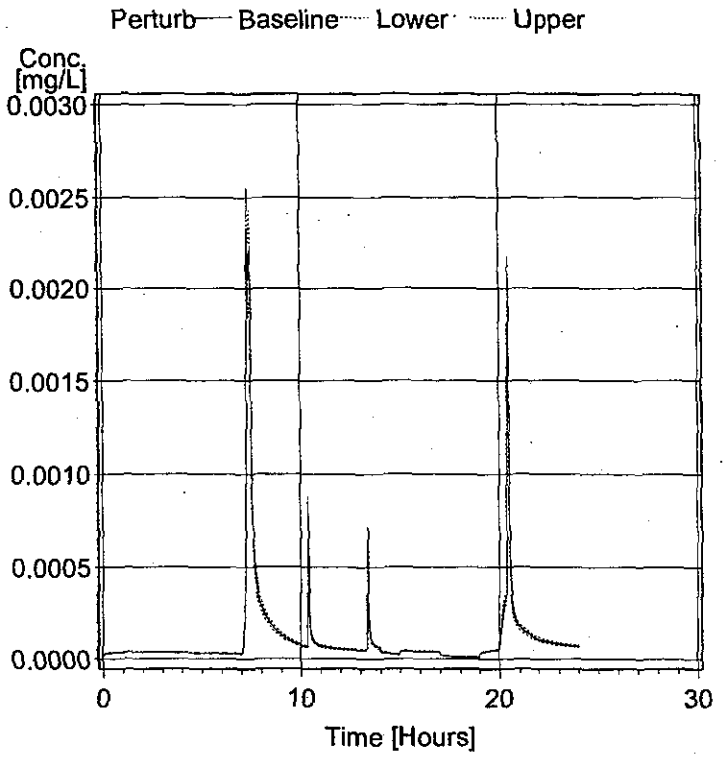


(d) AUC in the Testes Perturbing on Partition Coefficient Testes/Blood

Figures 77c and d. Dose Metric Curves for Chloroform: AUC in the Liver and AUC in the Testes

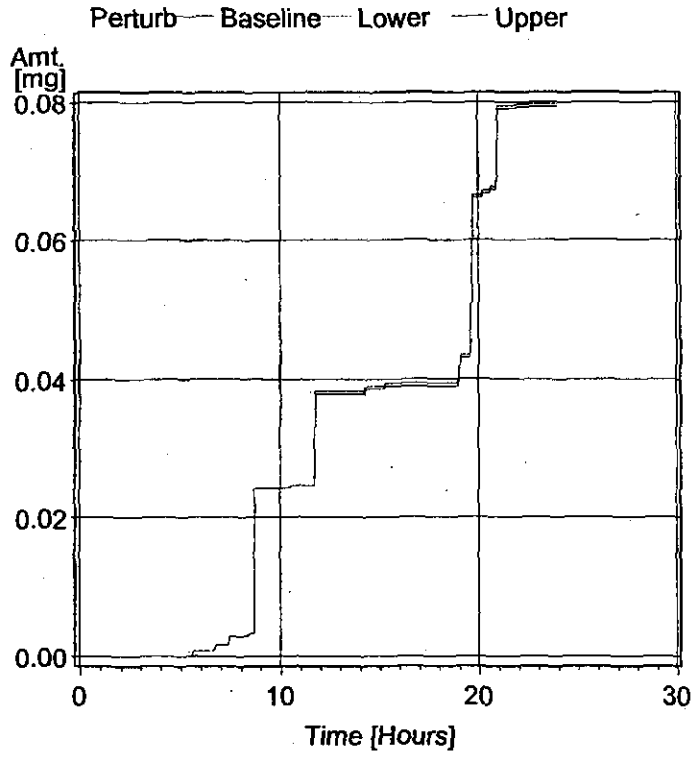


(e) Conc. in the Liver Perturbing on Liver Metabolism Vmax

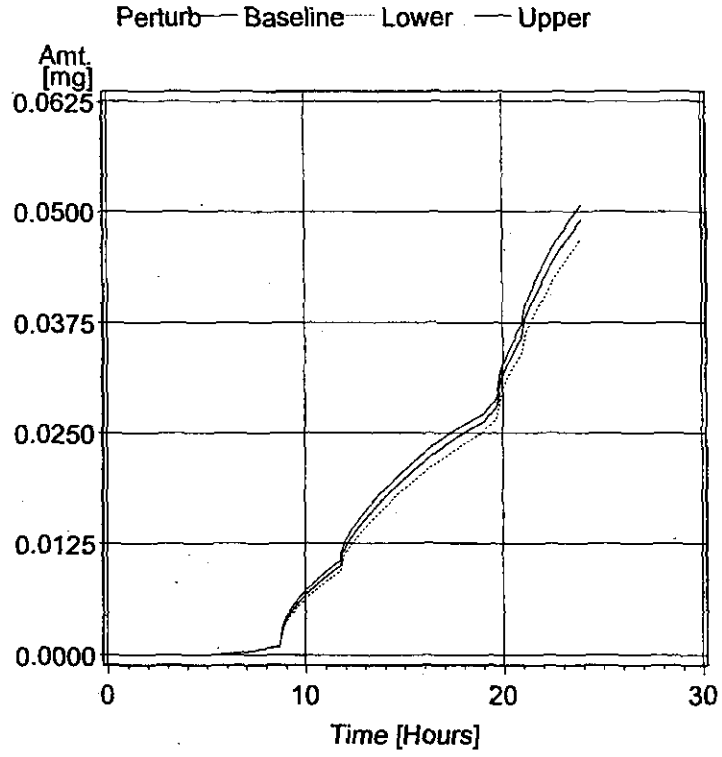


(f) Conc. In the Testes Perturbing on Partition Coefficient Testes/Blood

Figures 77e and f. Dose Metric Curves for Chloroform: Concentration in the Liver and Concentration in the Testes

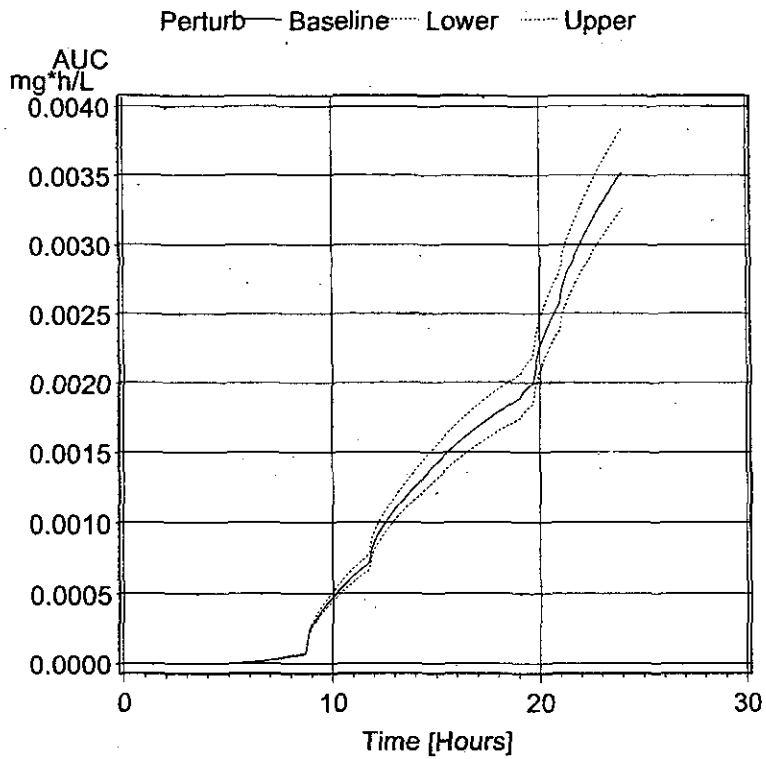


(a) Absorbed Dose Perturbing on Blood Flow in the Kidney

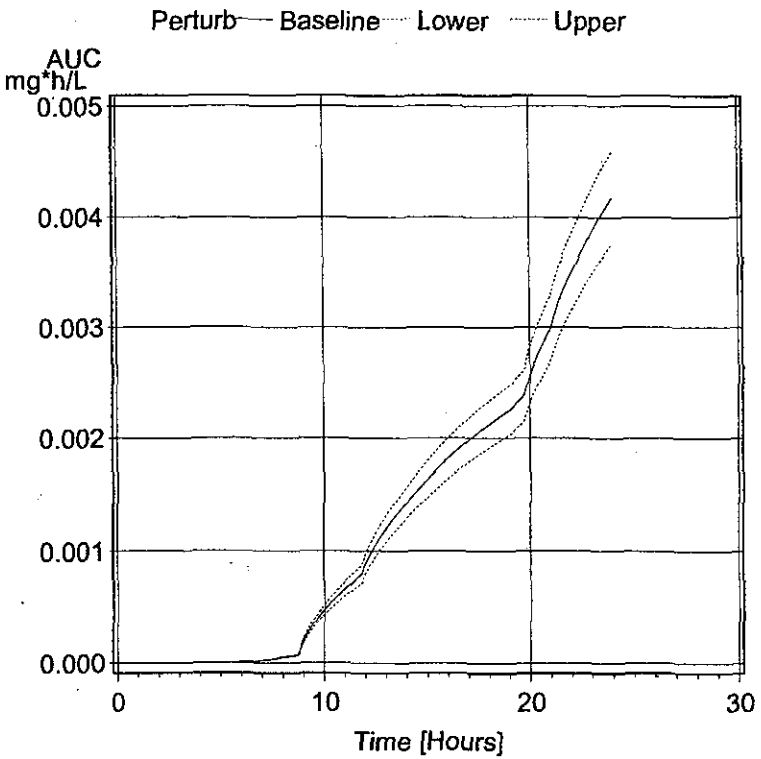


(b) Amount Eliminated in the Liver Perturbing on Volume in the Liver

Figures 78a and b. Dose Metric Curves for DCA: Absorbed Dose and Amount Eliminated in the Liver

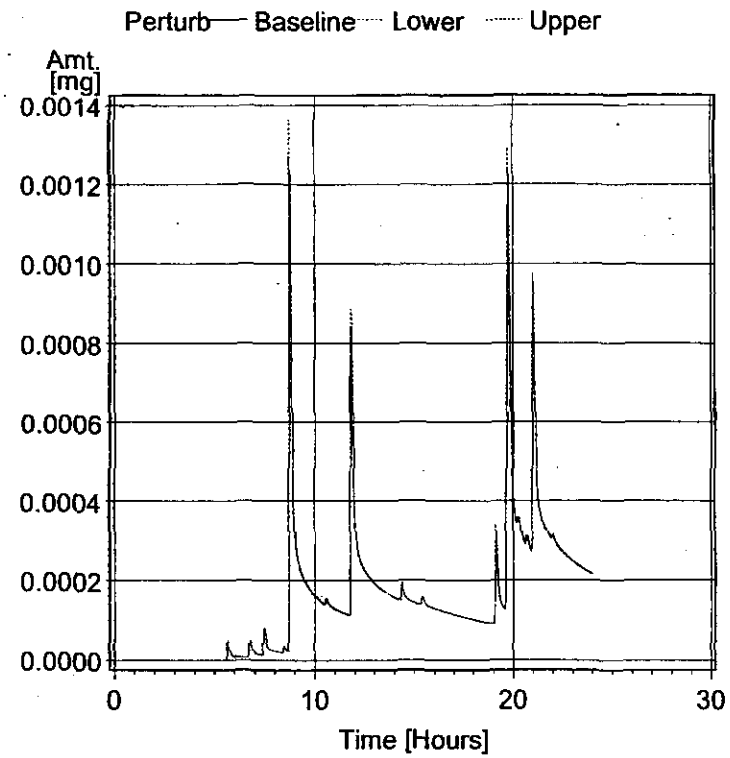


(c) AUC in the Liver Perturbing on Volume of the Body

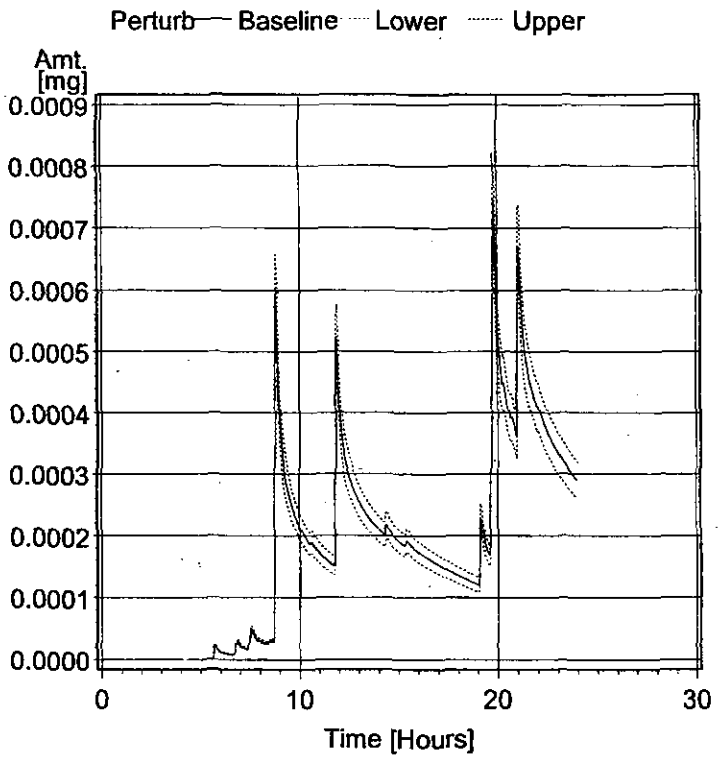


(d) AUC in the Testes Perturbing on Partition Coefficient Testes/Blood

Figures 78c and d. Dose Metric Curves for DCA: AUC in the Liver and AUC in the Testes



(e) Conc. in the Liver Perturbing on Stomach to Portal Blood Absorption Rate Constant



(f) Conc. in the Testes Perturbing on Partition Coefficient Testes/Blood

Figures 78e and f. Dose Metric Curves for DCA: Concentration in the Liver and Concentration in the Testes

Table 85. TEM Base-case Potential and Absorbed Dose for Chloroform

Metric [A]	Dose , mg		
	Male 15-45 yrs.	Female 15-45 yrs.	Child 6 yrs.
Potential Inhalation Dose	0.266010735	0.239679844	0.208615334
Absorbed Inhalation Dose	0.23151009	0.211023873	0.180522758
Absorbed Dermal Dose	0.02207942	0.02661466	0.025053723
Absorbed Ingestion Dose	0.014786	0.008045	0.009516
Total Absorbed Dose	0.26837551	0.245683534	0.215092481

A Potential Dose is defined as the mass available for uptake, or an exposure multiplied by a contact rate. For inhalation, the potential dose is the mass of the compound entering the lungs (C(t) * time * breathing rate). The Absorbed Dose is the mass that is absorbed into the blood stream. The methods for estimating absorbed dose are described in Section 3.7.

Table 86. TEM Base-case Potential and Absorbed Dose for DCA

Metric [A]	Dose , mg		
	Male 15-45 yrs.	Female 15-45 yrs.	Child 6 yrs.
Potential Inhalation Dose	8.25994E-06	6.41688E-06	3.1475E-06
Absorbed Inhalation Dose	8.25954E-06	6.4166E-06	3.14734E-06
Absorbed Dermal Dose	9.36504E-06	9.5867E-06	6.08603E-06
Absorbed Ingestion Dose	0.045075	0.024519	0.029001
Total Absorbed Dose	0.045092625	0.024535003	0.029010233

A. Potential Dose is defined as the mass available for uptake, or an exposure multiplied by a contact rate. For inhalation, the potential dose is the mass of the compound entering the lungs (C(t) * time * breathing rate). The Absorbed Dose is the mass that is absorbed into the blood stream. The methods for estimating absorbed dose are described in Section 3.7.

Table 87. Relative Sensitivity Analysis of Potential and Absorbed Dose to Changes in Environmental and Chemical Parameters for Chloroform

Parameter *	Metric	Male 15-45 yrs.		Female 15-45 yrs.		Child 6 yrs.	
		-10%	10%	-10%	10%	-10%	10%
House and Zone Volumes (m^3)	Potential Inhalation Dose, mg	-32.95	-28.92	-14.37	-13.78	-30.82	-24.96
	Absorbed Inhalation Dose, mg	-32.89	-28.87	-14.34	-13.77	-30.78	-24.93
	Total Absorbed Dose, mg	-28.37	-24.90	-12.32	-11.82	-25.83	20.93
House Air Exchange Rate (hr-1) and Inter-zonal Air Flows (m^3/hr)	Potential Inhalation Dose, mg	-71.98	-61.34	-88.81	-75.76	-78.72	-63.63
	Absorbed Inhalation Dose, mg	-72.05	-61.40	-88.84	-75.79	-78.76	-63.67
	Total Absorbed Dose, mg	-62.15	-52.97	-76.31	65.10	-66.10	53.43
Henry's Law Constant (Dimensionless), Chloroform	Potential Inhalation Dose, mg	3.38	2.74	3.64	2.94	2.58	2.14
	Absorbed Inhalation Dose, mg	3.38	2.74	3.64	2.94	2.58	2.14
	Total Absorbed Dose, mg	2.92	2.37	3.13	2.53	2.17	1.80
Overall Mass Transfer Coefficient (K_{OLA}), Chloroform	Potential Inhalation Dose, mg	92.99	92.93	93.56	93.60	90.06	85.05
	Absorbed Inhalation Dose	92.97	92.91	93.55	93.59	90.06	85.05
	Total Absorbed Dose	80.20	80.15	80.35	80.39	75.58	71.38

* Doses reflect the impact of changing the parameter by 10%

Table 88. Relative Sensitivity Analysis of Potential and Absorbed Dose for Water Use Parameters for Chloroform

Parameter *	Metric	Male 15-45 yrs.		Female 15-45 yrs.		Child 6 yrs.	
		-10%	10%	-10%	10%	-10%	10%
Shower Mean Duration, minutes	Potential Inhalation Dose, mg	28.16	32.16	22.61	15.96	3.73	3.16
	Absorbed Inhalation Dose, mg	28.12	32.11	22.59	15.95	3.75	3.18
	Potential Dermal Dose, mg	92.73	92.73	92.35	92.32	0.00	0.00
	Absorbed Dermal Dose, mg	85.75	85.75	87.65	87.62	0.00	0.00
	Total Absorbed Dose, mg	31.31	34.76	28.90	23.19	3.15	2.67
Shower Flowrate, gal/min	Potential Inhalation Dose, mg	39.64	39.48	37.25	37.09	5.53	5.50
	Absorbed Inhalation Dose, mg	39.59	39.43	37.23	37.06	5.55	5.53
	Potential Dermal Dose, mg	0.00	0.00	0.00	0.00	0.00	0.00
	Absorbed Dermal Dose, mg	0.00	0.00	0.00	0.00	0.00	0.00
	Total Absorbed Dose, mg	34.15	34.02	31.98	31.83	4.66	4.64
Bath Mean Duration, minutes	Potential Inhalation Dose, mg	1.03	0.97	0.34	0.32	10.99	9.25
	Absorbed Inhalation Dose, mg	1.03	0.97	0.34	0.32	10.97	9.23
	Potential Dermal Dose, mg	0.00	0.00	0.00	0.00	97.34	97.34
	Absorbed Dermal Dose, mg	0.00	0.00	0.00	0.00	95.05	95.05
	Total Absorbed Dose, mg	0.89	0.84	0.29	0.28	20.28	18.82
Bath Volume, gallons	Potential Inhalation Dose, mg	0.33	0.29	0.10	0.09	5.48	4.72
	Absorbed Inhalation Dose, mg	0.33	0.29	0.10	0.09	5.47	4.71
	Potential Dermal Dose, mg	0.00	0.00	0.00	0.00	0.00	0.00
	Absorbed Dermal Dose, mg	0.00	0.00	0.00	0.00	0.00	0.00
	Total Absorbed Dose, mg	0.29	0.25	0.09	0.08	4.59	3.96
Bath Flowrate, gal/min	Potential Inhalation Dose, mg	1.06	1.03	0.33	0.32	20.82	20.24
	Absorbed Inhalation Dose, mg	1.06	1.03	0.33	0.32	20.79	20.21
	Potential Dermal Dose, mg	0.00	0.00	0.00	0.00	0.00	0.00
	Absorbed Dermal Dose, mg	0.00	0.00	0.00	0.00	0.00	0.00
	Total Absorbed Dose, mg	0.92	0.89	0.28	0.27	17.45	16.96
Toilet Volume, gallons/flush	Potential Inhalation Dose, mg	0.00	0.00	0.00	0.00	0.00	0.00
	Absorbed Inhalation Dose, mg	0.00	0.00	0.00	0.00	0.00	0.00
	Total Absorbed Dose, mg	0.00	0.00	0.00	0.00	0.00	0.00
Dishwasher Mean Duration, minutes	Potential Inhalation Dose, mg	0.13	0.11	0.15	0.13	0.14	0.12
	Absorbed Inhalation Dose, mg	0.13	0.11	0.15	0.13	0.14	0.12
	Total Absorbed Dose, mg	0.11	0.09	0.13	0.11	0.12	0.10
Dishwasher Volume, gallons	Potential Inhalation Dose, mg	1.62	1.60	1.44	1.43	1.40	1.39
	Absorbed Inhalation Dose, mg	1.62	1.60	1.44	1.43	1.41	1.40
	Total Absorbed Dose, mg	1.40	1.38	1.24	1.23	1.18	1.17
Clothes Washer Mean Duration, minutes	Potential Inhalation Dose, mg	3.48	3.95	2.78	3.16	3.45	3.93
	Absorbed Inhalation Dose, mg	3.50	3.99	2.79	3.18	3.47	3.95
	Total Absorbed Dose, mg	3.02	3.44	2.40	2.73	2.91	3.32

Table 88. Relative Sensitivity Analysis of Potential and Absorbed Dose for Water Use Parameters for Chloroform (Continued)

Parameter *	Metric	Male 15-45 yrs.		Female 15-45 yrs.		Child 6 yrs.	
		-10%	10%	-10%	10%	-10%	10%
Clothes Washer Volume, gallons	Potential Inhalation Dose	1.64	1.42	1.31	1.14	1.64	1.43
	Absorbed Inhalation Dose	1.65	1.43	1.32	1.15	1.65	1.44
	Total Absorbed Dose	1.42	1.24	1.13	0.98	1.39	1.21
Kitchen Faucet Mean Duration, minutes	Potential Inhalation Dose	7.96	6.88	3.15	3.10	7.20	6.26
	Absorbed Inhalation Dose	7.95	6.88	3.15	3.10	7.19	6.25
	Potential Dermal Dose	3.04	3.04	2.94	2.93	1.04	1.04
	Absorbed Dermal Dose	2.84	2.82	2.79	2.78	1.02	1.02
	Total Absorbed Dose	7.09	6.16	3.01	2.96	6.15	5.37
Kitchen Faucet Flowrate, gallons/minutes	Potential Inhalation Dose	9.50	9.49	5.70	5.70	9.19	9.18
	Absorbed Inhalation Dose	9.50	9.49	5.71	5.71	9.19	9.18
	Potential Dermal Dose	0.00	0.00	0.00	0.00	0.00	0.00
	Absorbed Dermal Dose	0.00	0.00	0.00	0.00	0.00	0.00
	Total Absorbed Dose	8.20	8.19	4.90	4.90	7.71	7.71
Bathroom Faucet Mean Duration, minutes	Potential Inhalation Dose	7.93	4.98	12.16	4.97	4.34	1.80
	Absorbed Inhalation Dose	7.92	4.97	12.15	4.97	4.34	1.80
	Potential Dermal Dose	3.67	3.67	7.02	1.37	1.62	1.62
	Absorbed Dermal Dose	3.39	3.39	6.66	1.30	1.59	1.59
	Total Absorbed Dose	7.11	4.57	11.15	4.41	3.83	1.69
Bathroom Faucet Flowrate, gallons/minute	Potential Inhalation Dose	7.50	7.50	10.20	10.19	3.84	3.84
	Absorbed Inhalation Dose	7.50	7.49	10.19	10.19	3.84	3.84
	Potential Dermal Dose	0.00	0.00	0.00	0.00	0.00	0.00
	Absorbed Dermal Dose	0.00	0.00	0.00	0.00	0.00	0.00
	Total Absorbed Dose	6.47	6.46	8.76	8.75	3.22	3.22
Consumption Volume, liters/day	Absorbed Ingestion Dose	100.03	99.96	99.94	100.06	100.04	98.89
	Total Absorbed Dose	5.51	5.51	3.27	3.28	4.43	4.37

* Doses reflect the impact of changing the parameter by 10%. The exposure routes not shown do not impact the parameters, e.g. dishwashers impact only via the inhalation route not via ingestion or dermal exposure.

Table 89. Six Dose Metric Outputs with All Parameters at Baseline Values

Dose Metrics	Output Value for Given Dose Metric	
	Chloroform	DCA
Absorbed Dose at 24 hr (mg)	0.290179	0.079672
Amount Metabolized in Liver at 24 hr (mg)	0.159827	n/a
Amount Eliminated in Liver at 24 hr (mg)	n/a	0.0490569
AUC in Liver at 24 hr (mg*h /L)	0.00021678	0.00352027
AUC in Testes at 24 hr (mg*h /L)	0.00256914	0.00417252
Peak Conc. in Liver (mg/L)	0.00018316 at 7.35 hr	0.00127294 at 8.75 hr
Peak Conc. in Testes (mg/L)	0.00232539 at 7.35 hr	0.00074819 at 19.8 hr

Table 90. Chloroform - Relative Sensitivity of Absorbed Dose at 24 hrs.

Description	Perturbation	Absorbed Dose	Relative Sensitivity*, %
Alveolar Ventilation Rates (L/hr)	Lower	0.264291	89.21389901
Alveolar Ventilation Rates (L/hr)	Upper	0.316116	89.3827603

*Note: In the adult male study of exposure to disinfection byproducts of chloroform ($CHCl_3$), with three multiple routes dermis, inhalation, and ingestion in a 24 h time period, with the exposure and dose model TEM and the PBPK model ERDEM, the dose metric Absorbed Dose is given with the dose estimate and relative sensitivity. The base-case value for the Absorbed Dose is 0.290179. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 91. Chloroform - Relative Sensitivity of Amount Metabolized in the Liver at 24 hrs.

Description	Perturbation	Amount Metabolized in Liver	Relative Sensitivity*, %
Alveolar Ventilation Rates (L/hr)	Lower	0.15136	52.97603033
Alveolar Ventilation Rates (L/hr)	Upper	0.167699	49.25325508
Cardiac Output (L/hr)	Lower	0.153462	39.82431004
Cardiac Output (L/hr)	Upper	0.165516	35.59473681
Liver (%) - Blood Flow	Lower	0.152928	43.16542261
Liver (%)- Blood Flow	Upper	0.166024	38.77317349
Static Lung/Air - Partition Coef.	Lower	0.153769	37.90348314
Static Lung/Air - Partition Coef.	Upper	0.16519	33.55503138
Static Lung/Blood - Partition Coef.	Lower	0.165754	-37.08384691
Static Lung/Blood - Partition Coef.	Upper	0.154364	-34.18070789

*Note: The base-case value for the amount metabolized in the liver is 0.159827. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 92. Chloroform - Relative Sensitivity of Area Under the Curve for Liver at 24 hrs.

Description	Perturbation	Area Under the Curve for Liver	Relative Sensitivity*, %
Volume of the Body (Kg)	Lower	0.0002341	-79.89666943
Volume of the Body (Kg)	Upper	0.00020217	-67.39551619
Fat (%) - Volume	Lower	0.00022006	-15.1305471
Fat (%)- Volume	Upper	0.00021376	-13.93117446
Slowly Perfused Tissue (%) - Volume	Lower	0.0002258	-41.60900452
Slowly Perfused Tissue (%) - Volume	Upper	0.00020857	-37.87249746
Alveolar Ventilation Rates (L/hr)	Lower	0.00020529	53.00304456
Alveolar Ventilation Rates (L/hr)	Upper	0.00022746	49.2665375
Cardiac Output (L/hr)	Lower	0.00020815	39.80994557
Cardiac Output (L/hr)	Upper	0.0002245	35.61214134
Liver (%) - Blood Flow	Lower	0.00020742	43.17741489
Liver (%) - Blood Flow	Upper	0.00022519	38.7950918
Static Lung/Air - Partition Coef.	Lower	0.00020856	37.91862718
Static Lung/Air - Partition Coef.	Upper	0.00022406	33.5824338
Static Lung/Blood - Partition Coef.	Lower	0.00022482	-37.08829228
Static Lung/Blood - Partition Coef.	Upper	0.00020937	-34.18212012
Liver Metabolism Vmax (mg/hr/kg)	Lower	0.00024005	-107.3438509
Liver Metabolism Vmax (mg/hr/kg)	Upper	0.00019764	-88.29227789
Liver Metabolism Michaelis-Menten Constant (mg/L)	Lower	0.00019571	97.19531322
Liver Metabolism Michaelis-Menten Constant (mg/L)	Upper	0.00023775	96.73401605

*Note: The base-case value for the area under the curve for the liver is 0.00021678. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 93. Chloroform - Relative Sensitivity of Area Under the Curve for Testes at 24 hrs.

Description	Perturbation	Area Under the Curve for Testes	Relative Sensitivity*, %
Alveolar Ventilation Rates (L/hr)	Lower	0.00242395	56.51307441
Alveolar Ventilation Rates (L/hr)	Upper	0.00270414	52.54676662
Cardiac Output (L/hr)	Lower	0.00271439	-56.53642853
Cardiac Output (L/hr)	Upper	0.00244102	-49.8688277
Liver (%) - Blood Flow	Lower	0.00270471	-52.76863075
Liver (%) - Blood Flow	Upper	0.00244852	-46.94956289
Static Lung/Air - Partition Coef.	Lower	0.00246523	40.44544089
Static Lung/Air - Partition Coef.	Upper	0.0026612	35.83300248
Static Lung/Blood - Partition Coef.	Lower	0.00267083	-39.5813385
Static Lung/Blood - Partition Coef.	Upper	0.00247527	-36.53751839
Testes/Blood - Partition Coef.	Lower	0.00231218	100.0179048
Testes/Blood - Partition Coef.	Upper	0.0028266	100.2125225

*Note: The base-case value for the area under the curve for the testes is 0.00256914. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 94. Chloroform - Relative Sensitivity of Peak Concentration in Liver at 7.35 hrs.

Description	Perturbation	Peak Concentration in Liver	Relative Sensitivity* %
Volume of the Body (Kg)	Lower	0.00020033	-93.74317537
Volume of the Body (Kg)	Upper	0.00016886	-78.07381524
Dermis (%) - Volume	Lower	0.00018558	-13.21249181
Dermis (%) - Volume	Upper	0.00018103	-11.62917668
Fat (%) - Volume	Lower	0.00018531	-11.73837082
Fat (%) - Volume	Upper	0.00018106	-11.46538546
Rapidly Perfused Tissue (%) - Volume	Lower	0.00018564	-13.54007425
Rapidly Perfused Tissue (%) - Volume	Upper	0.00018092	-12.22974449
Slowly Perfused Tissue (%) - Volume	Lower	0.00019095	-42.53112033
Slowly Perfused Tissue (%) - Volume	Upper	0.00017616	-38.21795152
Alveolar Ventilation Rates (L/hr)	Lower	0.00016959	74.08822887
Alveolar Ventilation Rates (L/hr)	Upper	0.00019613	70.81240446
Cardiac Output (L/hr)	Lower	0.00017628	37.56278664
Cardiac Output (L/hr)	Upper	0.00018942	34.17776807
Liver (%) - Blood Flow	Lower	0.00017068	68.13714785
Liver (%) - Blood Flow	Upper	0.00019485	63.82397904
Slowly Perfused Tissue (%) - Blood Flow	Lower	0.000187	-20.96527626
Slowly Perfused Tissue (%) - Blood Flow	Upper	0.00017963	-19.27276698
Rapidly Perfused Tissue/Blood - Partition Coef.	Lower	0.00018506	-10.37344398
Static Lung/Air - Partition Coef.	Lower	0.00017901	22.65778554
Static Lung/Air - Partition Coef.	Upper	0.00018677	19.70954357
Static Lung/Blood - Partition Coef.	Lower	0.00018681	-19.92793186
Static Lung/Blood - Partition Coef.	Upper	0.00017965	-19.16357283
Liver Metabolism Vmax (mg/hr/kg)	Lower	0.00020312	-108.9757589
Liver Metabolism Vmax (mg/hr/kg)	Upper	0.00016685	-89.04782704
Liver Metabolism Michaelis-Menten Constant (mg/L)	Lower	0.00016514	98.38392662
Liver Metabolism Michaelis-Menten Constant (mg/L)	Upper	0.00020113	98.11094125

*Note: The base-case value for the peak concentration in the liver is 0.00018316. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 95. Chloroform - Relative Sensitivity of Peak Concentration in Testes at 7.35 hrs.

Description	Perturbation	Peak Concentration in Testes	Relative Sensitivity* %
Volume of the Body (Kg)	Lower	0.00238841	-27.1008304
Volume of the Body (Kg)	Upper	0.00226551	-25.75051927
Alveolar Ventilation Rates (L/hr)	Lower	0.00214884	75.92274844
Alveolar Ventilation Rates (L/hr)	Upper	0.00249441	72.68458194
Cardiac Output (L/hr)	Lower	0.00245547	-55.93900378
Cardiac Output (L/hr)	Upper	0.00220859	-50.22813378
Liver (%) - Blood Flow	Lower	0.0023853	-25.76342033
Liver (%) - Blood Flow	Upper	0.00226804	-24.66252973
Slowly Perfused Tissue (%) - Blood Flow	Lower	0.00236983	-19.11077282
Slowly Perfused Tissue (%) - Blood Flow	Upper	0.0022822	-18.57322858
Static Lung/Air - Partition Coef.	Lower	0.00227382	22.17692516
Static Lung/Air - Partition Coef.	Upper	0.00236856	18.56462787
Static Lung/Blood - Partition Coef.	Lower	0.0023725	-20.25896731
Static Lung/Blood - Partition Coef.	Upper	0.0022795	-19.73432413
Testes/Blood - Partition Coef.	Lower	0.00209401	99.50158898
Testes/Blood - Partition Coef.	Upper	0.00255444	98.49960652

*Note: The base-case value for the peak concentration in the testes is 0.00232539. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 96. DCA - Relative Sensitivity of Amount Eliminated in the Liver at 24 hrs.

Description	Perturbation	Amount Eliminated in Liver	Relative Sensitivity*, %
Fat (%) - Volume	Lower	0.0497513	-14.15499145
Fat (%) - Volume	Upper	0.0481616	-18.25023595
Liver (%) - Volume	Lower	0.0468566	44.85199839
Liver (%) - Volume	Upper	0.0507773	35.06948054
Slowly Perfused Tissue (%) - Volume	Lower	0.0498701	-16.57666913
Slowly Perfused Tissue (%) - Volume	Upper	0.0480279	-20.97564257
Stomach to Portal Blood Absorption Rate Constant (1/hr)	Lower	0.0485266	10.80989626
Stomach to Intestine Absorption Rate Constant (1/hr)	Upper	0.0485567	-10.19632305
Fat/Blood - Partition Coef.	Lower	0.0499402	-18.00562204
Fat/Blood - Partition Coef.	Upper	0.048244	-16.57055379
Liver/Blood - Partition Coef.	Lower	0.0471381	39.11376381
Liver/Blood - Partition Coef.	Upper	0.0505815	31.07819695
Slowly Perfused Tissue/Blood - Partition Coef.	Lower	0.0495909	-10.88531888
Liver Elimination Rate Constant (1/hr/kg)	Lower	0.0470954	39.98418163
Liver Elimination Rate Constant (1/hr/kg)	Upper	0.0508403	36.35370356

*Note: The base-case value for the amount eliminated in the liver is 0.0490569. In the adult male study of exposure to disinfection byproducts of dichloroacetic acid (DCA), with two multiple routes dermis and ingestion in a 24 hr time period, with the exposure and dose model TEM and the PBPK model ERDEM, the dose metric Amount Eliminated in Liver is given with the dose estimate and relative sensitivity. This table displays only the results for the parameters whose relative sensitivity is >10%. *For a complete list of all parameters see Tables 83 and 84.*

Table 97. DCA - Relative Sensitivity of Area Under the Curve for Liver at 24 hrs.

Description	Perturbation	Area Under Curve for Liver	Relative Sensitivity*%
Volume of the Body (Kg)	Lower	0.00383383	-89.07271317
Volume of the Body (Kg)	Upper	0.00325814	-74.46303835
Fat (%) - Volume	Upper	0.00347062	-14.10403179
Liver (%) - Volume	Lower	0.00373356	-60.58910254
Liver (%) - Volume	Upper	0.00331463	-58.41597377
Stomach to Portal Blood Rate Absorption Constant (1/hr)	Lower	0.00348222	10.80883001
Stomach to Intestine Absorption Rate Constant (1/hr)	Upper	0.00348438	-10.19524071
Fat/Blood - Partition Coef.	Lower	0.00358366	-18.0071415
Fat/Blood - Partition Coef.	Upper	0.00346194	-16.56975175
Liver/Blood - Partition Coef.	Lower	0.00338258	39.11347709
Liver/Blood - Partition Coef.	Upper	0.00362968	31.08000239
Slowly Perfused Tissue/Blood - Partition Coef.	Lower	0.00355859	-10.88552867
Liver Elimination Rate Constant (1/hr/kg)	Lower	0.00375502	-66.68522585
Liver Elimination Rate Constant (1/hr/kg)	Upper	0.00331659	-57.8591983

*Note: The base-case value for the area under the curve for the liver is 0.00352027. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 98. DCA - Relative Sensitivity of Area Under the Curve for Testes at 24 hrs.

Description	Perturbation	Area Under the Curve for Testes	Relative Sensitivity* %
Volume of the Body (Kg)	Lower	0.00456356	-93.71794503
Volume of the Body (Kg)	Upper	0.0038456	-78.35073289
Fat (%) - Volume	Lower	0.0042237	-12.26596877
Fat (%) - Volume	Upper	0.00410349	-16.54395905
Liver (%) - Volume	Lower	0.0044206	-59.45567667
Liver (%) - Volume	Upper	0.0039322	-57.59588929
Stomach to Portal Blood Absorption Rate Constant (1/hr)	Lower	0.00412679	10.95980367
Stomach to Intestine Absorption Rate Constant (1/hr)	Upper	0.00412953	-10.30312617
Fat/Blood - Partition Coef.	Lower	0.00425809	-20.50799038
Fat/Blood - Partition Coef.	Upper	0.00409361	-18.91183266
Liver/Blood - Partition Coef.	Lower	0.0044507	-66.66954263
Liver/Blood - Partition Coef.	Upper	0.00391417	-61.91701897
Slowly Perfused Tissue/Blood - Partition Coef.	Lower	0.00422405	-12.34985093
Slowly Perfused Tissue/Blood - Partition Coef.	Upper	0.00412586	-11.18269056
Testes/Blood - Partition Coef.	Lower	0.00375753	99.45788157
Testes/Blood - Partition Coef.	Upper	0.00459209	100.5555396
Liver Elimination Rate Constant (1/hr/kg)	Lower	0.00444646	-65.65337015
Liver Elimination Rate Constant (1/hr/kg)	Upper	0.00393475	-56.98474783

*Note: The base-case value for the area under the curve for the testes is 0.00417252. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 99. DCA - Relative Sensitivity of Peak Concentration in Liver at 8.75 hrs.

Description	Perturbation	Peak Concentration in Liver	Relative Sensitivity* %
Volume of the Body (Kg)	Lower	0.00133066	-45.34384967
Volume of the Body (Kg)	Upper	0.00122181	-40.16685783
Liver (%) - Volume	Lower	0.00131732	-34.8641727
Liver (%) - Volume	Upper	0.00123098	-32.96306189
Cardiac Output (L/hr)	Lower	0.0013474	-58.49450877
Cardiac Output (L/hr)	Upper	0.00120687	-51.90346756
Liver (%) - Blood Flow	Lower	0.00134695	-58.14099643
Liver (%) - Blood Flow	Upper	0.00120887	-50.3323016
Stomach to Portal Blood Absorption Rate Constant (1/hr)	Lower	0.00117726	75.16457964
Stomach to Portal Blood Absorption Rate Constant (1/hr)	Upper	0.00136351	71.1502506
Liver/Blood - Partition Coef.	Lower	0.00118527	68.87205996
Liver/Blood - Partition Coef.	Upper	0.00135408	63.74220309

*Note: The base-case value for the peak concentration in the liver is 0.00127294. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 100. DCA - Relative Sensitivity of Peak Concentration in Testes at 19.8 hrs.

Description	Perturbation	Peak Concentration in Testes	Relative Sensitivity*, %
Volume of the Body (Kg)	Lower	0.00080629	-77.65407183
Volume of the Body (Kg)	Upper	0.00069742	-67.85709512
Arterial Blood (%) - Volume	Lower	0.00075761	-12.5903848
Arterial Blood (%) - Volume	Upper	0.00073797	-13.65963191
Liver (%) - Volume	Lower	0.00077579	-36.88902551
Liver (%) - Volume	Upper	0.00072209	-34.88418717
Slowly Perfused Tissue (%) - Volume	Lower	0.00075795	-13.04481482
Slowly Perfused Tissue (%) - Volume	Upper	0.00073839	-13.09827718
Cardiac Output (L/hr)	Lower	0.00076373	-20.77012524
Cardiac Output (L/hr)	Upper	0.000733	-20.30232962
Liver (%) - Blood Flow	Lower	0.0007399	11.08007324
Slowly Perfused Tissue (%) - Blood Flow	Lower	0.00076176	-18.13710421
Slowly Perfused Tissue (%) - Blood Flow	Upper	0.00073481	-17.88315802
Stomach to Portal Blood Absorption Rate Constant (1/hr)	Lower	0.00071976	37.9983694
Stomach to Portal Blood Absorption Rate Constant (1/hr)	Upper	0.00077154	31.20865021
Liver/Blood - Partition Coef.	Lower	0.00077707	-38.5998209
Liver/Blood - Partition Coef.	Upper	0.00072114	-36.15391812
Testes/Blood - Partition Coef.	Lower	0.00067383	99.38651947
Testes/Blood - Partition Coef.	Upper	0.00082257	99.41325065
Liver Elimination Rate Constant (1/hr/kg)	Lower	0.00077102	-30.51363958
Liver Elimination Rate Constant (1/hr/kg)	Upper	0.00072792	-27.09204881

*Note: The base-case value for the peak concentration in the testes is 0.00074819. This table displays only the results for the parameters whose relative sensitivity is >10%. For a complete list of all parameters see Tables 83 and 84.

Table 101. Average Relative Sensitivity Analysis of Absorbed Total Dose for Water Use, Environmental and Chemical Parameters for Chloroform and DCA, Ranked by Absolute Value

Parameter *	Chloroform Relative Sensitivity, % (Rank)			Parameter *	DCA Relative Sensitivity, % (Rank)		
	Male (15-45)	Female (15-45)	Child (6 yrs)		Male (15-45)	Female (15-	Child (6 yrs)
Overall Mass Transfer Coefficient (K_{OLA})	80.17 (1)	80.37 (1)	73.48 (1)	Consumption Volume, L/day	99.96 (1)	99.94 (1)	99.96 (1)
Air Exchange Rate (hr-1) and Interzonal Air Flows (m^3/hr)	-57.56 (2)	-70.70 (2)	-59.77 (2)	Shower Mean Duration, min	0.0135 (2)	0.0197 (2)	5.54E-4 (12)
Shower Flowrate, gal/min	34.08 (3)	31.91 (3)	4.65 (8)	Henry's Law Constant	0.0129 (3)	0.0188 (3)	0.00385 (5)
Shower Mean Duration, min	33.03 (4)	26.04 (4)	[illegible] (13)	Overall Mass Transfer Coefficient (KOLA)	0.00299 (4)	0.00383 (6)	0.00650 (3)
House and Zone Volumes (m^3)	-26.63 (5)	-12.07 (5)	[illegible] (3)	Air Exchange Rate (hr-1) and Interzonal Air Flows (m^3/hr)	-0.00177 (5)	-0.00874 (4)	-0.00548 (4)
Kitchen Faucet Flowrate, gal/min	8.19 (6)	[illegible] (8)	7.71 (6)	Shower Flowrate, gal/min	0.00165 (6)	0.00208 (8)	2.01E-4 (13)
Kitchen Faucet Mean Duration, min	6.63 (7)	[illegible]	5.76 (7)	House and Zone Volumes (m^3)	-0.00137 (7)	-0.00485 (5)	-0.00133 (7)
Bathroom Faucet Flowrate, gal/min	6.47 (8)	[illegible]	3.22 (11)	Kitchen Faucet Mean Duration, min	0.00134 (8)	0.00165 (9)	9.87E-4 (8)
Bathroom Faucet Mean Duration, min	5.84 (9)	[illegible] (7)	2.76 (14)	Bathroom Faucet Mean Duration, min	0.00103 (9)	0.00214 (7)	7.01E-4 (10)
Consumption Volume, L/day	5.51 (10)	[illegible] (9)	[illegible]	Kitchen Faucet Flowrate,	6.79E-4 (10)	6.67E-4 (10)	8.01E-4 (9)
Clothes Washer Mean Duration, min	3.23 (11)	[illegible] (12)	3.11 (12)	Bathroom Faucet Flowrate, gal/min	1.64E-4 (11)	4.62E-4 (11)	0.000191 (14)
Henry's Law Constant	2.64 (12)	2.83 (11)	[illegible] (15)	Clothes Washer Mean Duration, min	1.06E-4 (12)	1.41E-4 (13)	1.30E-4 (16)
Dishwasher Volume, gal	1.39 (13)	1.24 (13)	[illegible] (17)	Dishwasher Mean Duration,	9.36E-5 (13)	1.84E-4 (12)	1.30E-4 (15)
Clothes Washer Volume, gal	1.33 (14)	1.06 (14)	[illegible] (16)	Bath Mean Duration, min	8.81E-5 (14)	3.77E-5 (14)	0.0108 (2)
Bath Flowrate, gal/min	0.90 (15)	[illegible]	[illegible]	Bath Flowrate, gal/min	7.57E-5 (15)	2.94E-4 (15)	0.00211 (6)
Bath Mean Duration, min	0.86 (16)	[illegible]	[illegible]	Dishwasher Volume, gal	4.75E-9 (16)	8.50E-9 (16)	6.03E-09 (17)
Bath Volume, gal	0.27 (17)	[illegible]	[illegible]	Bath Volume, gal	4.71E-10 (17)	1.86E-10 (18)	1.18E-08 (16)
Dishwasher Mean Duration,	0.10 (18)	0.12 (17)	0.11 (18)	Clothes Washer Volume, gal	1.76E-10 (18)	2.33E-10 (17)	2.18E-10 (18)
Toilet Volume, gal/flush	0.00 (19)	0.00 (19)	0.00 (19)	Toilet Volume, gal/flush	0.00 (19)	0.00 (19)	0.00 (19)

Note: Shaded cells indicate parameters that have a different rank for the adult female and child as compared to the adult male. Negative values indicate that parameter is inversely related to absorbed dose.

Table 102. Summary of the Most Sensitive Model Parameters for Each Dose Metric

Dose Metrics	*Most Sensitive Model Parameters (Relative Sensitivity)*	
	Chloroform	*DCA*
Absorbed Dose at 24 hr (mg)	Alveolar Ventilation Rate (89.83%)	Blood Flow in Kidney (4.88%)
Amount Metabolized in Liver at 24 hr (mg)	Alveolar Ventilation Rate (52.98%)	n/a
Amount Eliminated in Liver at 24 hr (mg)	n/a	Volume in Liver (44.85%)
AUC in Liver at 24 hr (mg*h /L)	Liver Metabolism Vmax (-107.34%)	Volume in Body (-89.07%)
AUC in Testes at 24 hr (mg*h /L)	Partition Coef. Testes/Blood (100.21%)	Partition Coef. Testes/Blood (100.56%)
Concentration in Liver (mg/L)	Liver Metabolism Vmax (-108.98%)	Stomach to Portal Blood Rate (75.16%)
Concentration in Testes (mg/L)	Partition Coef. Testes/Blood (99.50%)	Partition Coef. Testes/Blood (99.41%)

Table 103. Chloroform - Sensitive Input Model Parameters

Dose Metrics	Sensitivity Parameters	Comments
Absorbed Dose at 24 hr		
	Alveolar Ventilation Rates	Affects inhalation
Amount Metabolized in the Liver		
	Alveolar Ventilation Rates	Affects inhalation
	Blood Flow in the Liver	Metabolism occurs in the Liver, and chemical passes through the Liver from oral exposure
	Cardiac Output	Total blood flow to compartments
AUC for Liver at 24 hr		
	Liver Metabolism Vmax	Directly affect the amount of chemical in the Liver
	Liver Metabolism Michaelis-Menten Constant	Determine the amount of metabolites in the Liver (with Vmax)
	Volume of the Body	The Liver metabolism Vmax is scaled to the body volume
AUC for Testes at 24 hr		
	Testes/Blood - Partition Coef.	Partly determines the amount of chemical in the Testes
	Alveolar Ventilation Rates	Affects inhalation
	Cardiac Output	Total blood flow to compartments
	Blood Flow in the Liver	Metabolism occurs in the Liver, and chemical passes through the Liver from oral exposure
Peak Concentration in Liver		
	Liver Metabolism Vmax	Directly affect the amount of chemical in the Liver
	Liver Metabolism Michaelis-Menten Constant	Determine the amount of metabolites in the Liver (with Vmax)
	Volume of the Body	The Liver metabolism Vmax is scaled to the body volume
	Blood Flow in the Liver	Metabolism occurs in the Liver, and chemical passes through the Liver from oral exposure
Peak Concentration in Testes		
	Testes/Blood - Partition Coef.	Partly determines the amount of chemical in the Testes
	Alveolar Ventilation Rates	Affects inhalation
	Cardiac Output	Total blood flow to compartments
	Blood Flow in the Liver	Metabolism occurs in the Liver, and chemical passes through the Liver from oral exposure

Table 104. DCA - Sensitive Input Model Parameters

Dose Metrics	Sensitivity Parameters	Comments
Amount Eliminated in the Liver at 24 hr		
	Liver Elimination Rate Constant	Determines the amount eliminated
	Liver/Blood - Partition Coef.	Determines the amount of chemical from arterial blood
	Volume of the Liver	The amount eliminated increases with volume of the Liver
AUC for Liver at 24 hr		
	Volume of the Body	Chemical remains in the body longer as the body volume increases
	Liver Elimination Rate Constant	Determines the amount eliminated
	Volume of the Liver	The amount eliminated increases with volume of the Liver
	Liver/Blood - Partition Coef.	Determines the amount of chemical from arterial blood
AUC for Testes at 24 hr		
	Testes/Blood - Partition Coef.	Partly determines the amount of chemical remaining in the Testes as blood passes through
	Volume of the Body	Chemical remains in the body longer as the body volume increases
	Liver/Blood - Partition Coef.	Determines the amount of chemical from arterial blood
	Liver Elimination Rate Constant	Determines the amount eliminated
	Volume of the Liver	The amount eliminated increases with volume of the Liver
Peak Concentration in Liver		
	Stomach/Portal Blood Rate Constant	Chemical moves from stomach to liver via portal blood
	Liver/Blood Partition Coef.	Partly determines the amount of chemical remaining in the Liver
	Cardiac Output	Total blood flow to compartments
	Blood Flow in the Liver	Partly determines the amount of chemical remaining in the Liver
	Volume of the Body	Chemical remains in the body longer as the body volume increases
Peak Concentration in Testes		
	Testes/Blood - Partition Coef.	Partly determines the amount of chemical remaining in the Testes as blood passes through
	Volume of the Body	Chemical remains in the body longer as the body volume increases
	Liver/Blood Partition Coef.	Determines the amount of chemical from arterial blood

6.0 Quality Assurance

The purpose of this section is to identify the sources and quality of secondary data used in conducting this modeling study. Secondary data are defined as the use of environmental, exposure, or health data developed for another purpose. This modeling study used secondary data as inputs to model algorithms for the purpose of estimating population-based exposure, absorbed dose, and tissue concentrations. This is a demonstration project, and as such, best available data are identified and utilized from a wide variety of sources. Consequently, the data vary in quality and documentation.

The data used in calculations, methods and models used to derive quantitative measures, including those of internal exposure, tissue dosimetry, and risk were taken from publications and other sources subjected to peer review where possible. These publications include peer reviewed journals and other open literature. The sources of all data contained within this report have been documented by reference or footnote describing the source of the data. In addition, a discussion of shortcomings of data used in this study is included in the text of this report in the section where the data are introduced.

Many diverse types of data are used in this study, including behavioral data, physical data, chemical data, and physiological data. These data are taken from a variety of sources including databases, peer-reviewed publications, and estimation techniques. In addition, numerous models are used to develop the exposure, dose and tissue concentrations, including fate and transport models, mass-transfer models, models to represent behavior, uptake and pharmacokinetic models. A general summary of the models and data utilized in this study are presented in the following tables. The data fall into 7 general categories, as described in Table 105. The sources of the major data utilized in this study are categorized and described in Table 106. The models and model algorithms utilized in this study are categorized and described in Tables 107 and 108.

Table 105. Categories of Data Sources and Models

Category	Description
I	Taken from peer reviewed literature, used for the purpose intended by the measurement
II	Taken from peer reviewed literature, used for the purpose other than intended by the measurement
III	Taken from peer-reviewed database compiled for the purposes in which it is being used.
IV	Taken from non peer-reviewed database compiled for the purposes other than those for which it is being used.
V	Taken from other non peer-reviewed source
VI	Estimated based on peer-reviewed method or data
VII	Estimated based on non peer-reviewed method

Table 106. Quality and Sources of Data Used in the Models

Variables	Category	Description	Citation
Mass-Transfer Coefficient	VI	Predicted based on peer reviewed algorithms	Corsi and Howard, 2000
Gas- and liquid-phase diffusivities	I, VI	Diffusivities are used in the prediction algorithm for the mass transfer coefficient, as described in Section 3.1. The sources of the diffusivities vary. Several were obtained from the Department of Energy, Risk Assessment Information System (RAIS) database. The values for many of the diffusivities were estimated using peer reviewed prediction algorithms as described in Section 3.1.3.	Risk Assessment Information System, Oak Ridge National Laboratory Lyman et al., 1990.
Henry's Law Constant	I, II, VI	Reported in literature or in databases at specific temperatures. A temperature adjustment was applied based on a peer-reviewed method as described in Section 3.1.3.	Various, see Table 2 and Section 3.1 for a listing of data sources and temperature adjustment algorithm
Exposure-Related Behavior	III	Activity patterns are sampled from the NHAPS database	Described in Section 3.2
Water Use Behavior	III, IV, V	Compiled from a variety of databases including REUWS, RECS, and NHAPS. NHAPS was compiled for this purpose; REUWS and RECS were compiled for other purposes.	Described in Section 3.2
Ingestion Behavior	III	Taken from the CSFII database	Jacobs et al., 2000
House Volume	I, IV	Household volumes are based on an analysis of RECS data from 1993 and 1997. The 1993 data are analyzed and presented in the Exposure Factors Handbook.	U.S. DOE, 1995 U.S. DOE, 1999 U.S. EPA, 1997b
Water-Use Zones	VII	Volumes are estimated based on architectural design standards.	Hoke, 1988 Hoke, 1994
Whole House Air Exchange Rate	I	Sampled from the national distribution recommended by the Exposure Factors Handbook.	U.S. EPA, 1997b
Interzonal Airflows	I	Interzonal airflows are based on several sources. The interzonal airflows between the non-water using zones and the kitchen and laundry room are based on a correlation from Koontz and Rector, 1995. The flows between the non-water using zones and the bathrooms are based on Giardino et al., 1996.	Koontz and Rector, 1995 Giardino et al., 1996
Water Concentrations	I	The water concentrations were characterized based on published measurement data.	The Cadmus Group, Inc., 2001
Ingestion Concentrations	I, VII	The ingestion concentrations were estimated for a plausible set of activities based on published results lab measurements.	Howard and Corsi, 1996 Batterman et al., 2000
Breathing Rates	I	Alveolar ventilation rates were assigned based on two assumed activity levels: resting and sedentary.	U.S. EPA, 1997b
Body Weight	I	Calculated from the Exposure Factors Handbook, Tables 7.2 and 7.3, adjusted for clothes	U.S. EPA, 1999

Table 106. Quality and Sources of Data Used in the Models (Continued)

Variables	Category	Description	Citation
Body Compartmental Blood Flow rates	I	Taken from the Fisher paper with modifications for the Ovaries and Testes. The flow to the Ovaries and Testicles was determined from their volume relative to their body weight.	Fisher, et al, 1998
Body Compartmental Volumes	VII	Blood, estimated from Blancato	
	I	Dermis, Kidney:	Corley, et al, 1990
	I	Fat and Slowly Perfused estimated from measurements from volunteers.	Fisher, et al, 1998
	I	Liver, Rapidly Perfused Tissue, Static Lung	Fisher, et al, 1998
	VII	Ovaries and Testes volumes were estimated. See Table 43, footnote "f".	ICRP-23, 1974
Skin Permeability Coefficients	VI	Taken from methods used by Krishnan -	Krishnan Personal Communication
	V	Chloroform taken from Blancato, Personal Communication.	Blancato, Personal Communication
	VI	DCA and TCA taken from McDougal, Personal Communication	McDougal, Personal Communication.
Skin Partition Coefficients	VI	Krishnan, Personal Communication Values for skin/Blood including Ovaries and Testes	Krishnan, Personal Communication
	I	Chloroform -	Corley, et al, 1990
	I	BDCM	Gargas, et al, 1989
	V	DCA, and TCA, estimated	
Gastro-Intestinal Absorption Rate	V	Chloroform, Blancato, Personal Communication	Blancato, Personal Communication
	II	BDCM, DCA, and TCA, from Abbas and Fisher, 1997; but modified using Staata, et al, 1990	Abbas and Fisher, 1997, Staats, et al, 1990
Tissue Partition Coefficients	I	Chloroform partition coefficients for Corley	Corley, et al, 1990
	II	BDCM, estimated from ratios of tissue to air and blood to air	Gargas, et al, 1989
	I	TCA and DCA estimates from Fisher	Fisher, et al, 1998
	V	Dermis, Fat and Rapidly Perfused were estimated for TCA and DCA	
	VII	Ovaries and Testes, from Personal Communication, Krishnan, and Lipscomb	Personal Communication Krishnan and Lipscomb,
Metabolism Rate Constants	V,I	Chloroform metabolism parameters are from Blancato, Personal Communication. The Michaelis Menten constants are from Corley	Blancato, Personal Communication, and Corley, et al, 1990
	V	BDCM Metabolism parameters are from Lipscomb, Personal Communication	Lipscomb, Personal Communication
Elimination Rate Constants	I	DCA Urine Rate Constant from Clewell	Clewell, et al, 2000
	II	TCA Urine Rate Constant estimated from Fisher	Fisher, et al, 1998
	II	DCA Liver Elimination Rate estimated from mouse data of Abbas and Fisher	Abbas and Fisher, 1997

Table 107. Categories of Model Approaches and Algorithms

Category	Description
A	Widely accepted modeling approach
B	Approach similar to commonly used and accepted approaches, but adapted to satisfy project specific requirements
C	Novel approach addressing specific requirements of estimating exposure and uptake of water borne contaminants

Table 108. Quality of Modeling Approaches and Algorithms

Model	Category	Description
Representation of the building	B	Building is represented as a collection of water using zones and a lumped non-water using zones. Similar approaches are widely used in the literature.
Fate and transport modeling	A	Commonly accepted approach based on mass balance. Method assumes well mixed zones, each zone constrained by mass and volumetric balance.
Fate and Transport Model Integration Method	A	Model solves set of differential equations using the 4th order Runge-Kutta method (Mathews, 1992). This method is widely cited, is very stable, self starting, and accurate.
Behavior Models	C	The behavior is sampled from the NHAPS database, but is modified to address known deficiencies in the dataset and to accommodate water-use related behavior not included in NHAPS.
Water Use Models	C, A	Approach to simulating water uses incorporate techniques for simulating water use occurrences as well as the duration of water uses. The occurrences of water uses is simulated based on survey data from NHAPS and REUWS using a Poisson process. The durations of the water uses are simulated by sampling from representative lognormal distributions. These techniques are used for similar purposes in peer-reviewed literature, but the implementation in this modeling effort is unique to exposure to water borne contaminants. This work has been published in several peer reviewed publications (Wilkes, 1999, Wilkes et al., 1996)
Exposure Models	A	The exposure model used in this study, TEM, has been published in several journal articles. The basic model algorithms have been validated (Wilkes, 1994).
Inhalation Uptake Model	A, C	The exposure model uptake algorithms are described in Section 3.7. These algorithms are taken from peer-reviewed literature (Olin, 1999), but there integration into an exposure model framework is unique to this exposure model.
Dermal Uptake Model	A, C	

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Appendix A

Figures Presenting Results of Pharmacokinetic Modeling

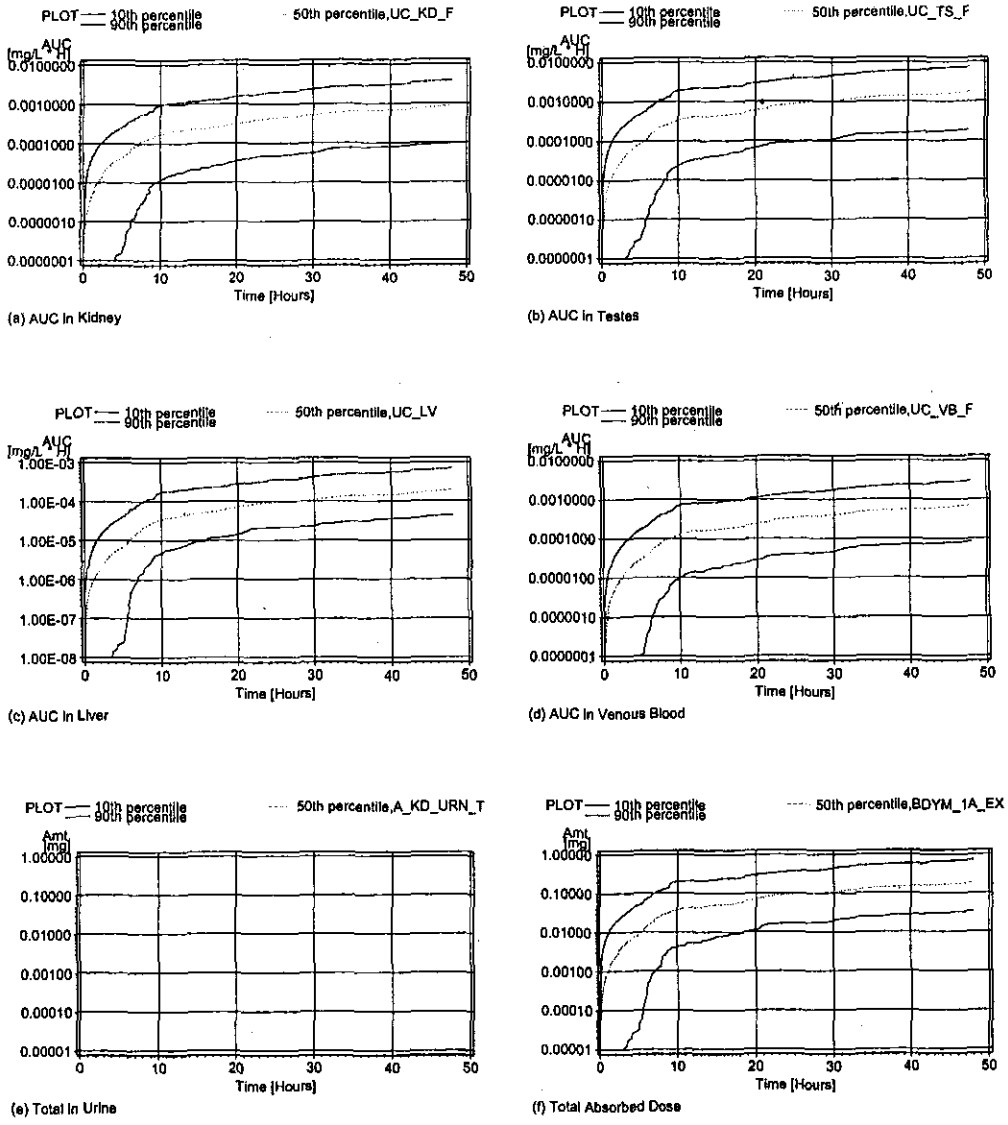


Figure A-1. Adult Male BDCM Percentile Plot: AUC, Total Urine, Total Absorbed Dose

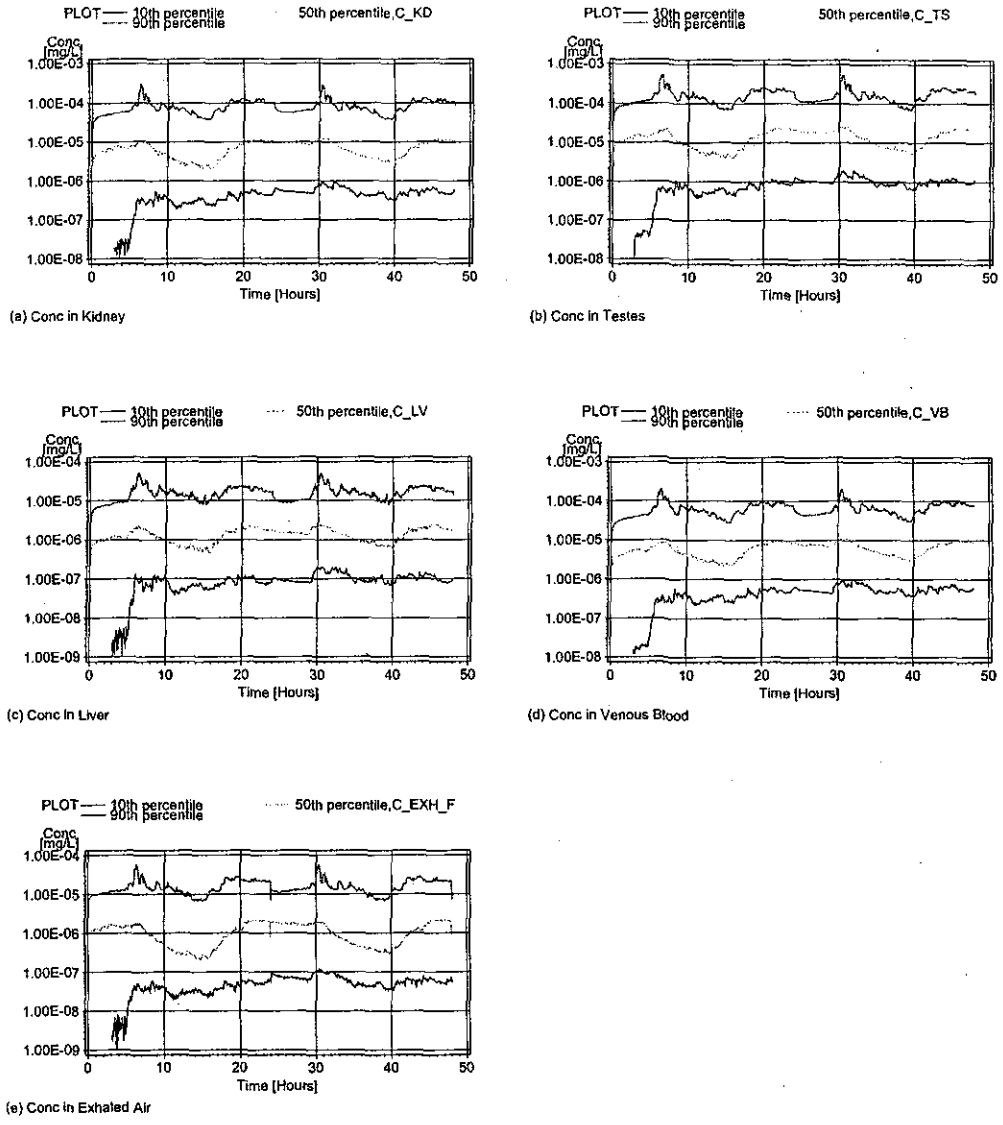


Figure A-2. Adult Male BDCM Percentile Plot: Concentration and Exhaled Air

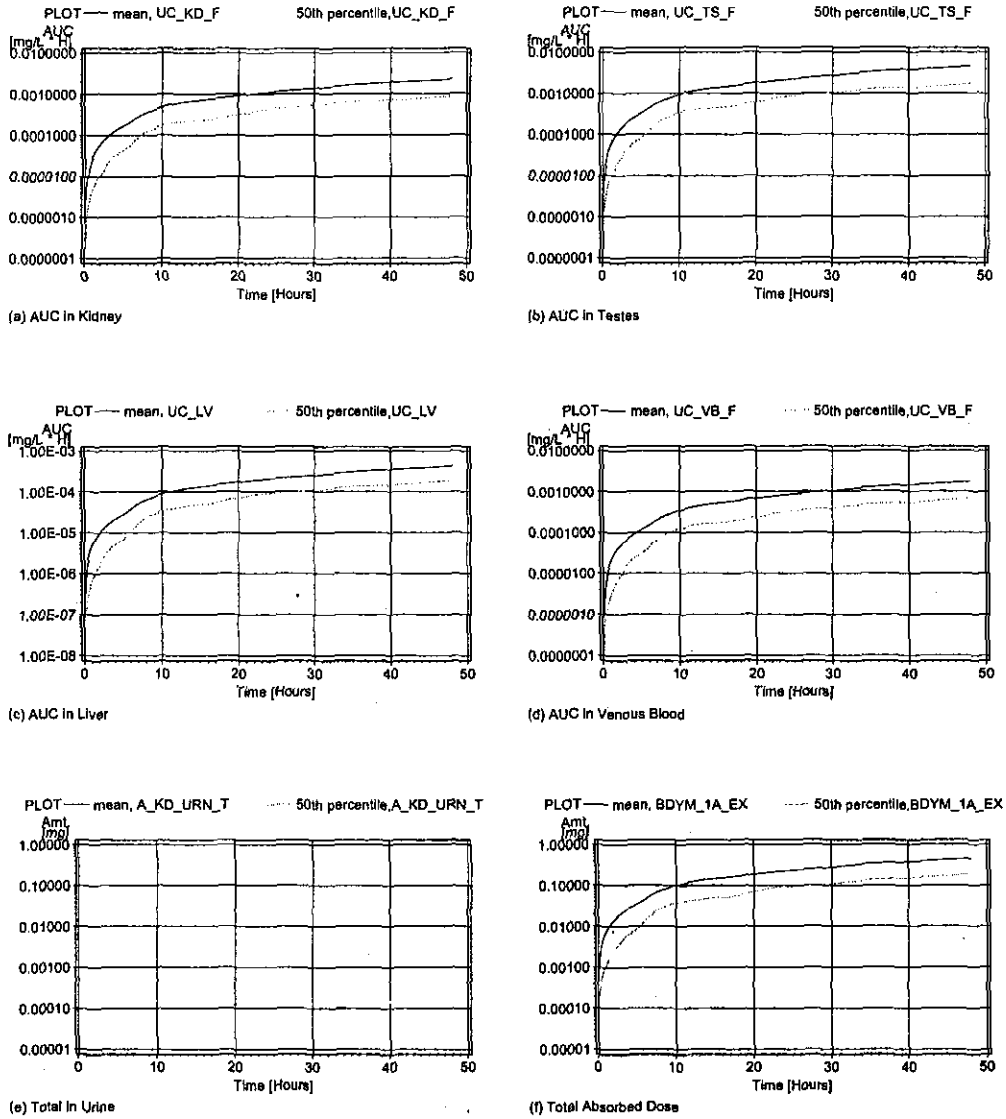
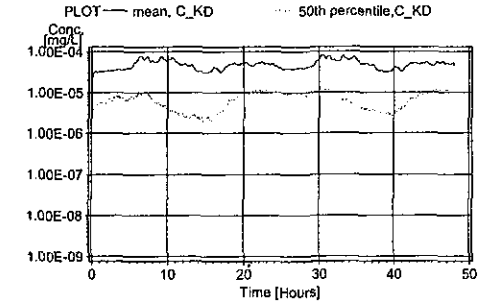
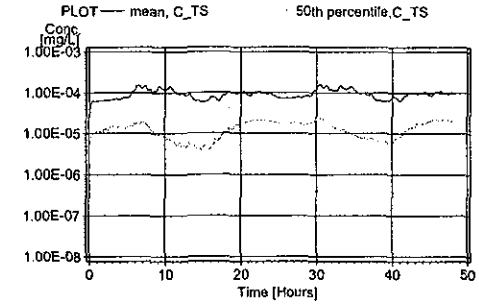


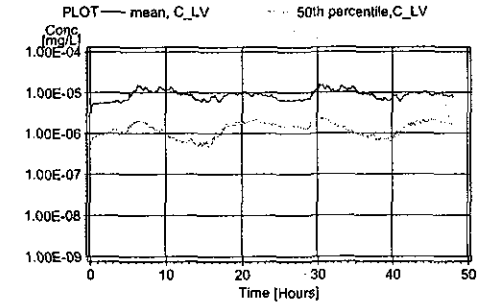
Figure A-3. Adult Male BDCM Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose



(a) Conc in Kidney



(b) Conc in Testes



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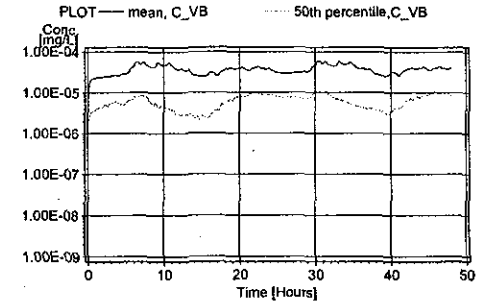
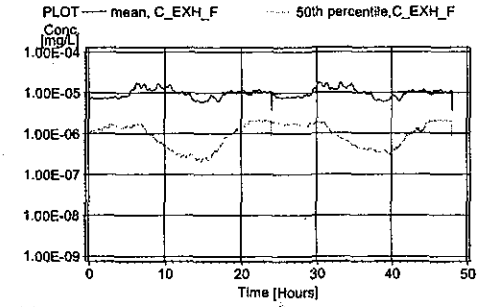


(d) Conc in Venous Blood



(e) Conc in Exhaled Air

Figure A-4. Adult Male BDCM Mean-Median Plot: Concentration and Exhaled Air

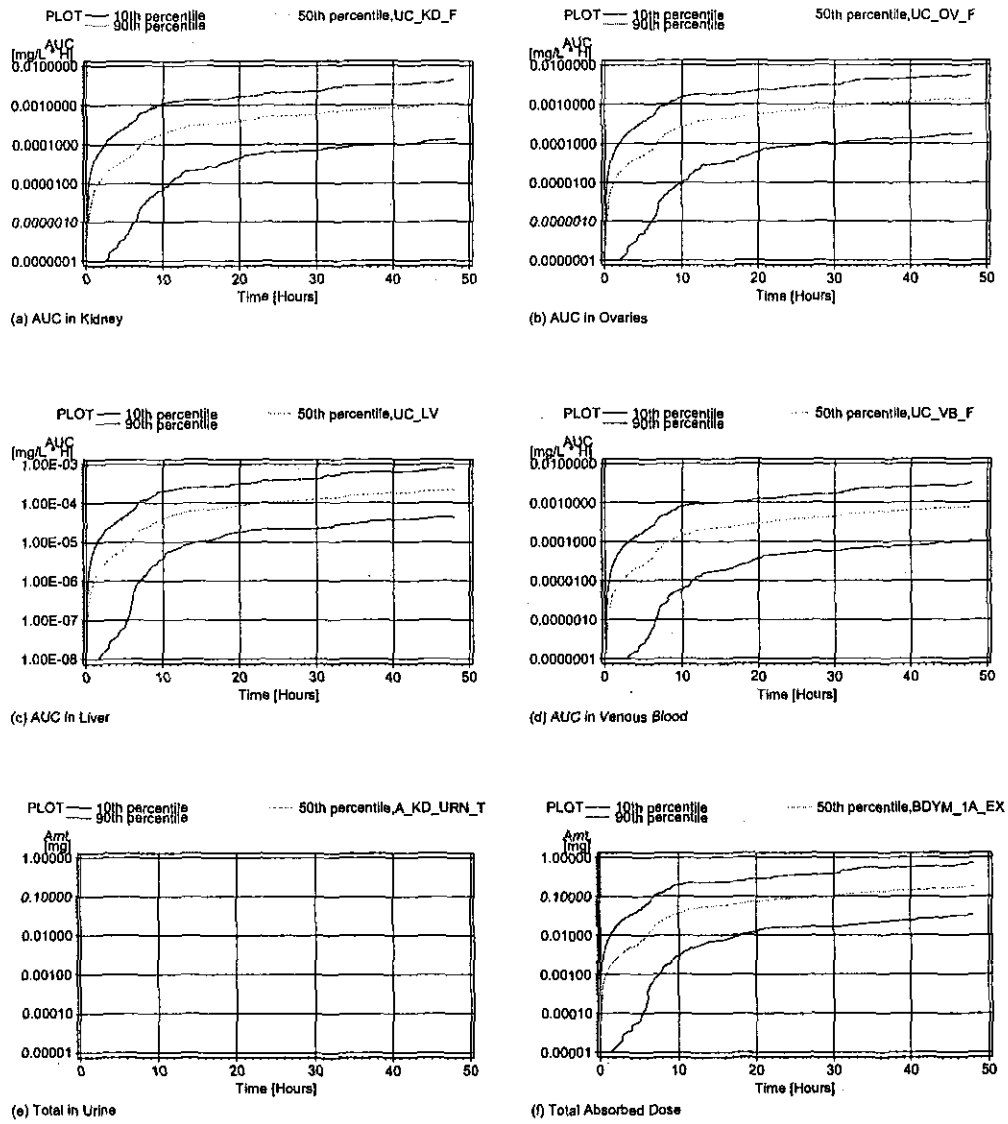


Figure A-5. Adult Female BDCM Percentile Plot: AUC, Total Urine, Total Absorbed Dose

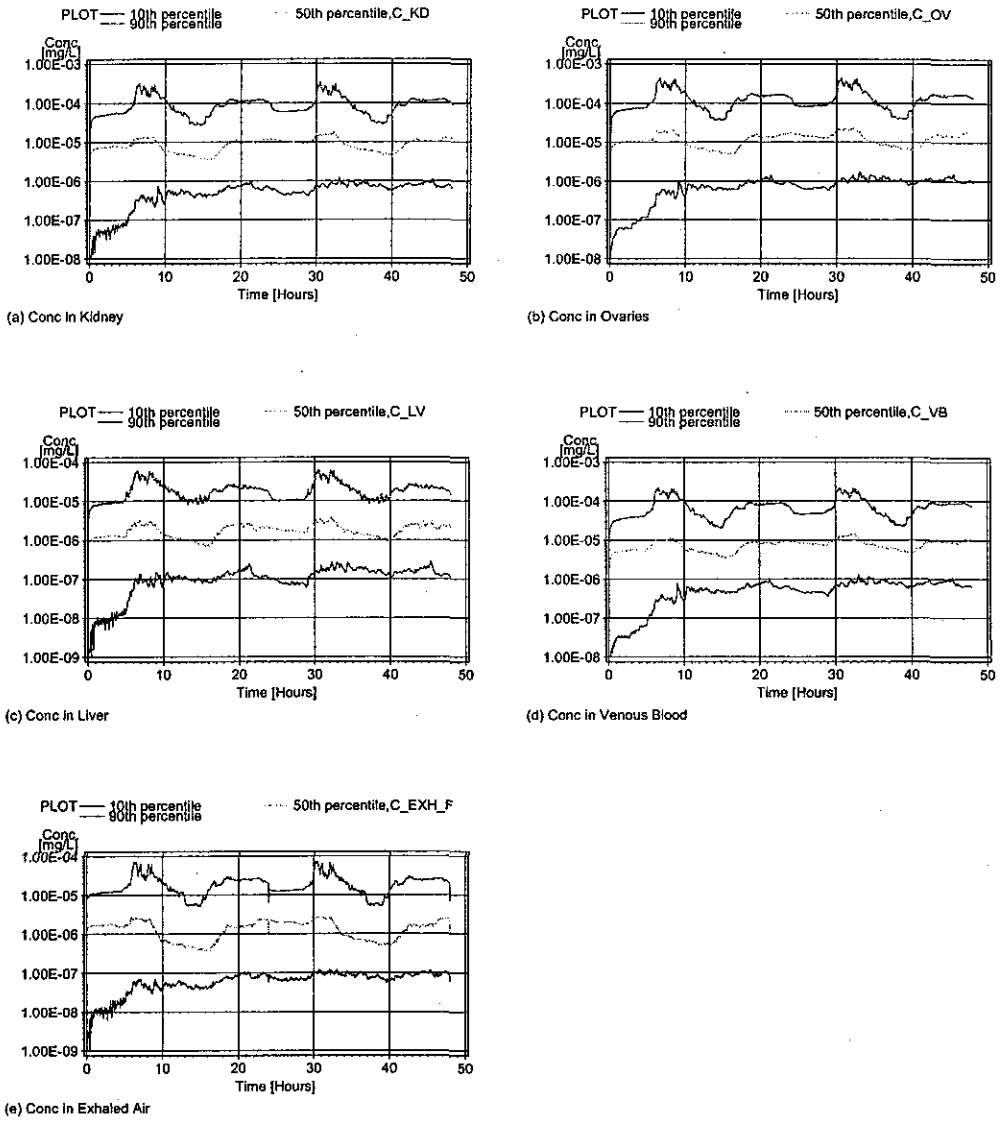


Figure A-6. Adult Female BDCM Percentile Plot: Concentration and Exhaled Air

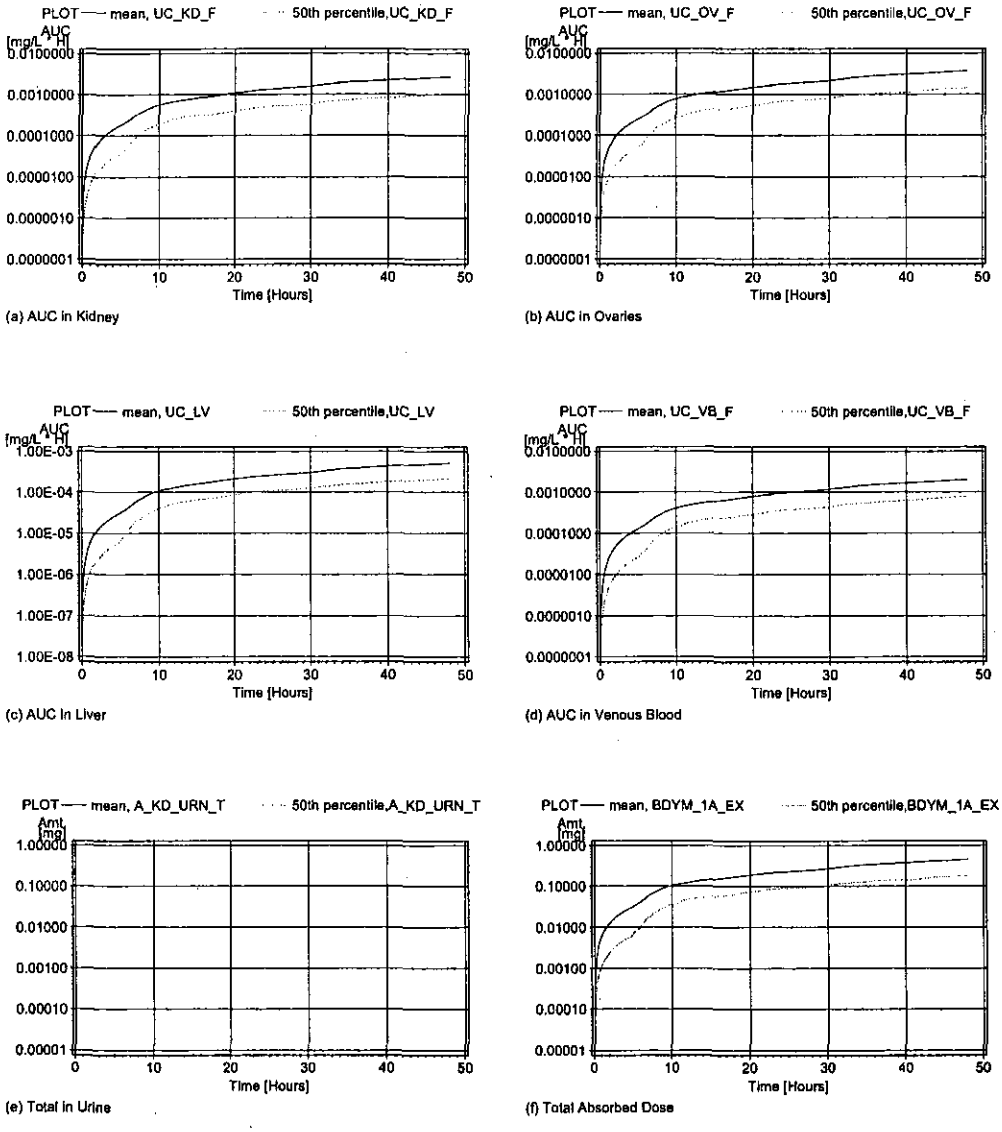
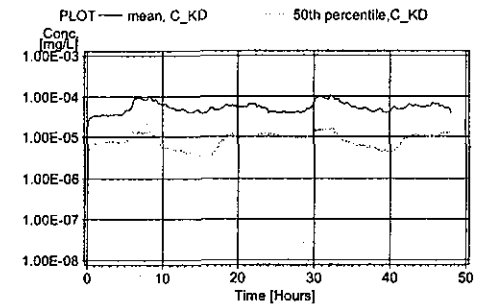
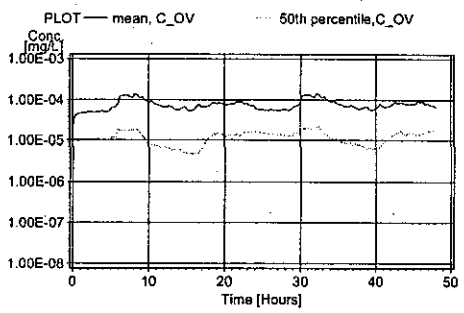


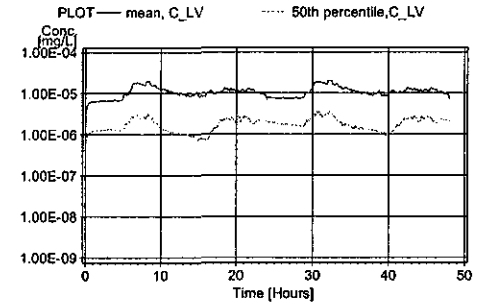
Figure A-7. Adult Female BDCM Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose



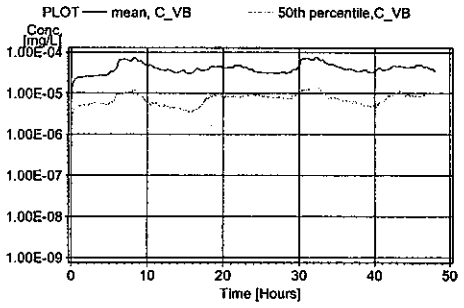
(a) Conc in Kidney



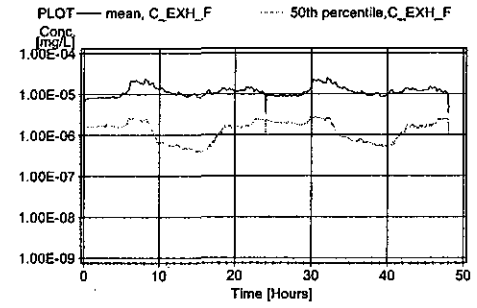
(b) Conc in Ovaries



(c) Conc in Liver



(d) Conc in Venous Blood



(e) Conc in Exhaled Air

Figure A-8. Adult Female BDCM Mean-Median Plot: Concentration and Exhaled Air

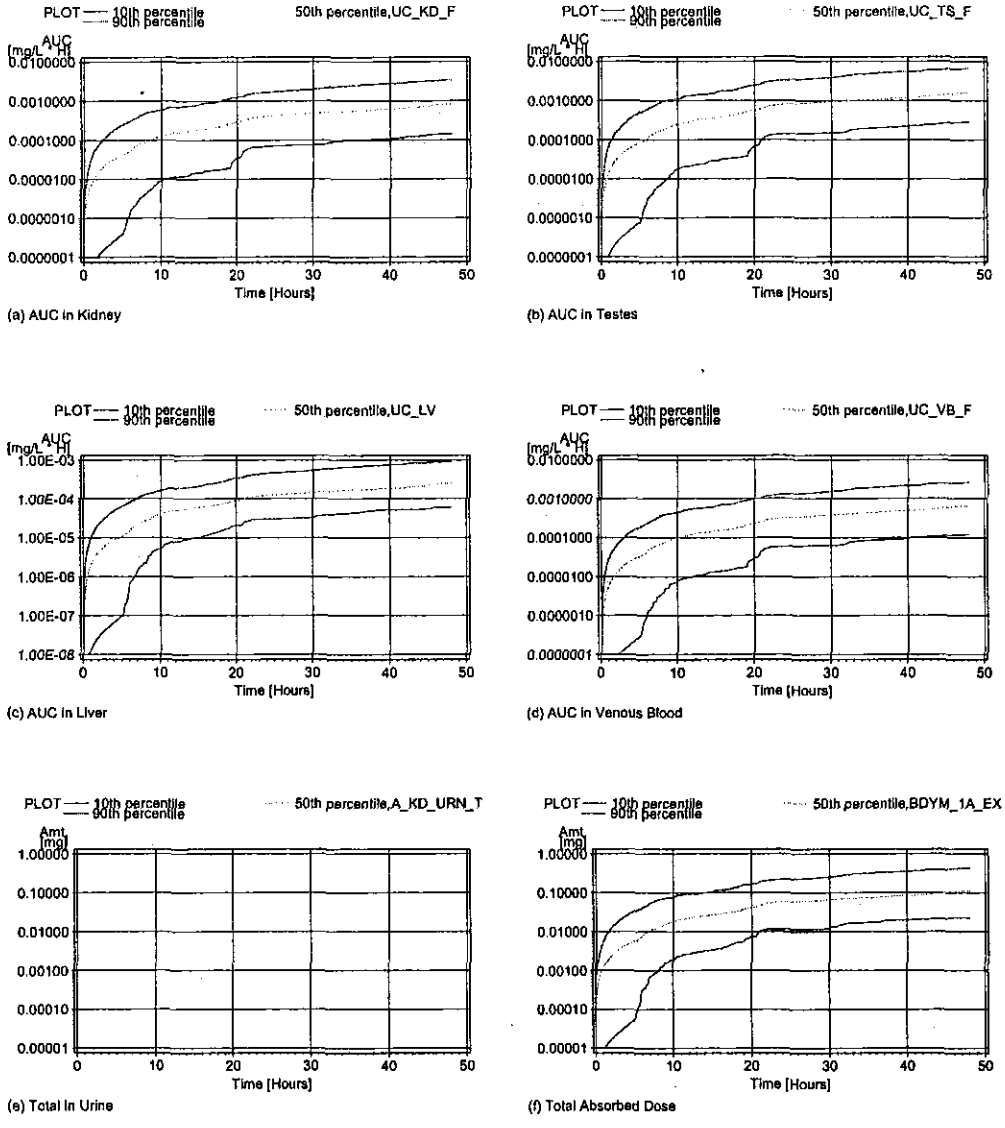


Figure A-9. Child BDCM Percentile Plot: AUC, Total Urine, Total Absorbed Dose

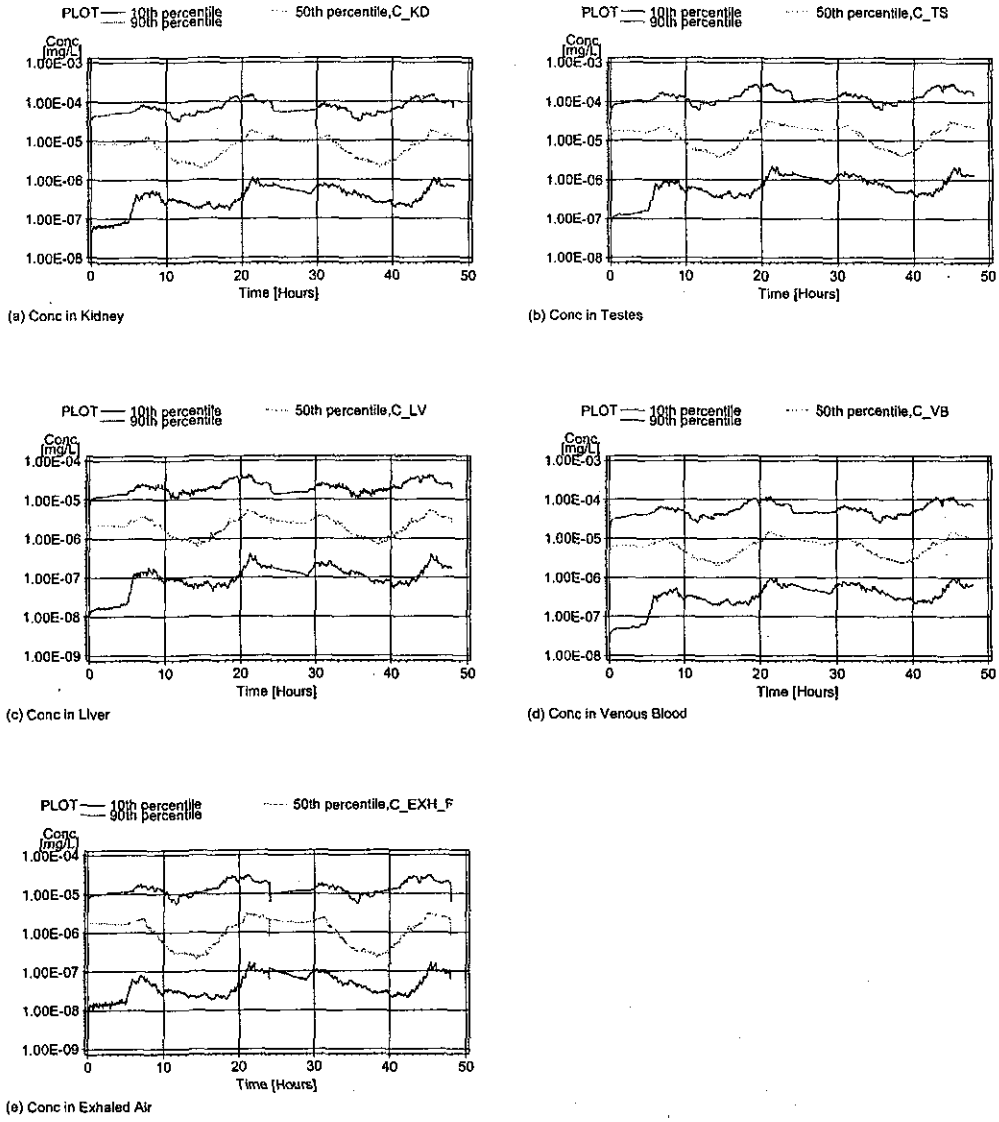


Figure A-10. Child BDCM Percentile Plot: Concentration and Exhaled Air

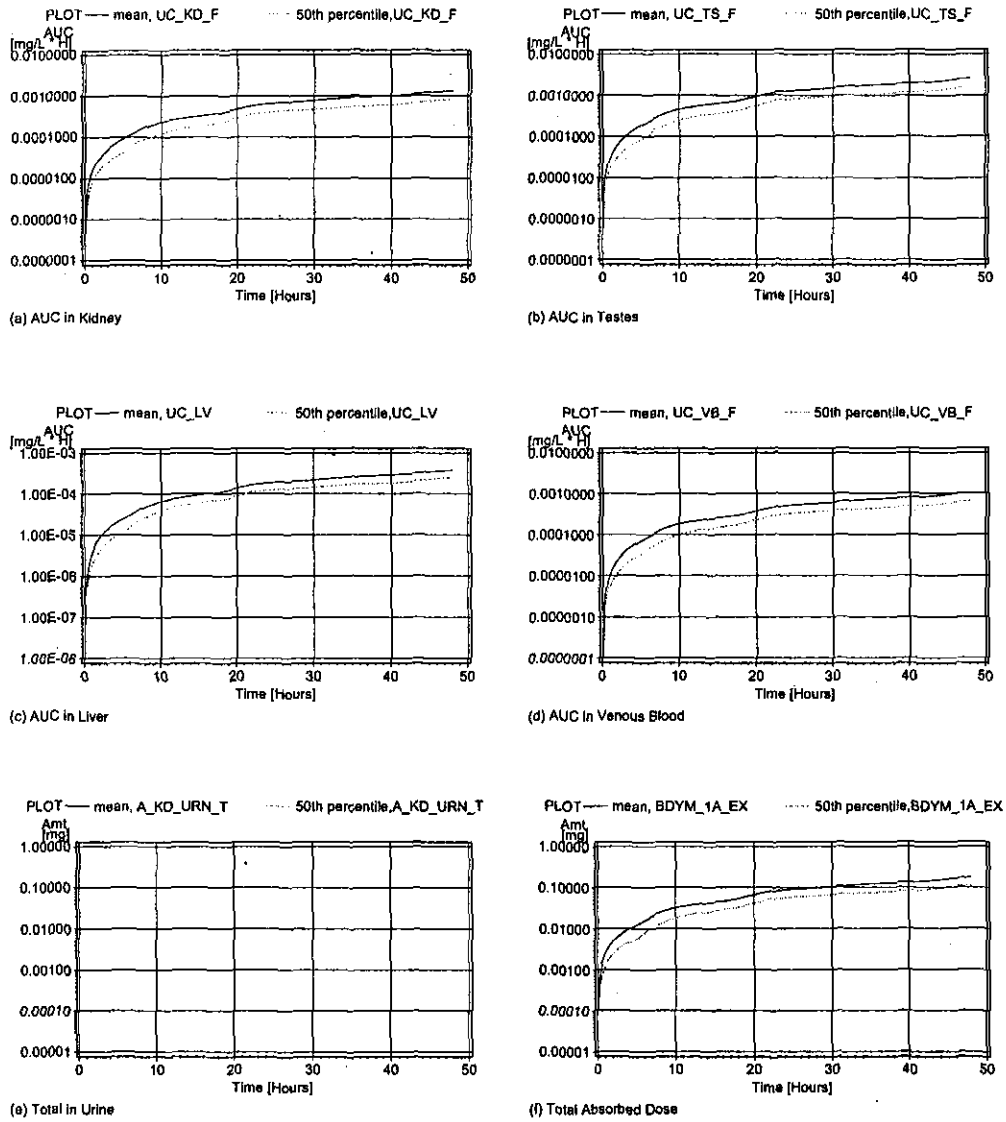
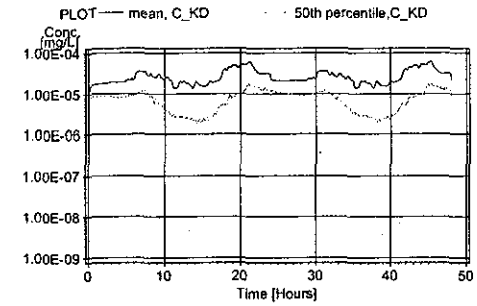
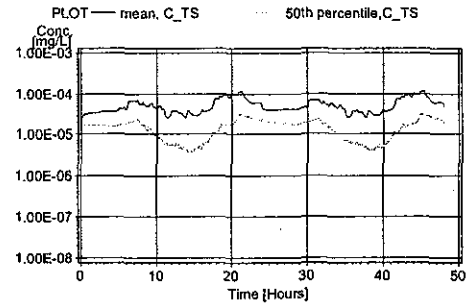


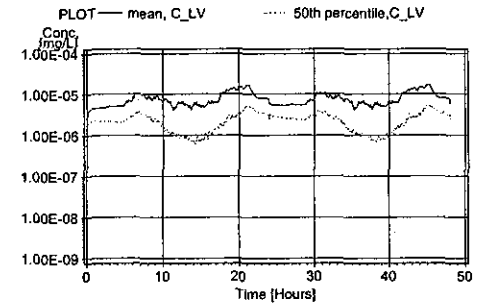
Figure A-11. Child BDCM Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose



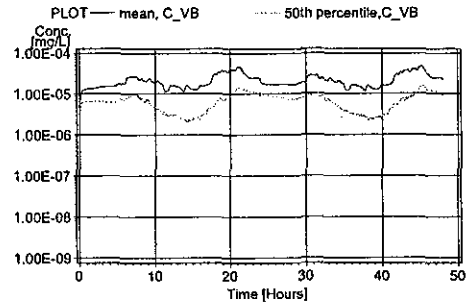
(a) Conc in Kidney



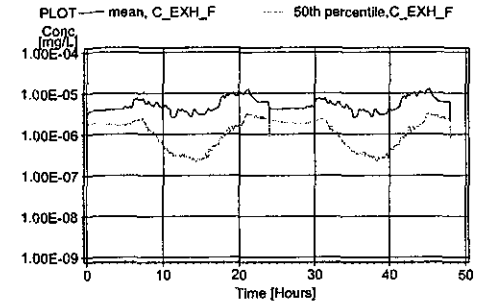
(b) Conc in Testes



(c) Conc in Liver



(d) Conc in Venous Blood



(e) Conc in Exhaled Air

Figure A-12. Child BDCM Mean-Median Plot: Concentration and Exhaled Air

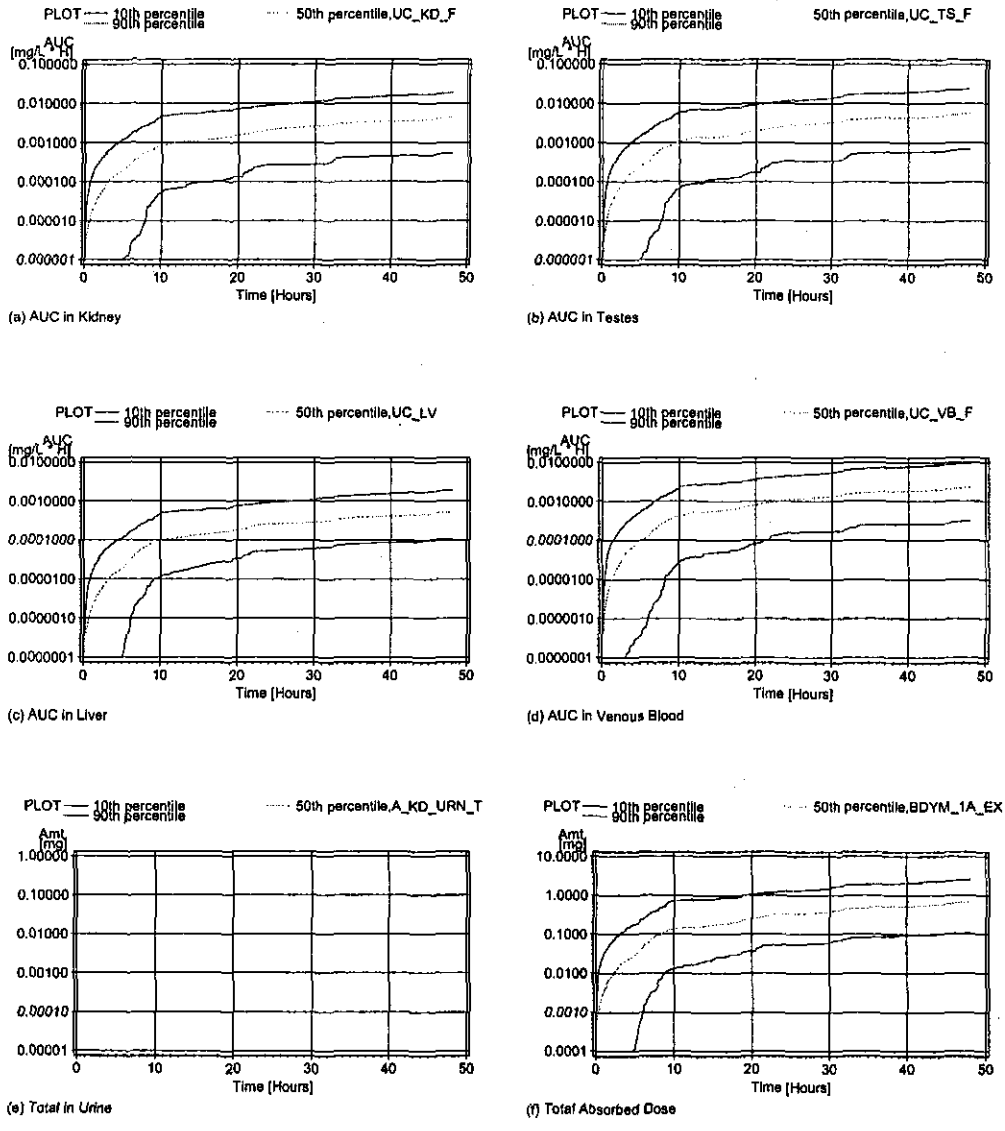


Figure A-13. Adult Male $CHCl_3$ Percentile Plot: AUC, Total Urine, Total Absorbed Dose

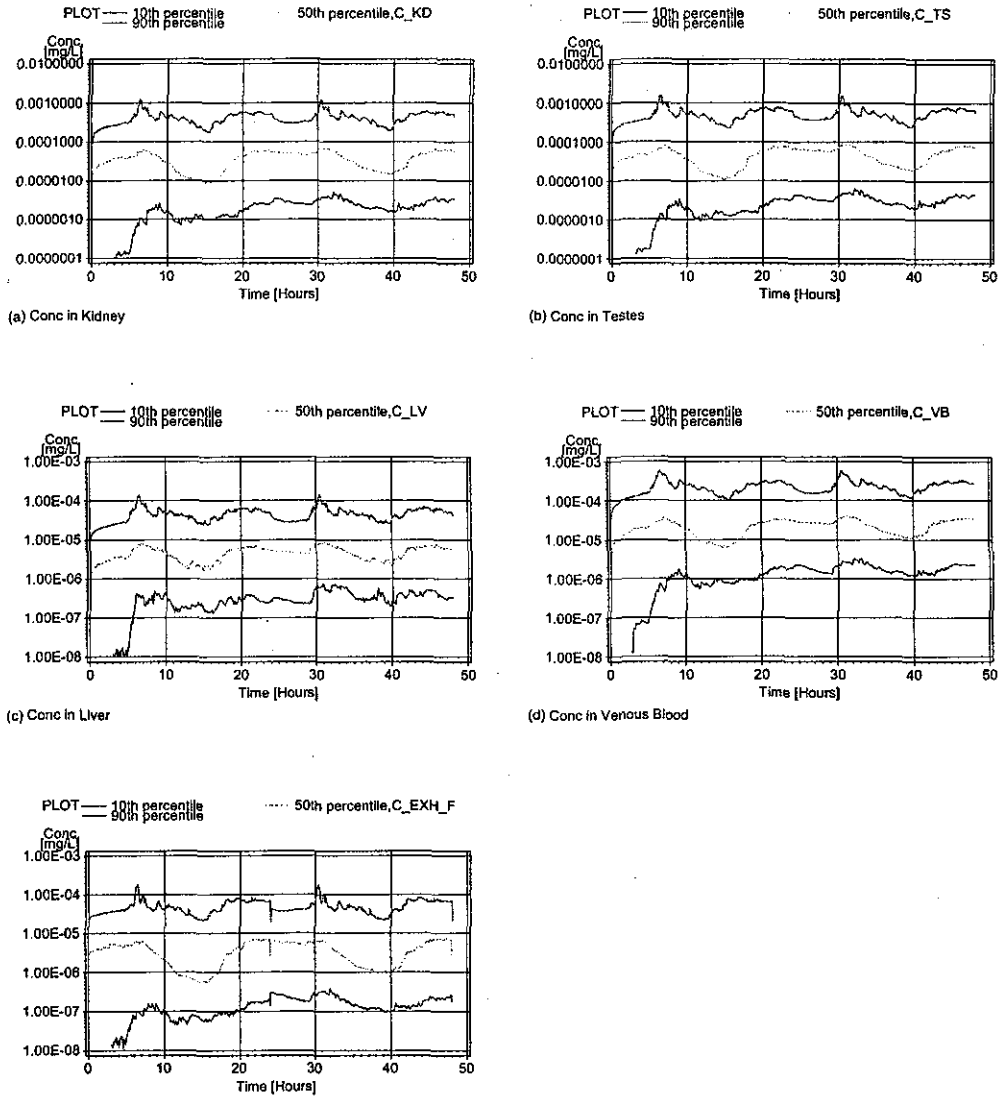


Figure A-14. Adult Male $CHCl_3$ Percentile Plot: Concentration and Exhaled Air

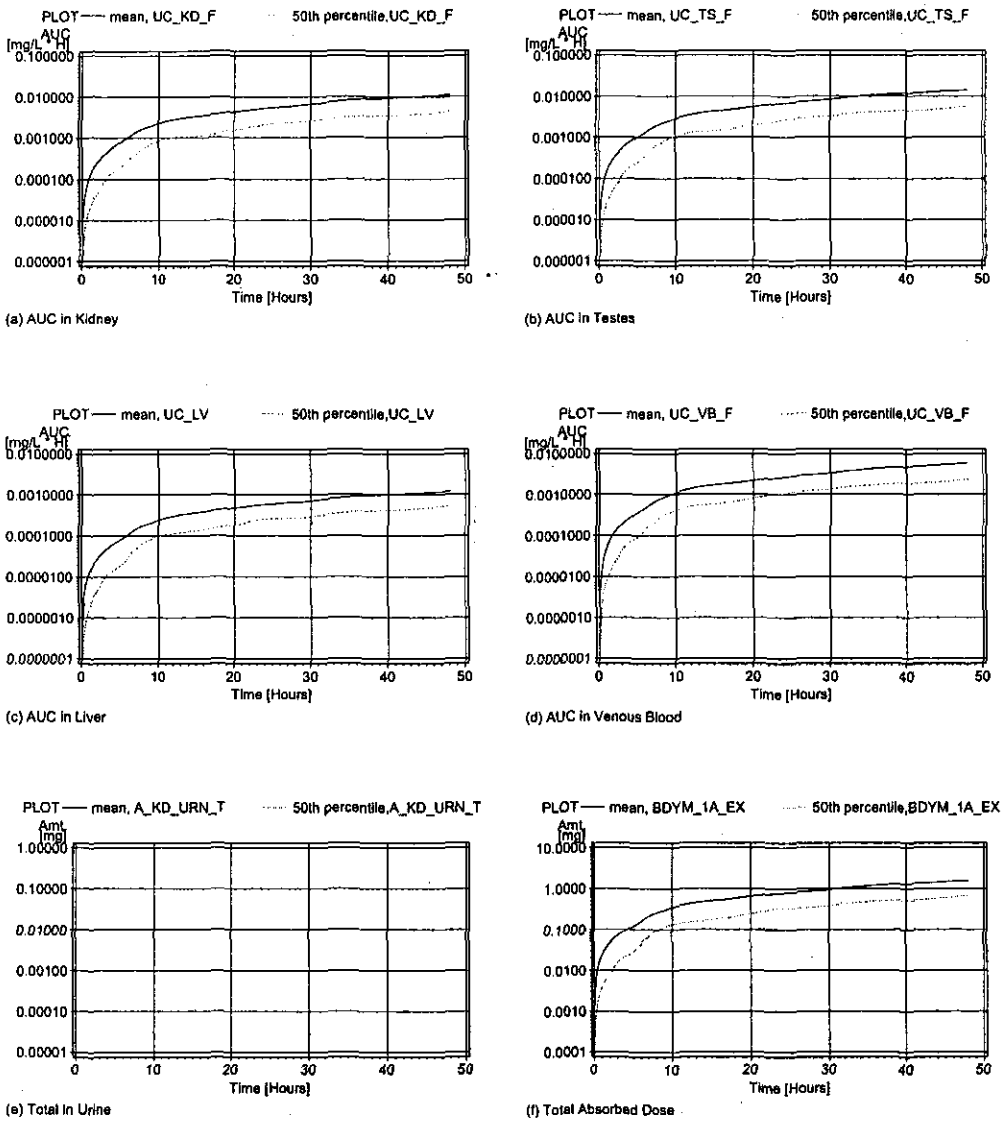


Figure A-15. Adult Male $CHCl_3$ Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose

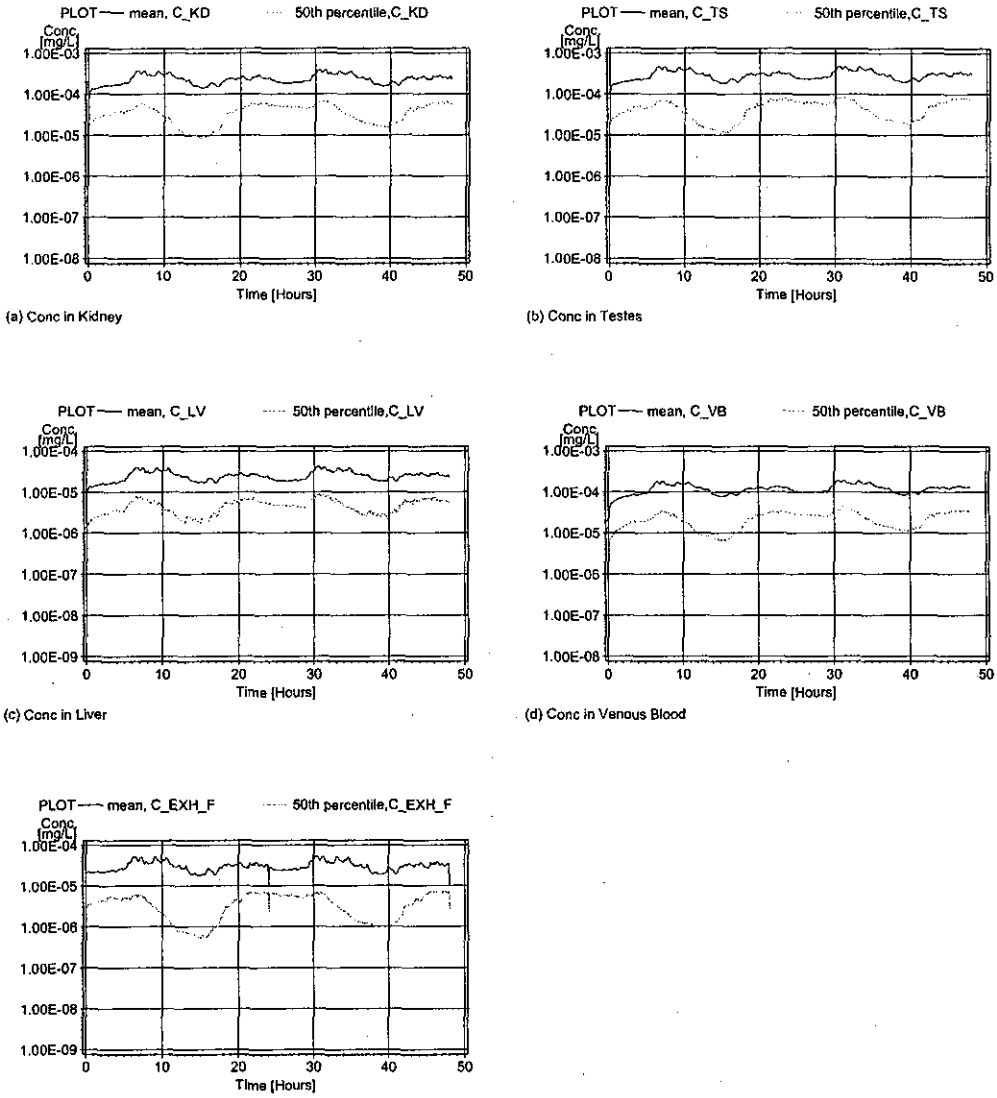


Figure A-16. Adult Male $CHCl_3$ Mean-Median Plot: Concentration and Exhaled Air

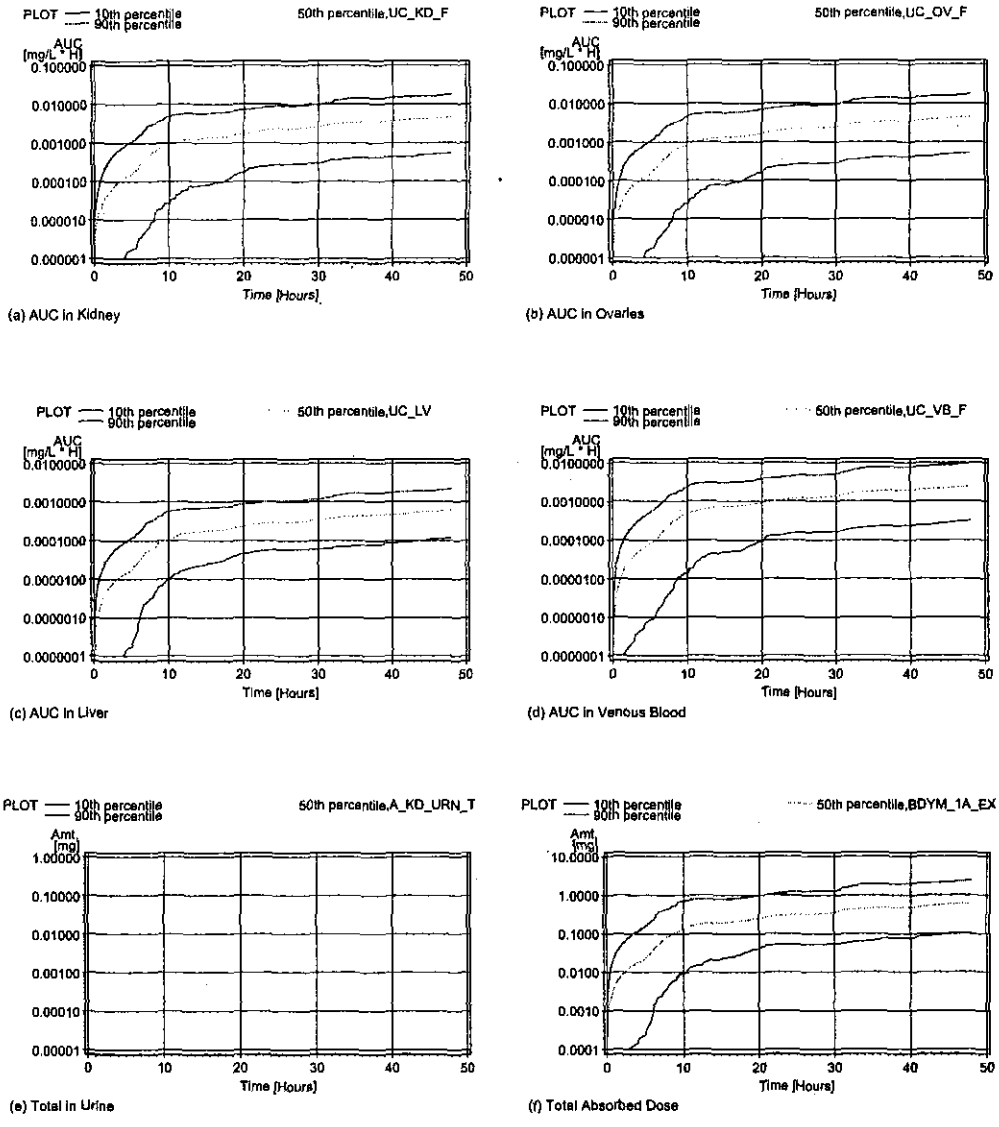
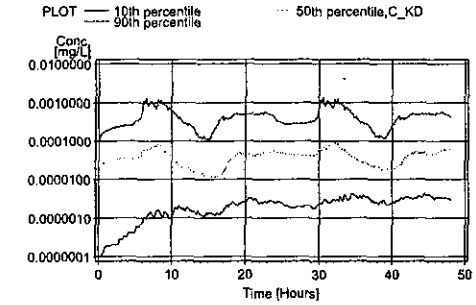
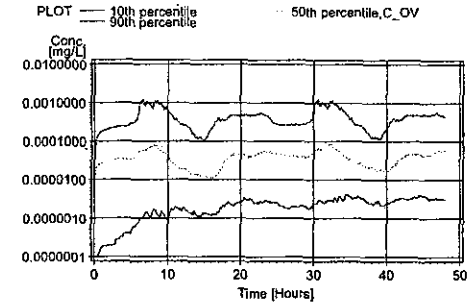


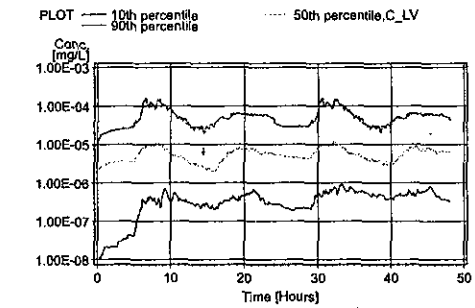
Figure A-17. Adult Female $CHCl_3$ Percentile Plot: AUC, *Total Urine*, *Total Absorbed Dose*



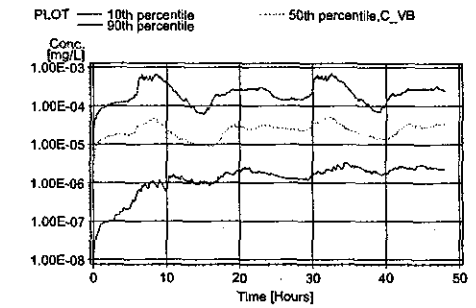
(a) Conc in Kidney



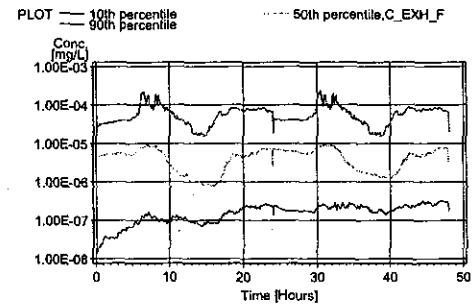
(b) Conc in Ovaries



(c) Conc in Liver



(d) Conc in Venous Blood



(e) Conc in Exhaled Air

Figure A-18. Adult Female $CHCl_3$ Percentile Plot: Concentration and Exhaled Air

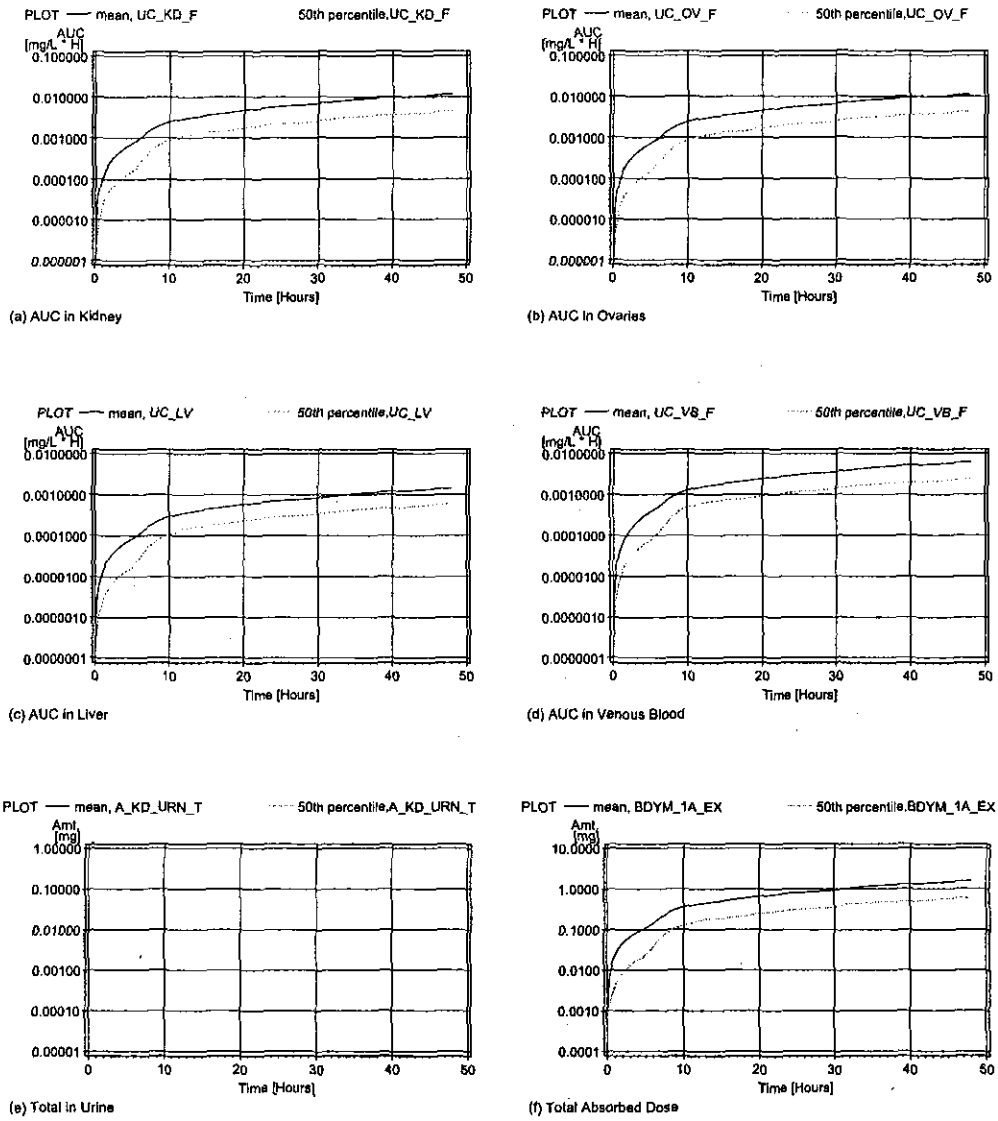
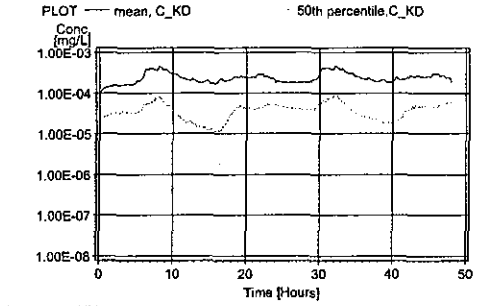
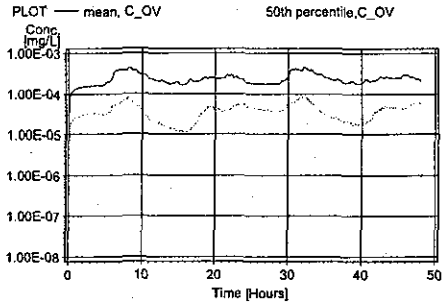


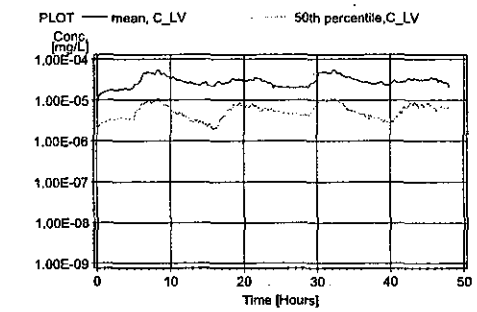
Figure A-19. Adult Female $CHCl_3$ Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose



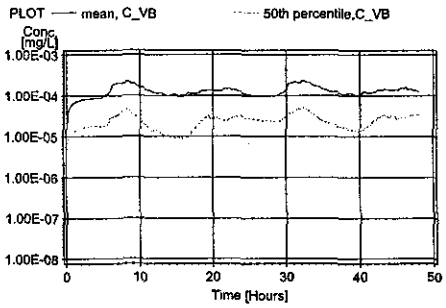
(a) Conc in Kidney



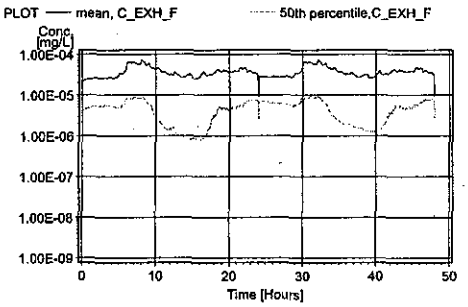
(b) Conc in Ovaries



(c) Conc in Liver



(d) Conc in Venous Blood



(e) Conc in Exhaled Air

Figure A-20. Adult Female $CHCl_3$ Mean-Median Plot: Concentration and Exhaled Air

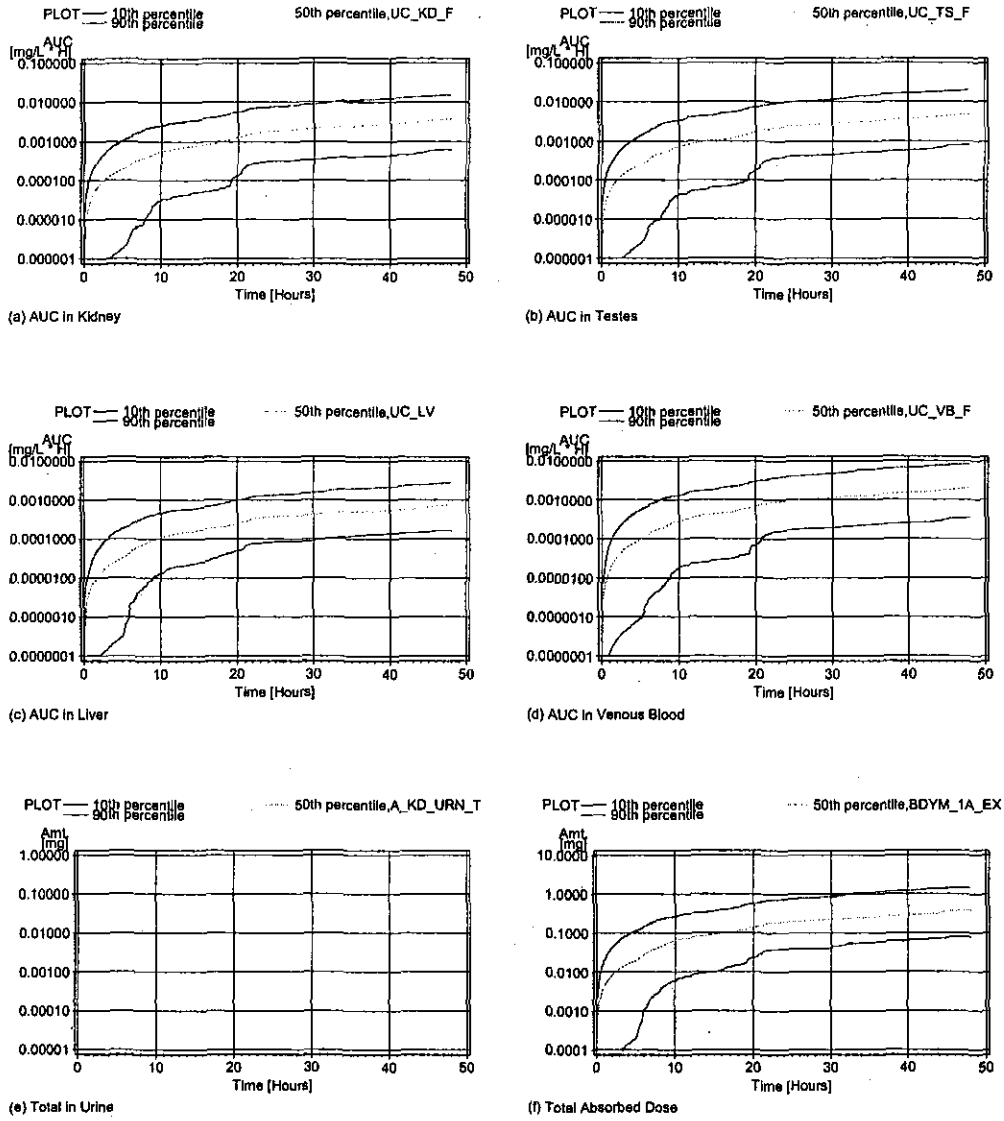


Figure A-21. Child $CHCl_3$ Percentile Plot: AUC, Total Urine, Total Absorbed Dose

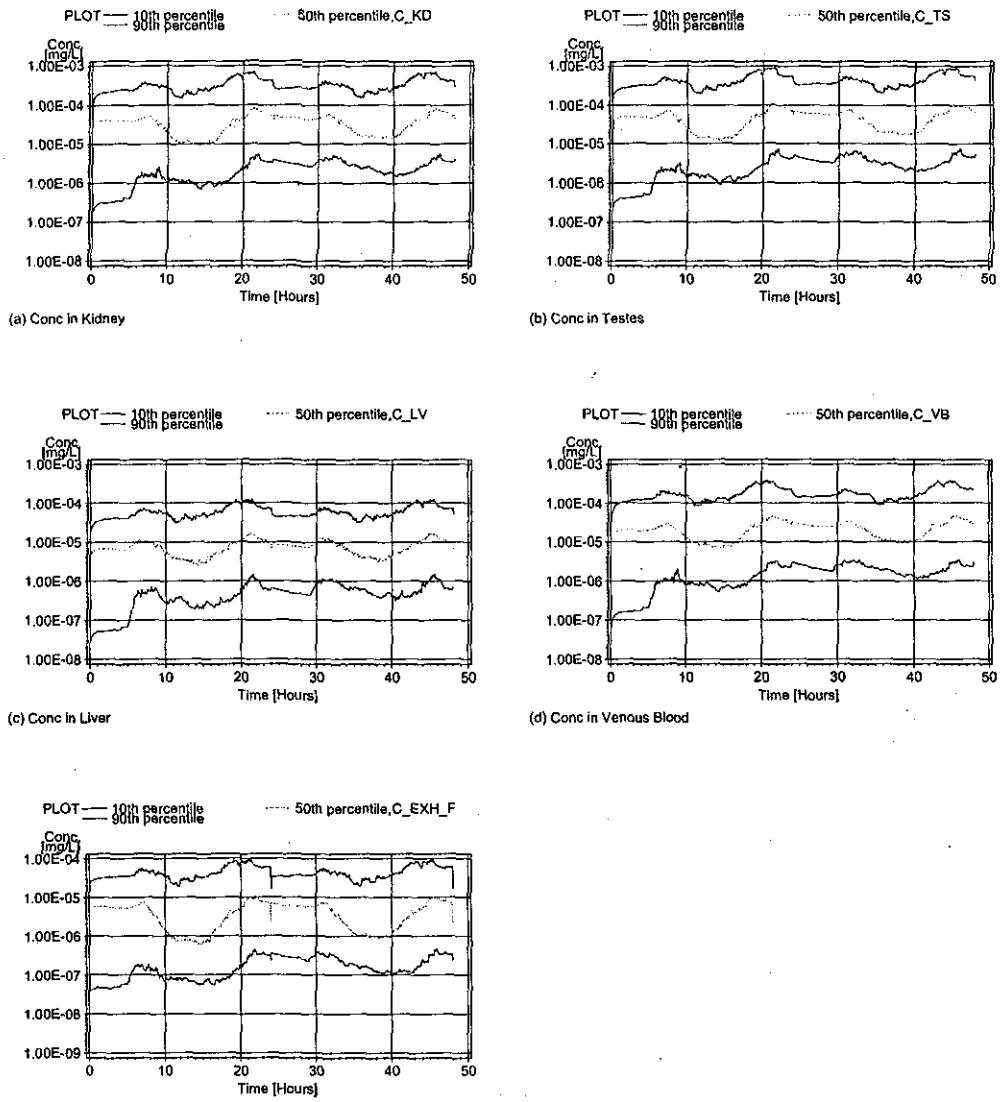


Figure A-22. Child $CHCl_3$ Percentile Plot: Concentration and Exhaled Air

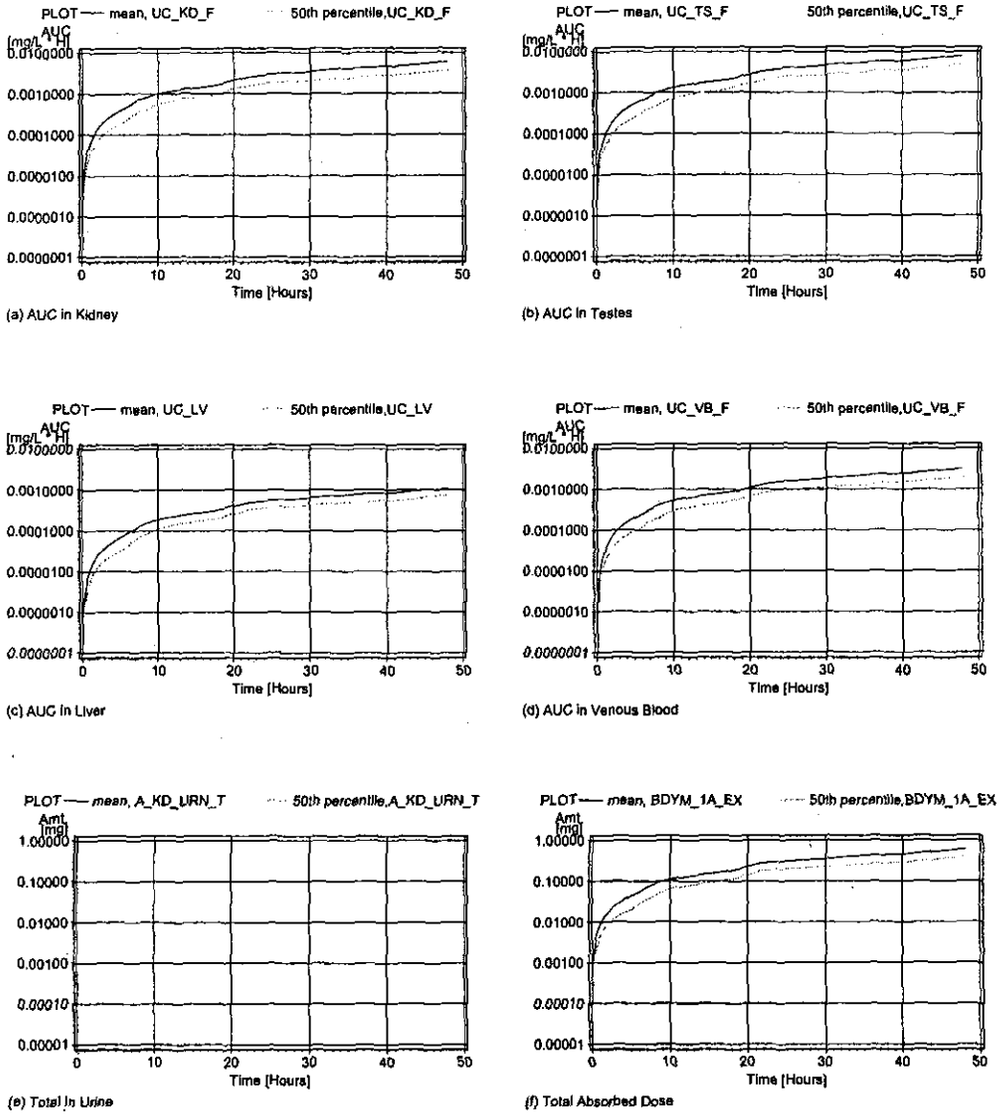


Figure A-23. Child $CHCl_3$ Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose

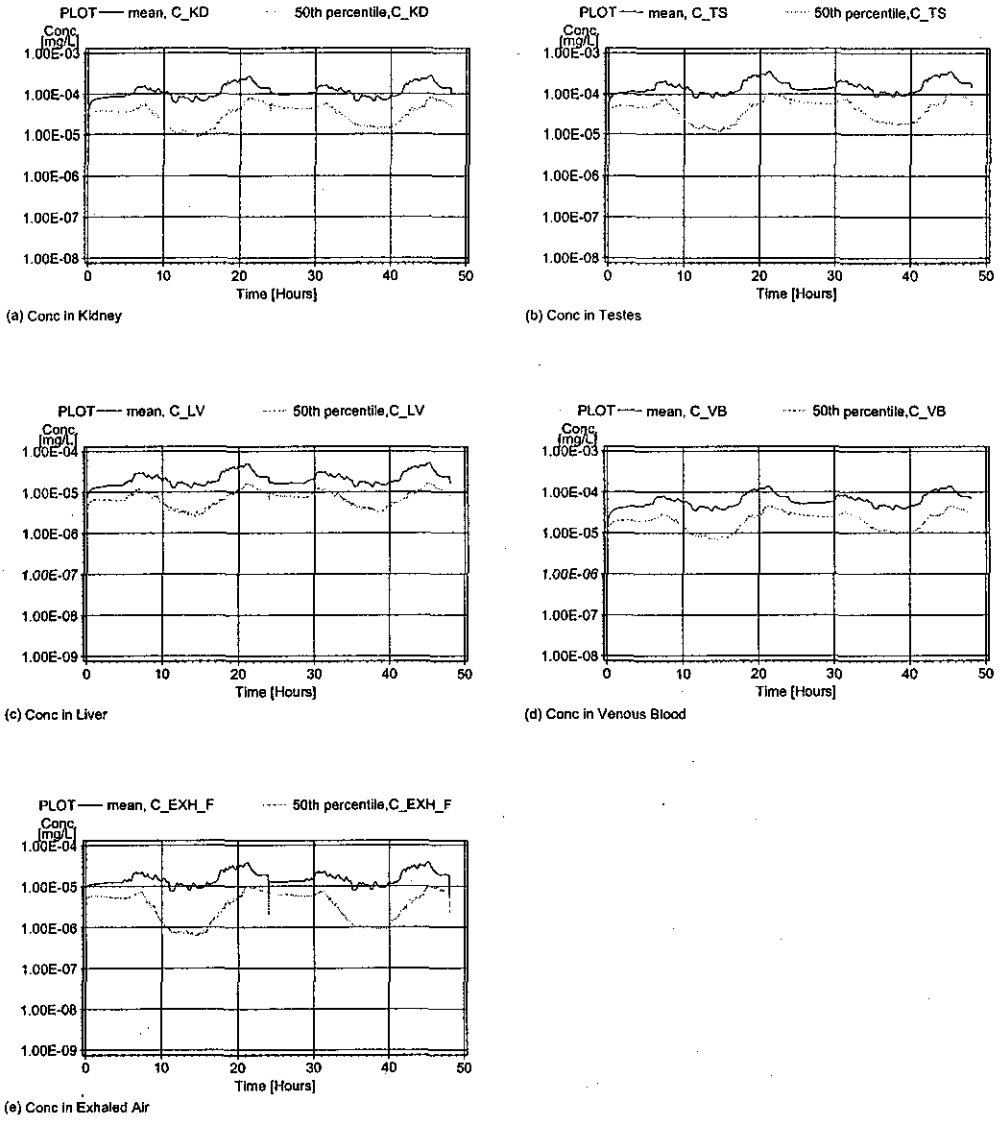


Figure A-24. Child $CHCl_3$ Mean-Median Plot: Concentration and Exhaled Air

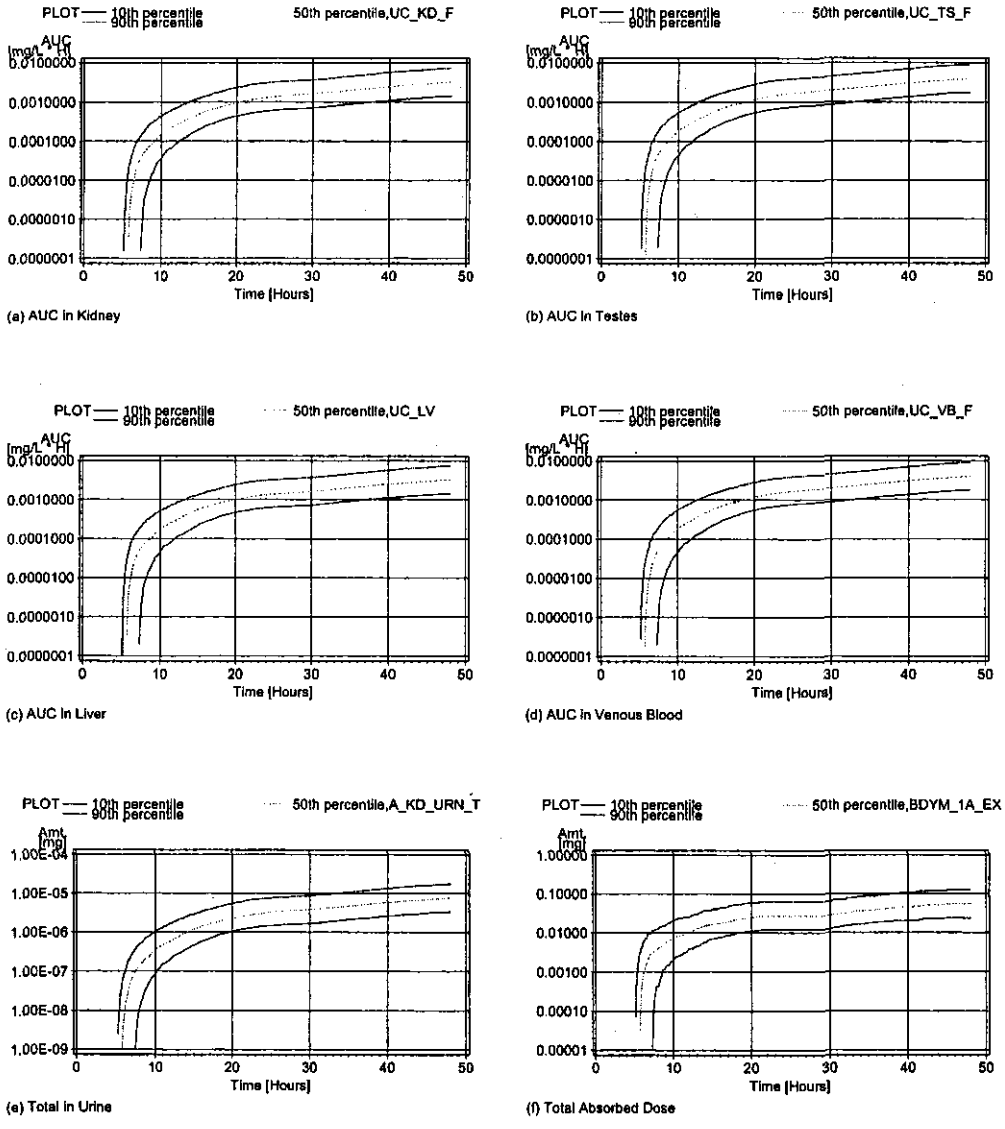


Figure A-25. Adult Male DCA Percentile Plot: AUC, Total Urine, Total Absorbed Dose

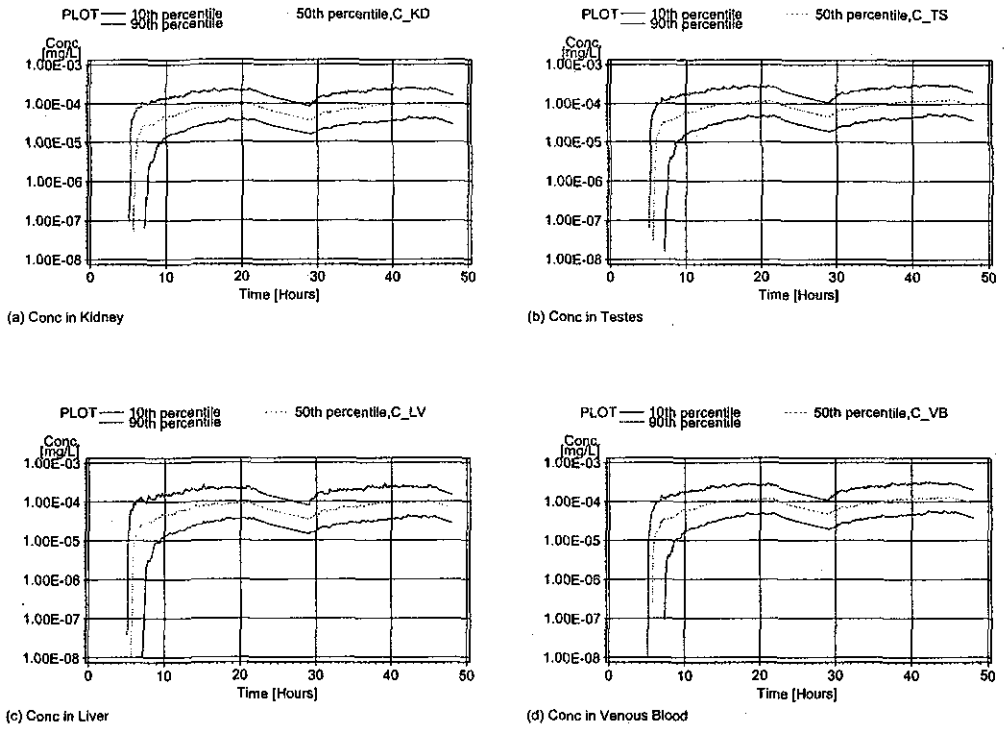


Figure A-26. Adult Male DCA Percentile Plot: Concentration

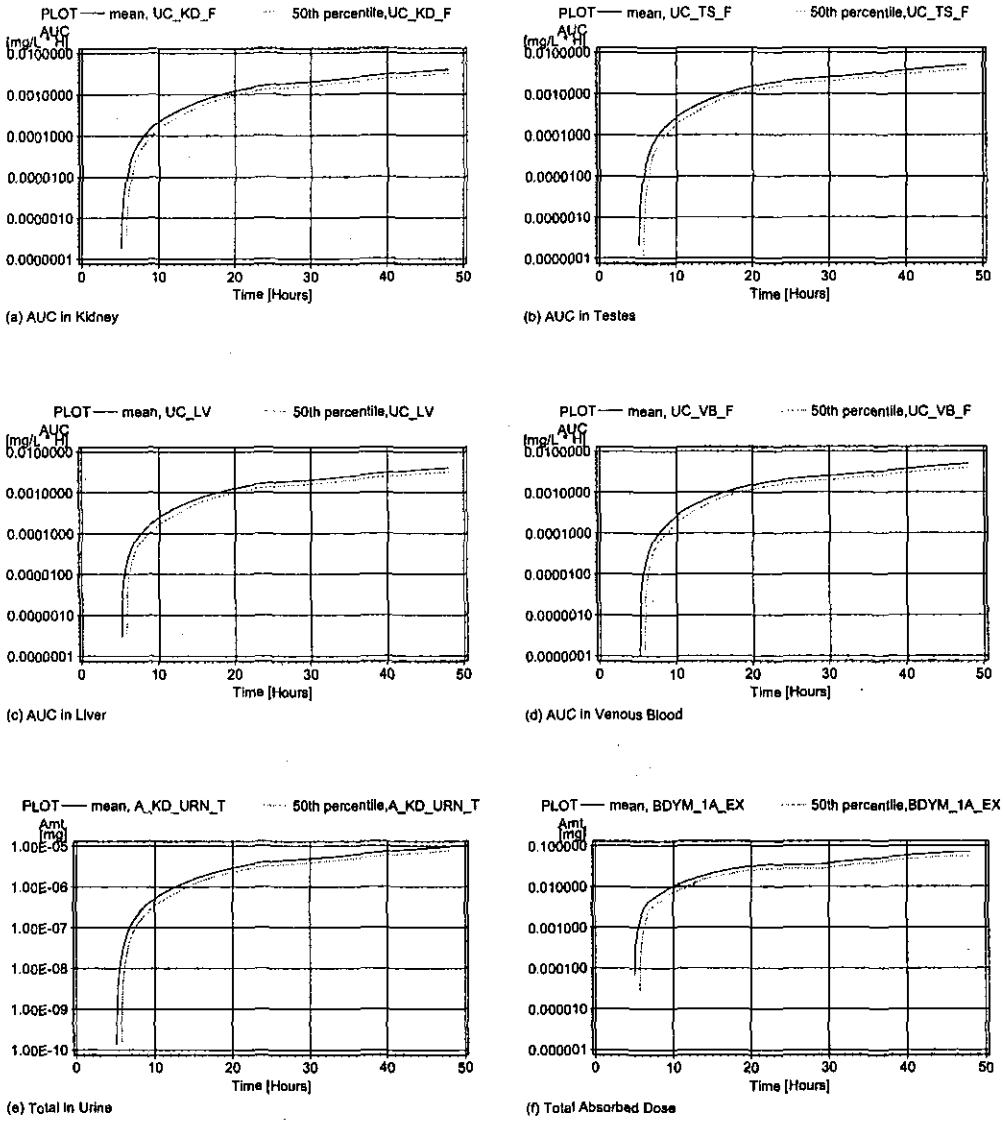


Figure A-27. Adult Male DCA Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose

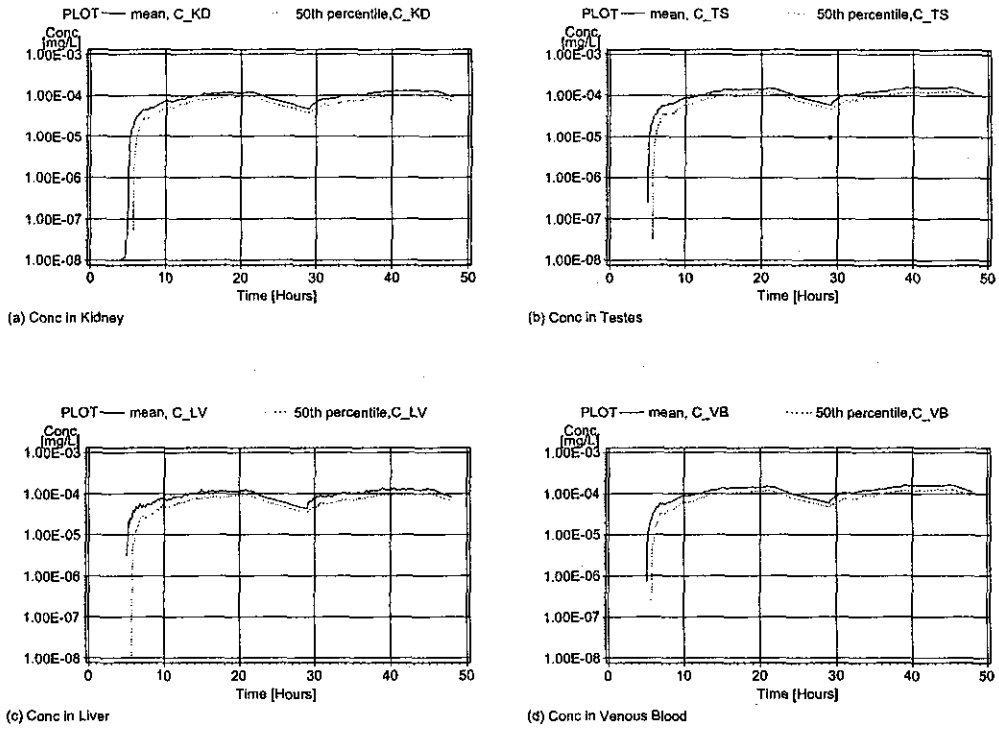


Figure A-28. Adult Male DCA Mean-Median Plot: Concentration

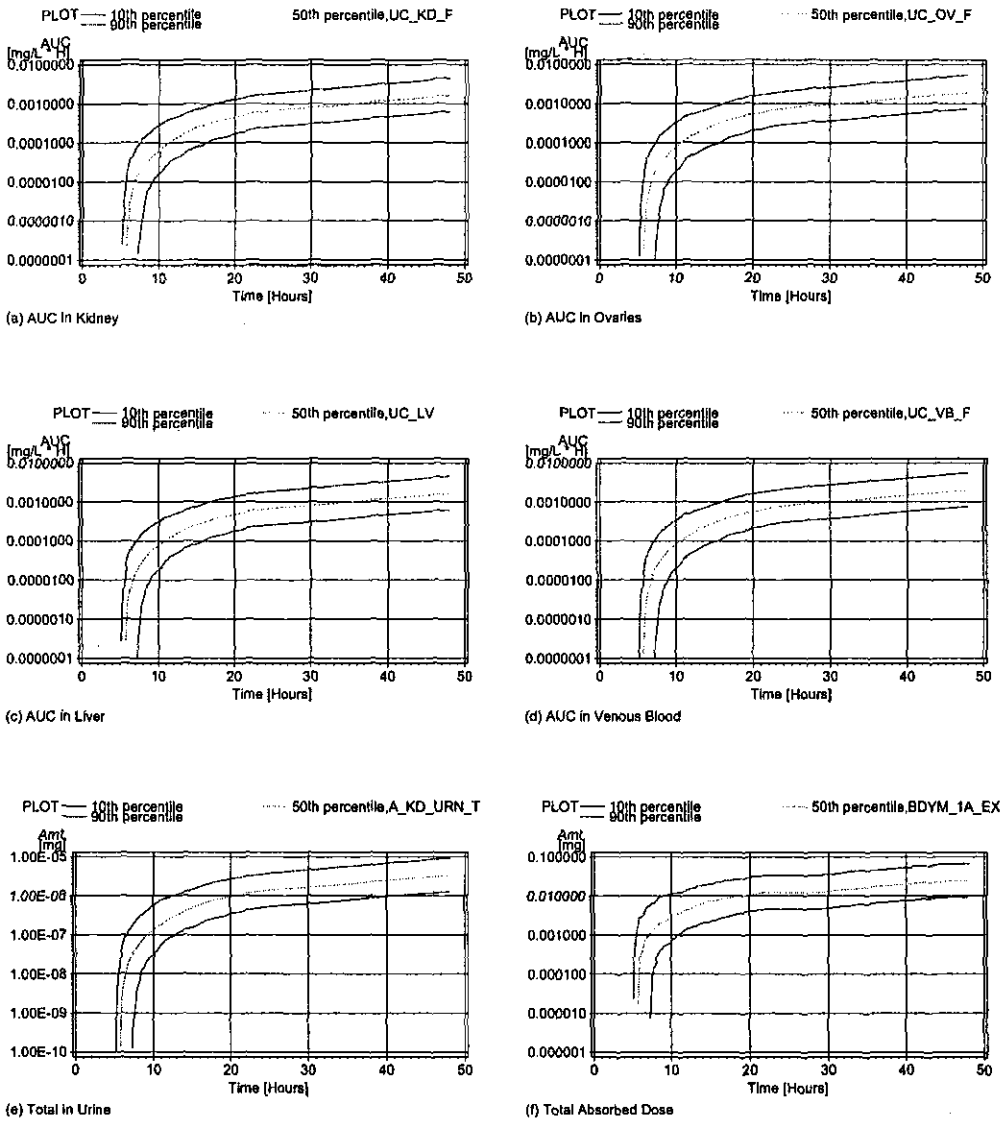


Figure A-29. Adult Female DCA Percentile Plot: AUC, Total Urine, Total Absorbed Dose

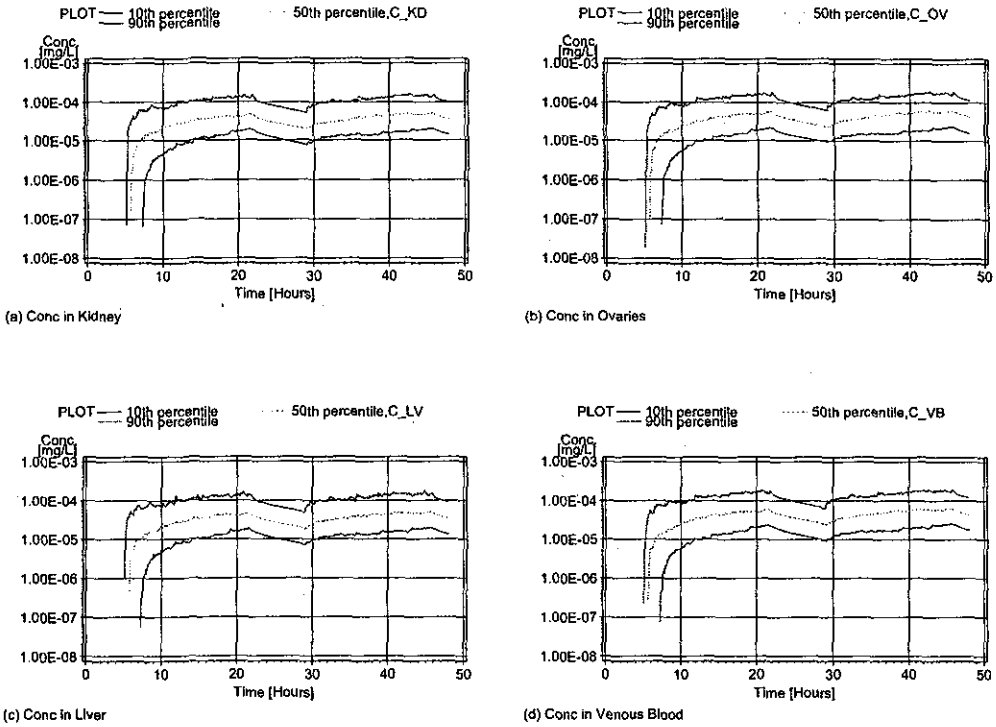


Figure A-30. Adult Female DCA Percentile Plot: Concentration

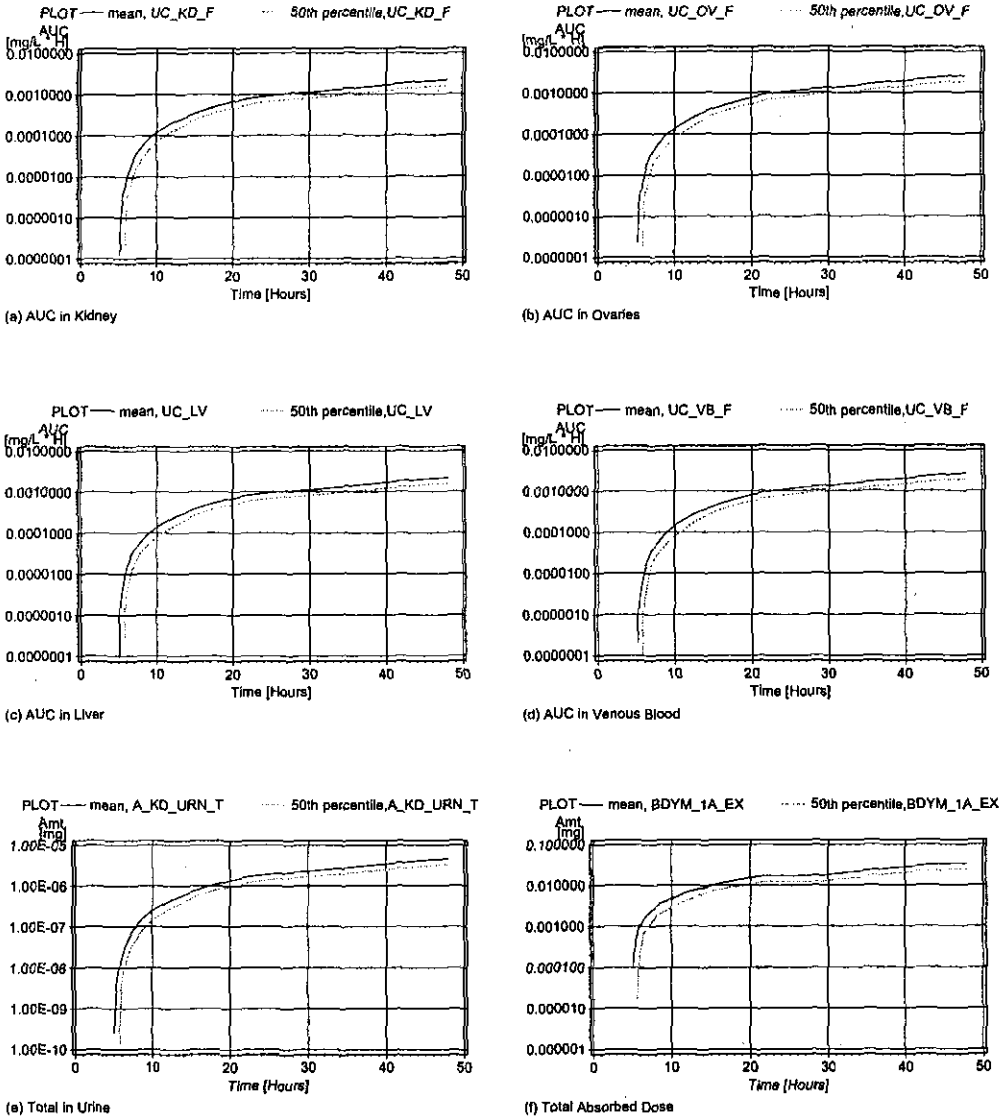


Figure A-31. Adult Female DCA Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose

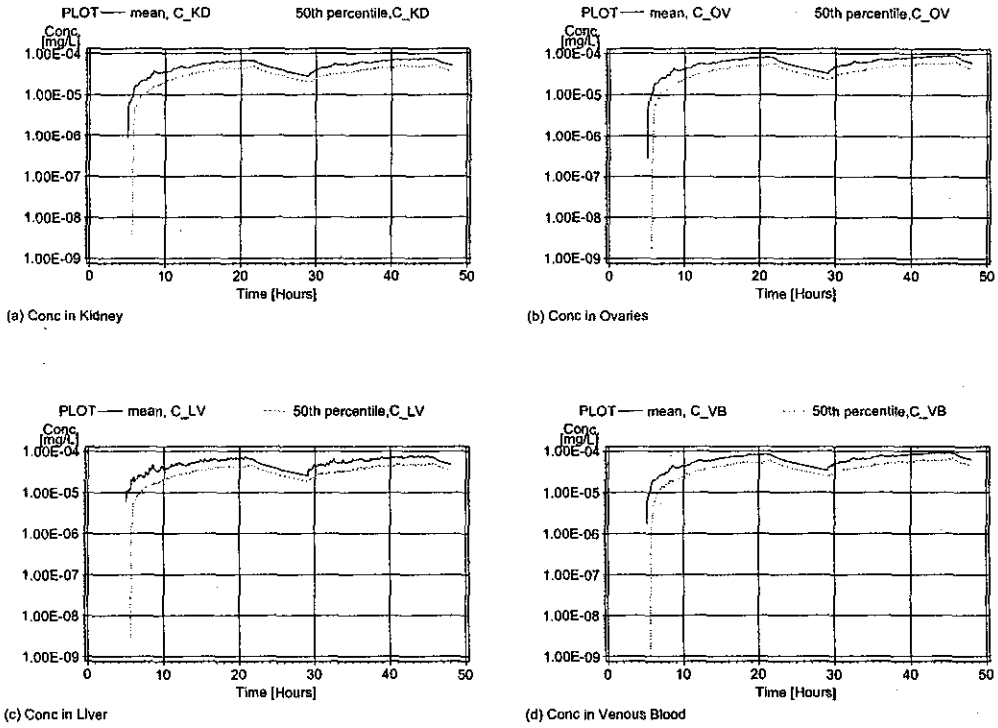


Figure A-32. Adult Female DCA Mean-Median Plot: Concentration

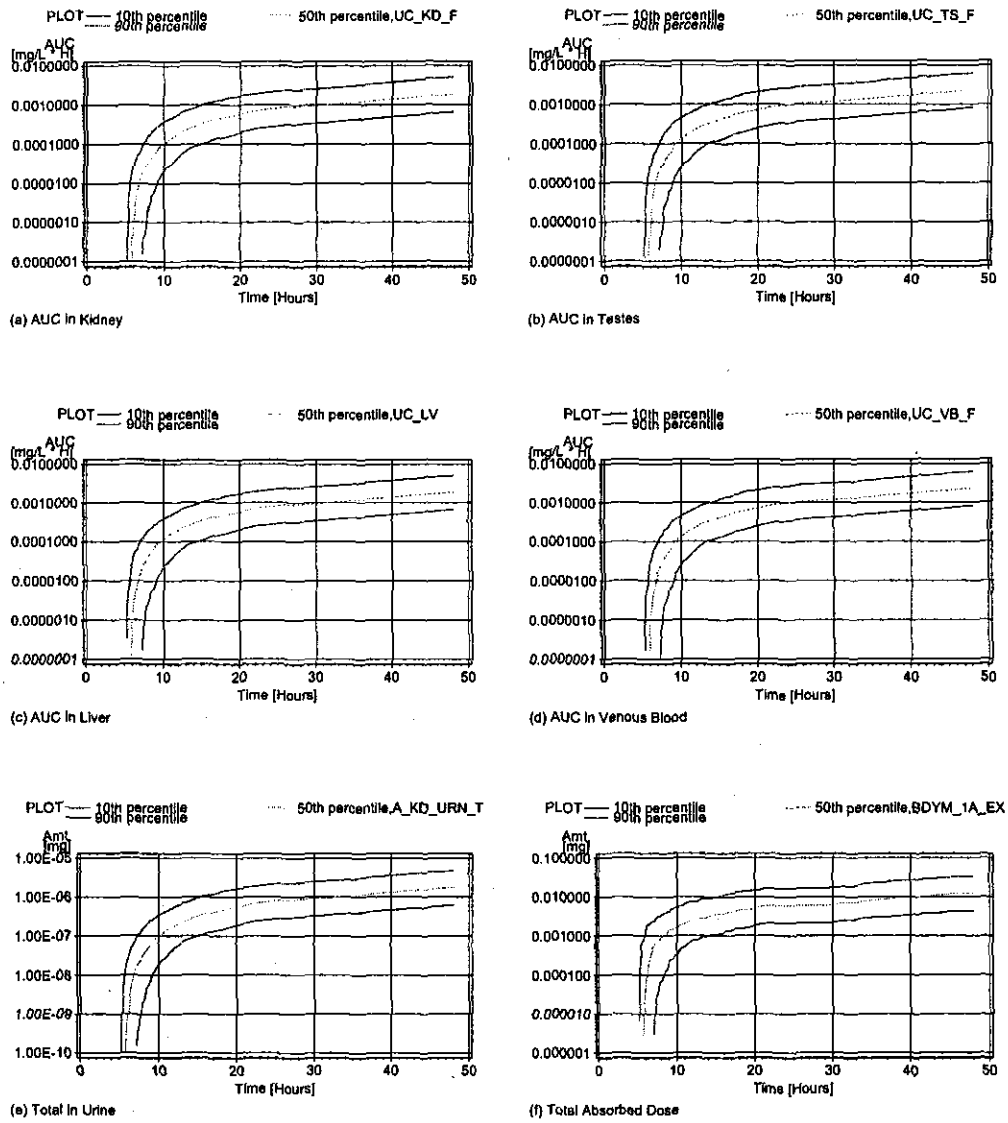


Figure A-33. Child DCA Percentile Plot: AUC, Total Urine, Total Absorbed Dose

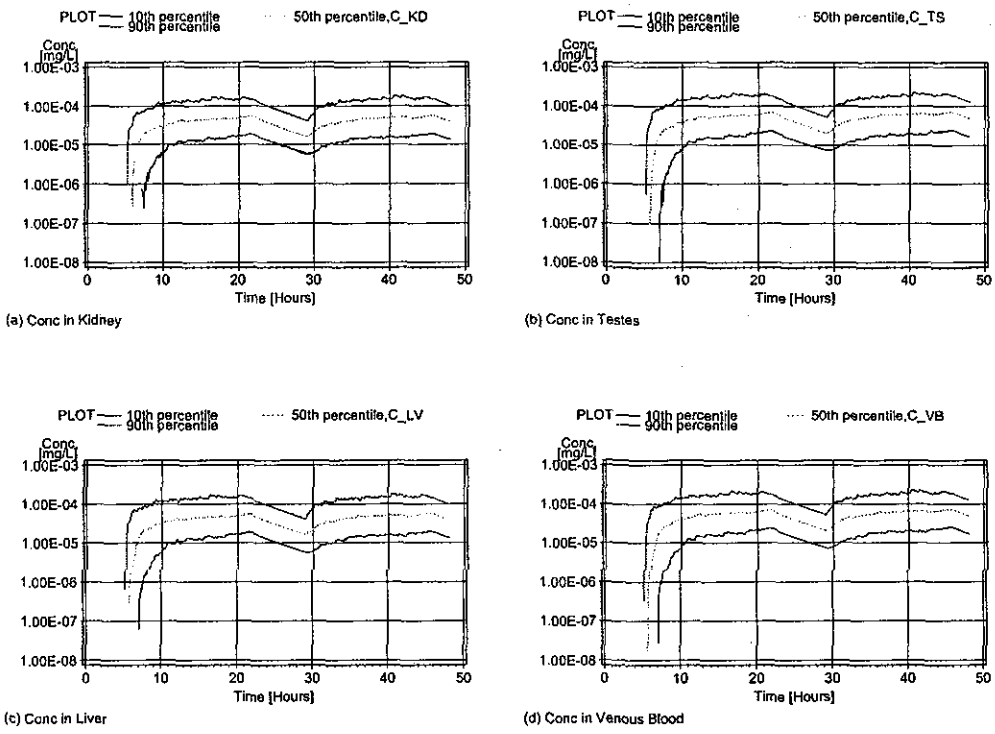


Figure A-34. Child DCA Percentile Plot: Concentration

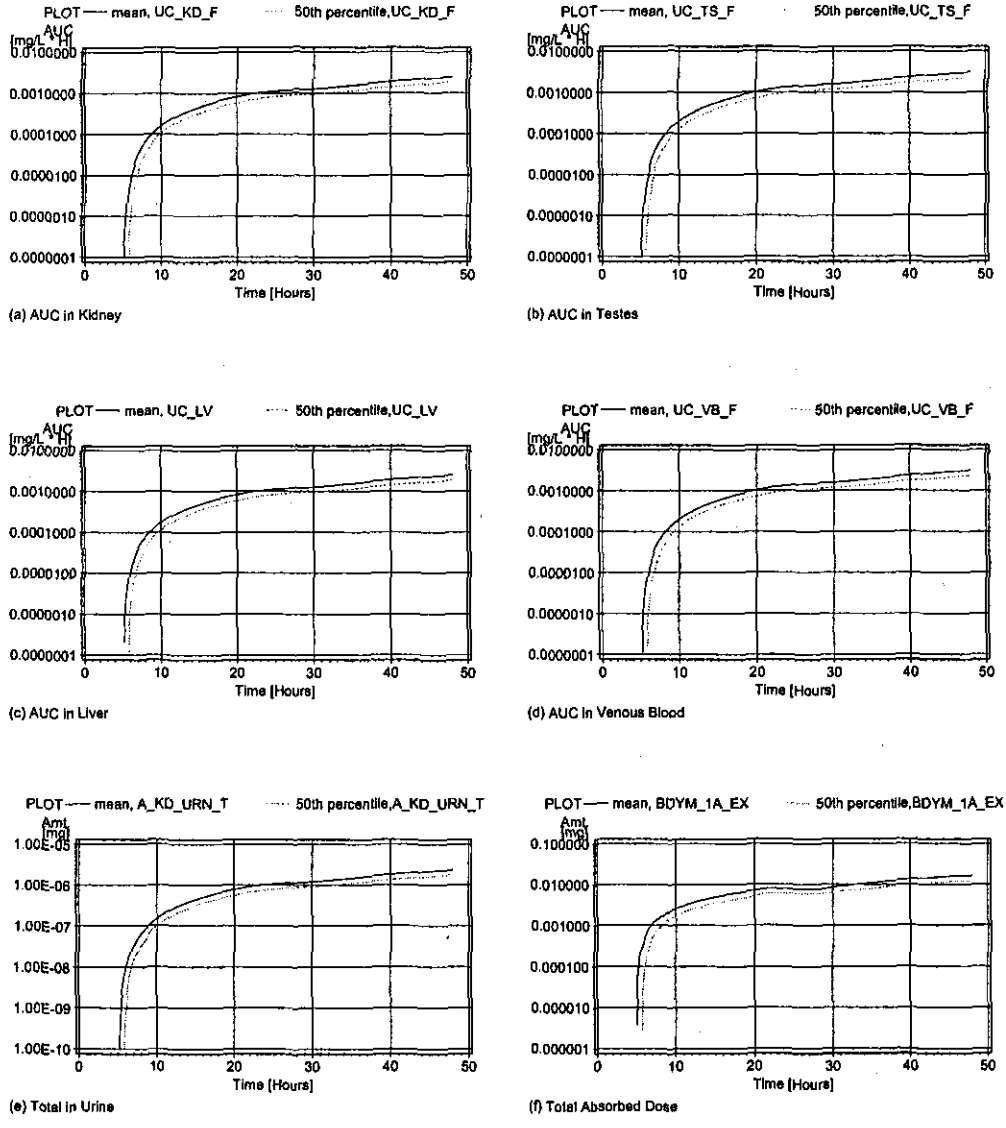
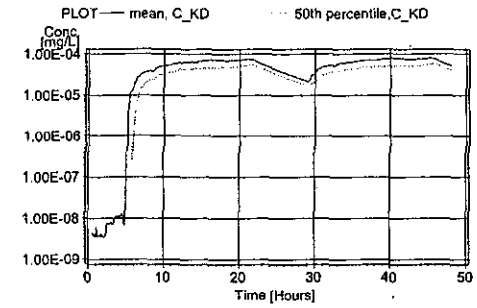
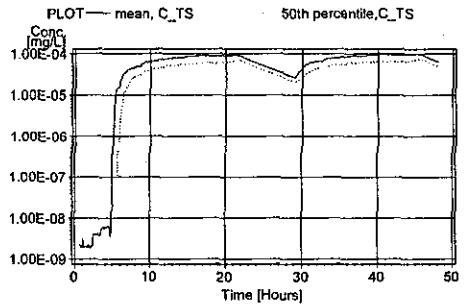


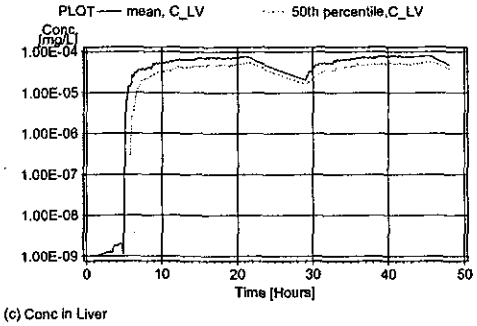
Figure A-35. Child DCA Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose



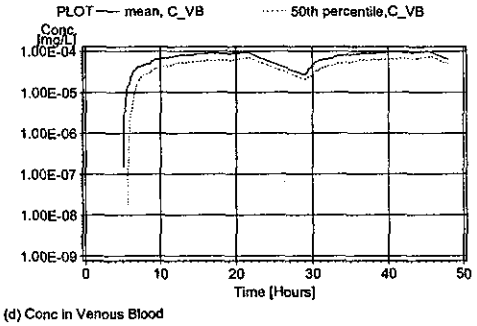
(a) Conc in Kidney



(b) Conc in Testes



(c) Conc in Liver



(d) Conc in Venous Blood

Figure A-36. Child DCA Mean-Median Plot: Concentration

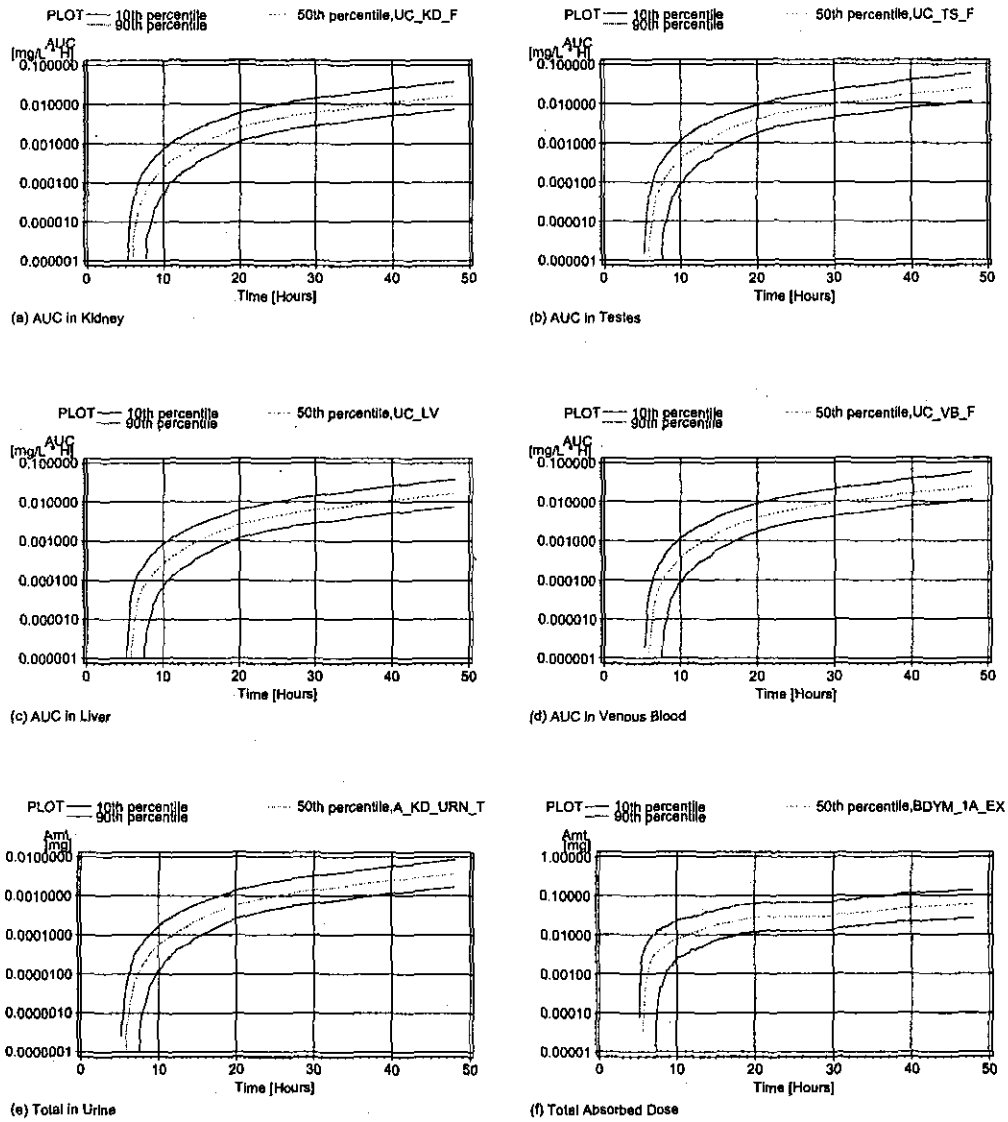


Figure A-37. Adult Male TCA Percentile Plot: AUC, Total Urine, Total Absorbed Dose

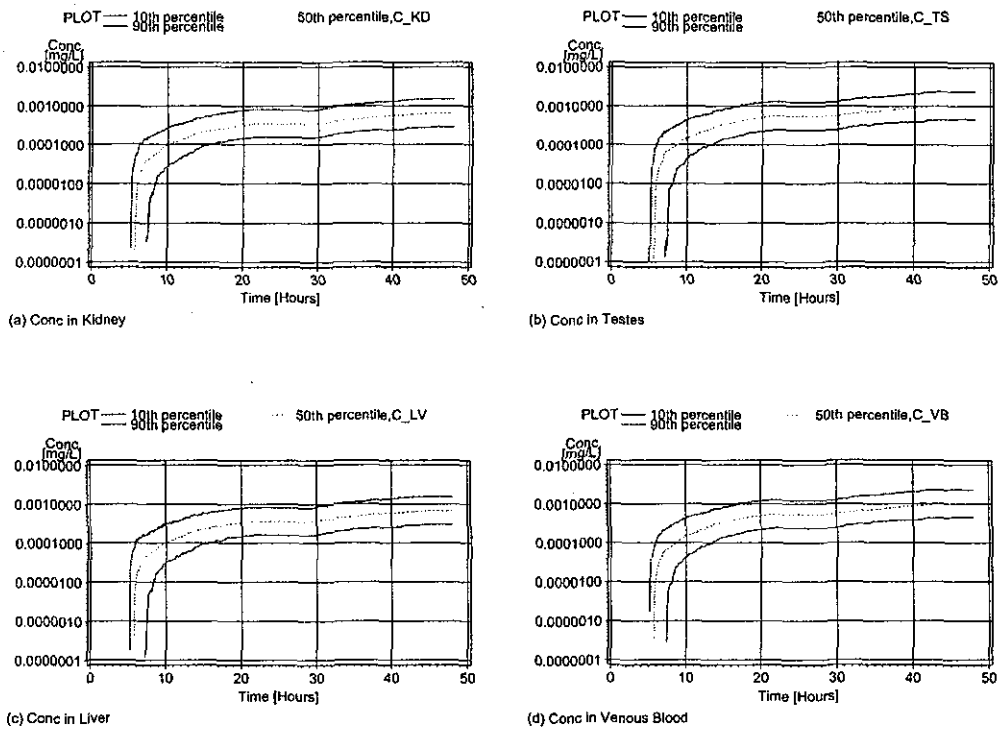


Figure A-38. Adult Male TCA Percentile Plot: Concentration

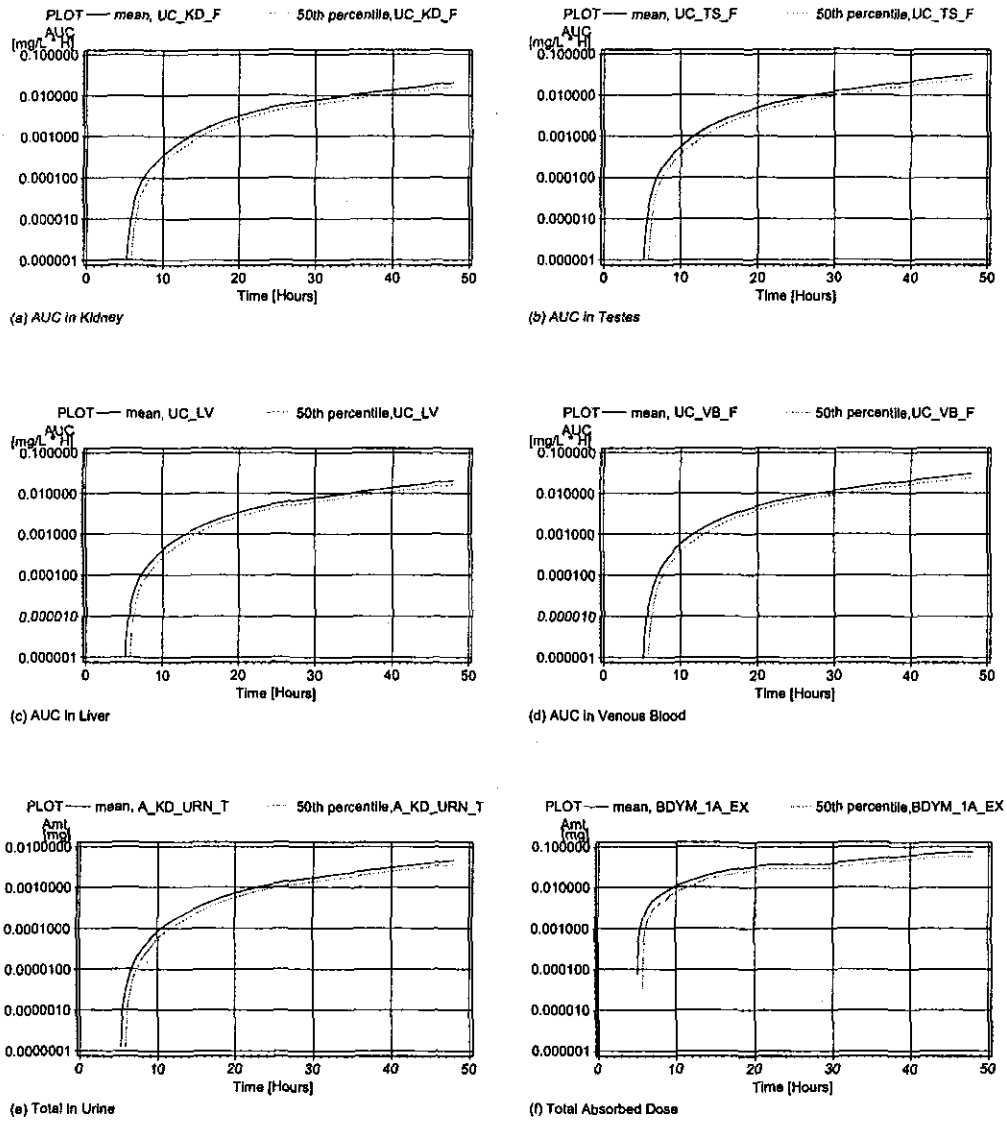


Figure A-39. Adult Male TCA Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose

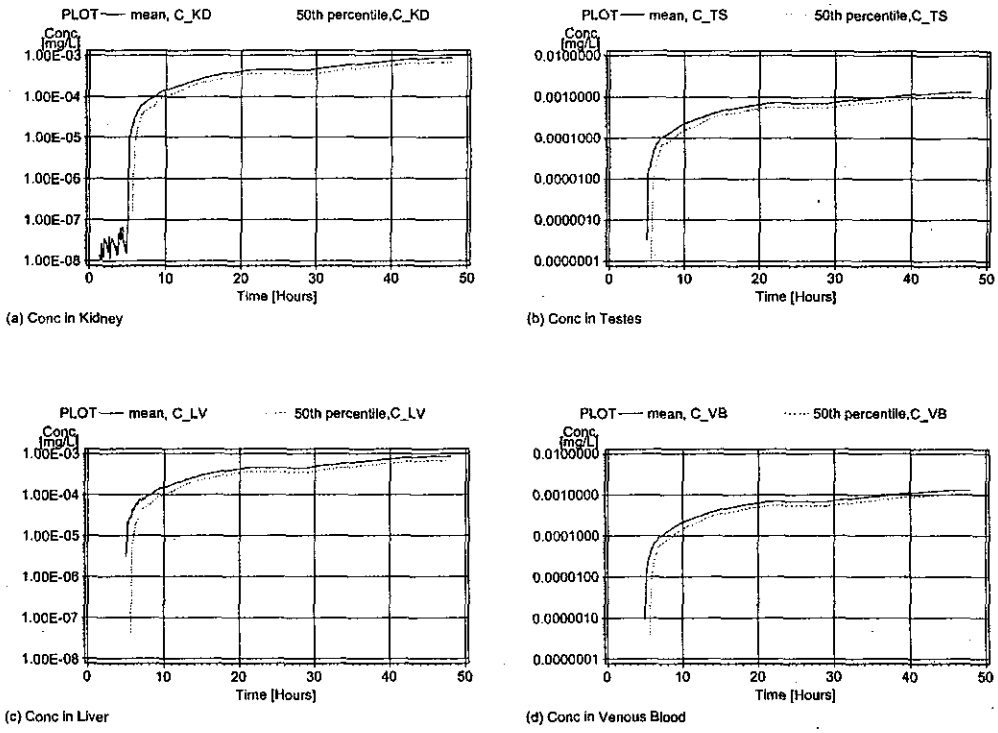


Figure A-40. Adult Male TCA Mean-Median Plot: Concentration

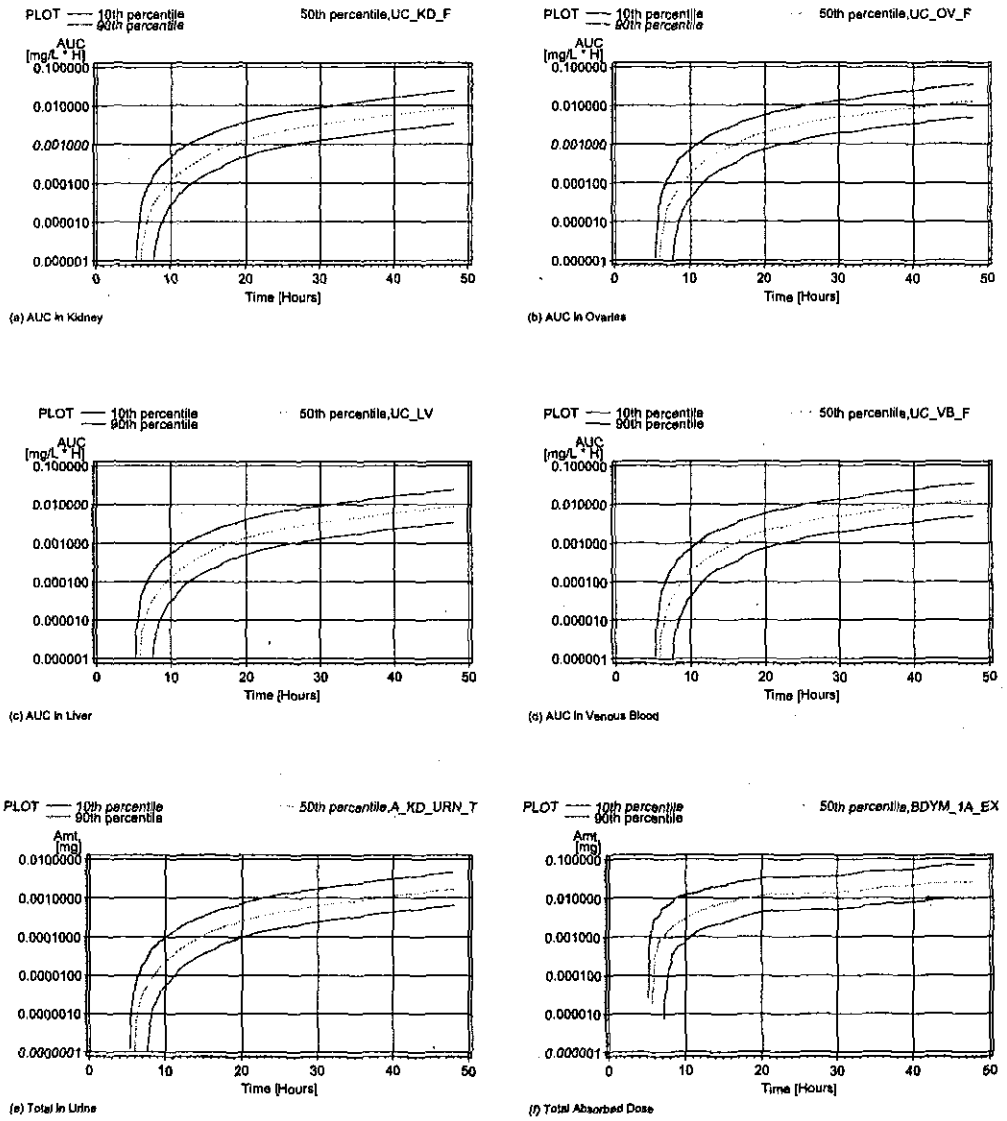


Figure A-41. Adult Female TCA Percentile Plot: AUC, Total Urine, Total Absorbed Dose

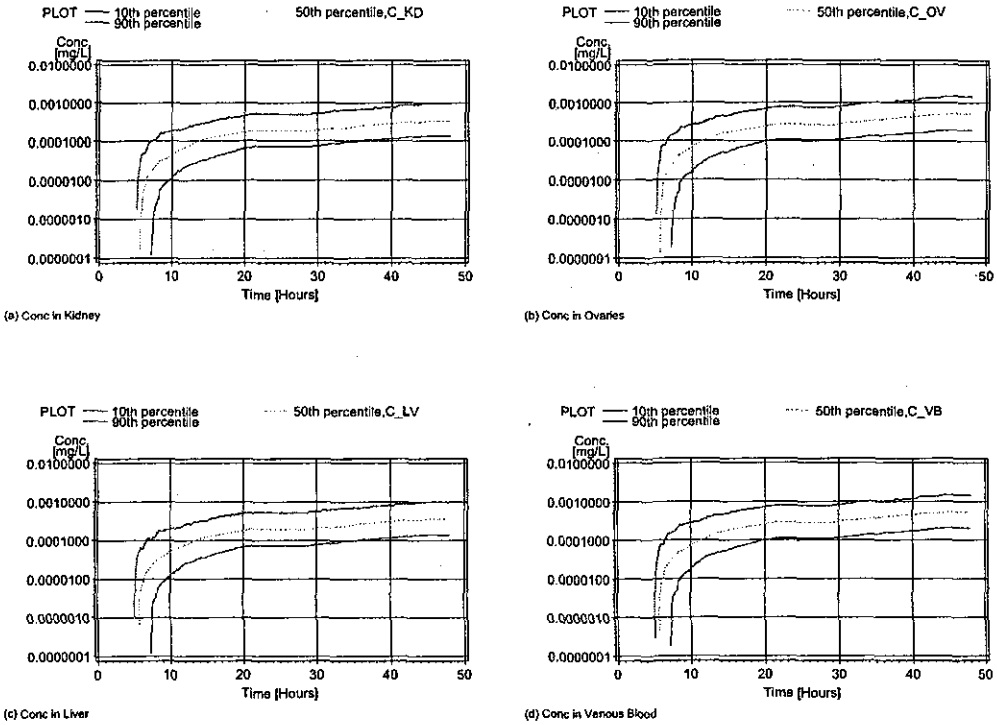


Figure A-42. Adult Female TCA Percentile Plot: Concentration

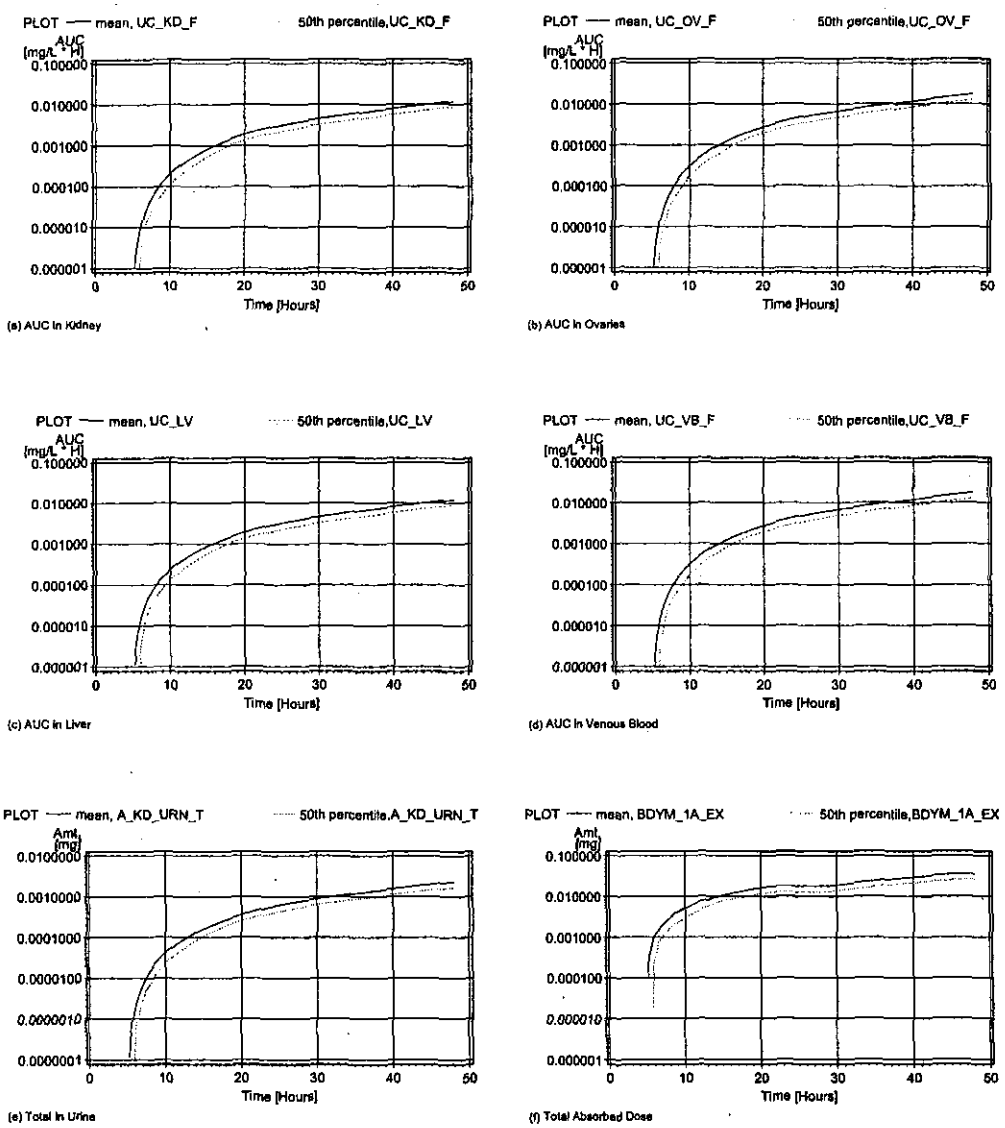


Figure A-43. Adult Female TCA Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose

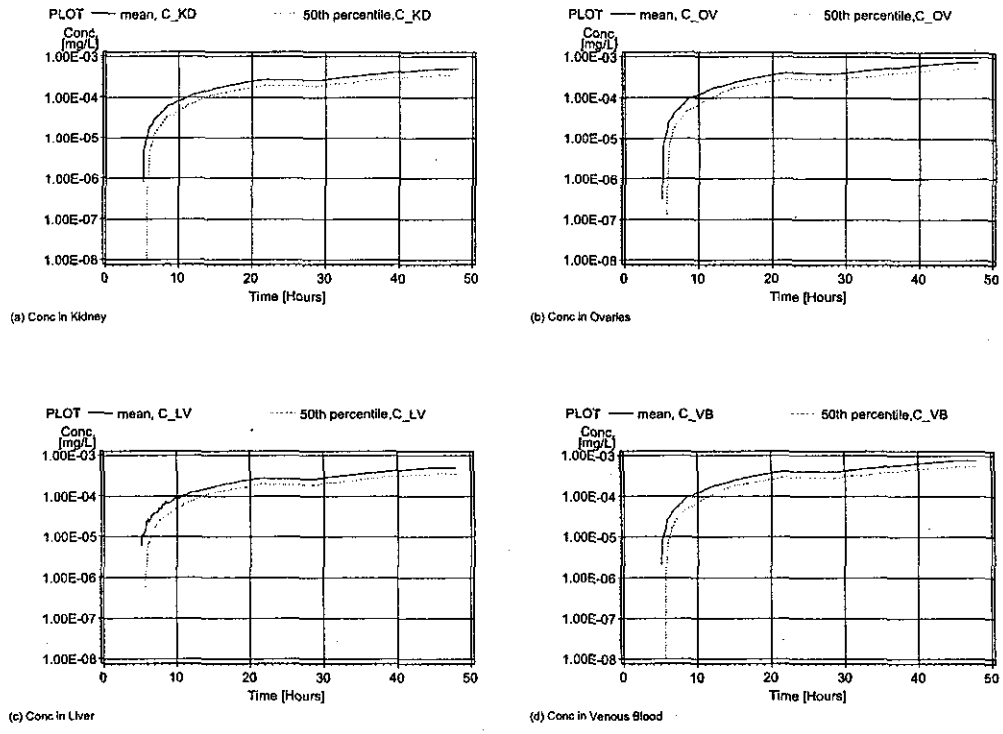


Figure A-44. Adult Female TCA Mean-Median Plot: Concentration

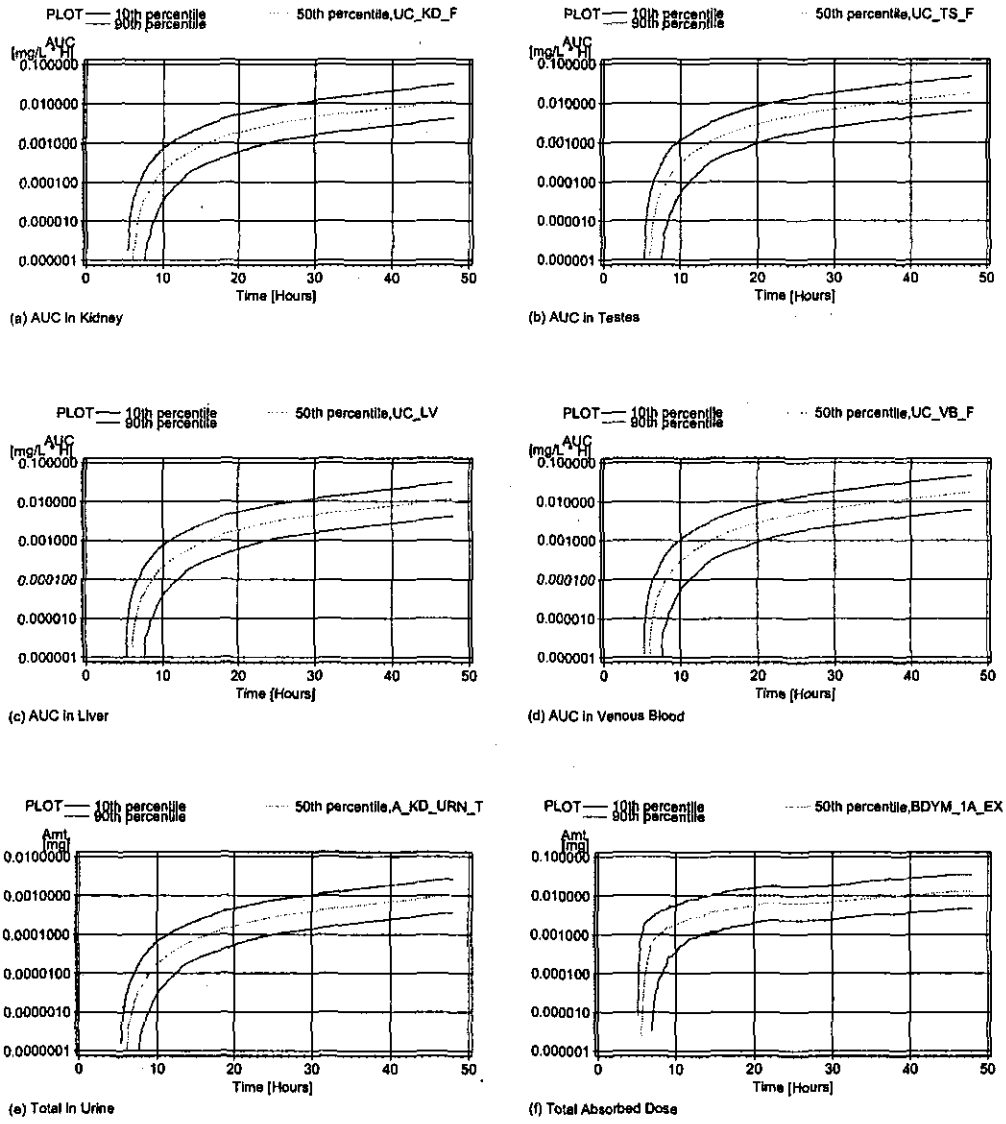
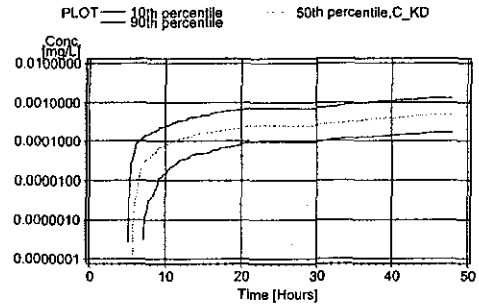
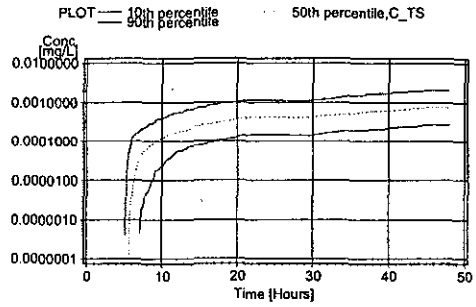


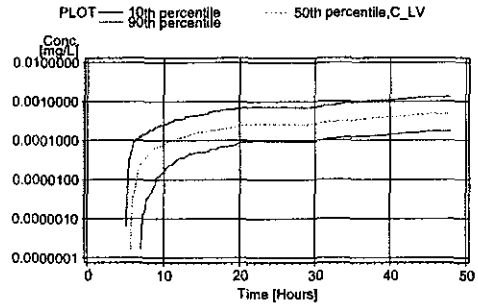
Figure A-45. Child TCA Percentile Plot: AUC, Total Urine, Total Absorbed Dose



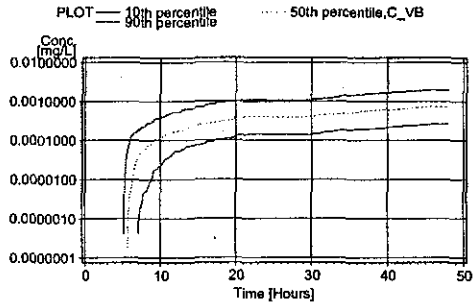
(a) Conc in Kidney



(b) Conc in Testes



(c) Conc in Liver



(d) Conc in Venous Blood

Figure A-46. Child TCA Percentile Plot: Concentration

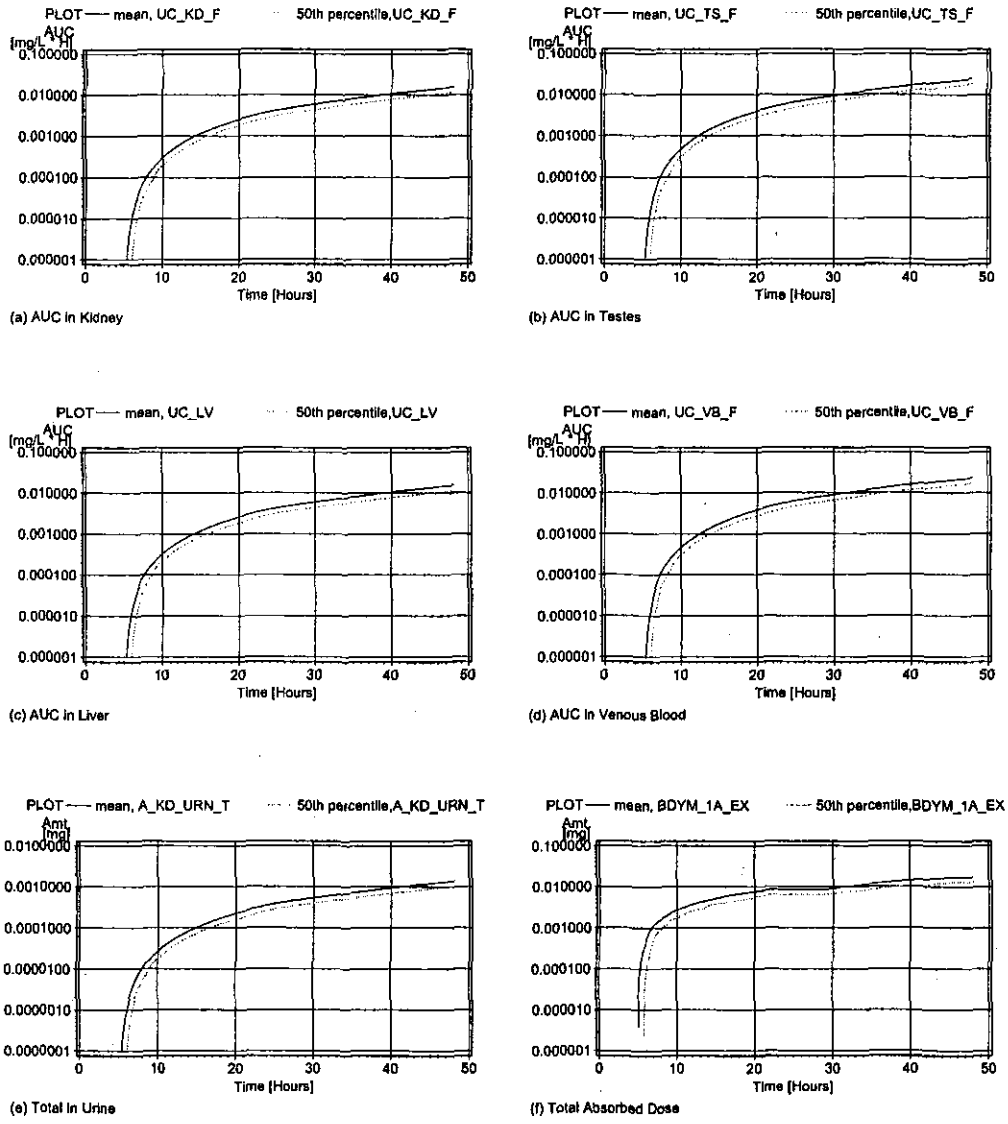
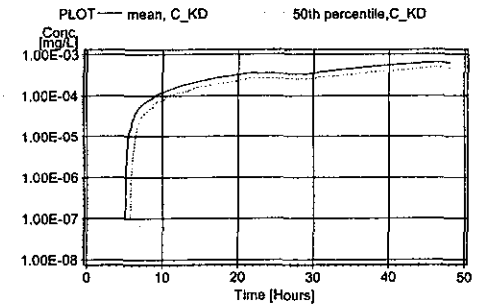
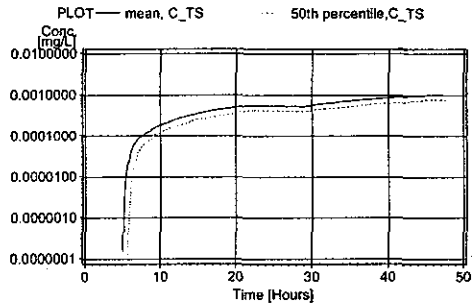


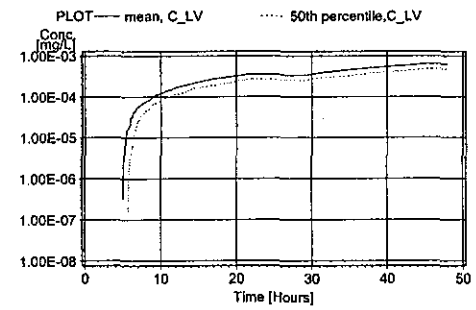
Figure A-47. Child TCA Mean-Median Plot: AUC, Total Urine, Total Absorbed Dose



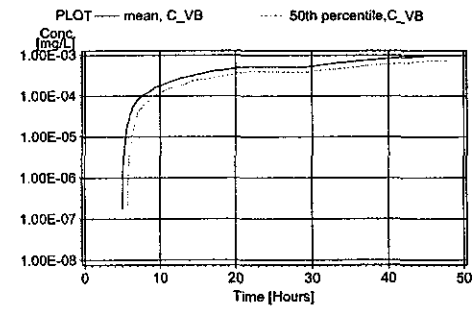
(a) Conc in Kidney



(b) Conc in Testes



(c) Conc in Liver



(d) Conc in Venous Blood

Figure A-48. Child TCA Mean-Median Plot: Concentration

APPENDIX 2

A CONCEPTUAL MODEL FOR A CUMULATIVE RISK APPROACH

The following text contains Chapter 4.0, excerpted in its entirety, from the U.S. EPA (2000a) report entitled, *Conducting a Risk Assessment of Mixtures of Disinfection By-products (DBPs) for Drinking Water Treatment Systems* (NCEA-C-0791). This chapter details the Cumulative Relative Potency Factors (CRPF) risk assessment approach that is discussed in the main report of this document and is provided here as reference material. It has been edited slightly to remove cross references within the EPA report (U.S. EPA, 2000a) that may cause confusion to the reader. Also note that the equations in this Appendix use a value of Y to represent tap water consumption. This is different from the equations found in Section 2.0 of the main document because water consumption is included in the exposure modeling that produces estimates of dose.

4. CONCEPTUAL MODEL FOR A CUMULATIVE RISK APPROACH

Several different risk characterization methods have been recommended for estimating DBP mixtures risk: response-addition, relative potency factors and proportional response addition. 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 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. 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. 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 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.

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, 2000b), 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

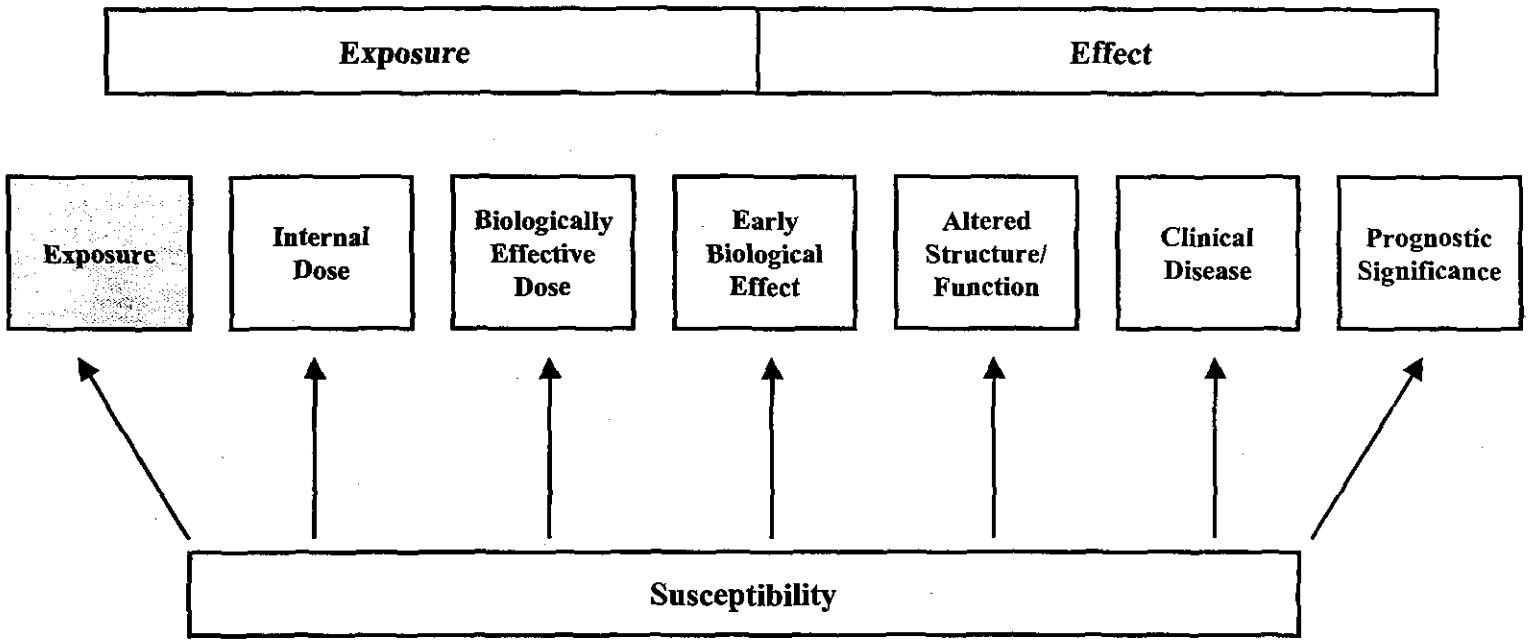


FIGURE 9

Biological Marker Components in Sequential Progression from Exposure to Disease

Source: Schulte (1989)

(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, 2000b). 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

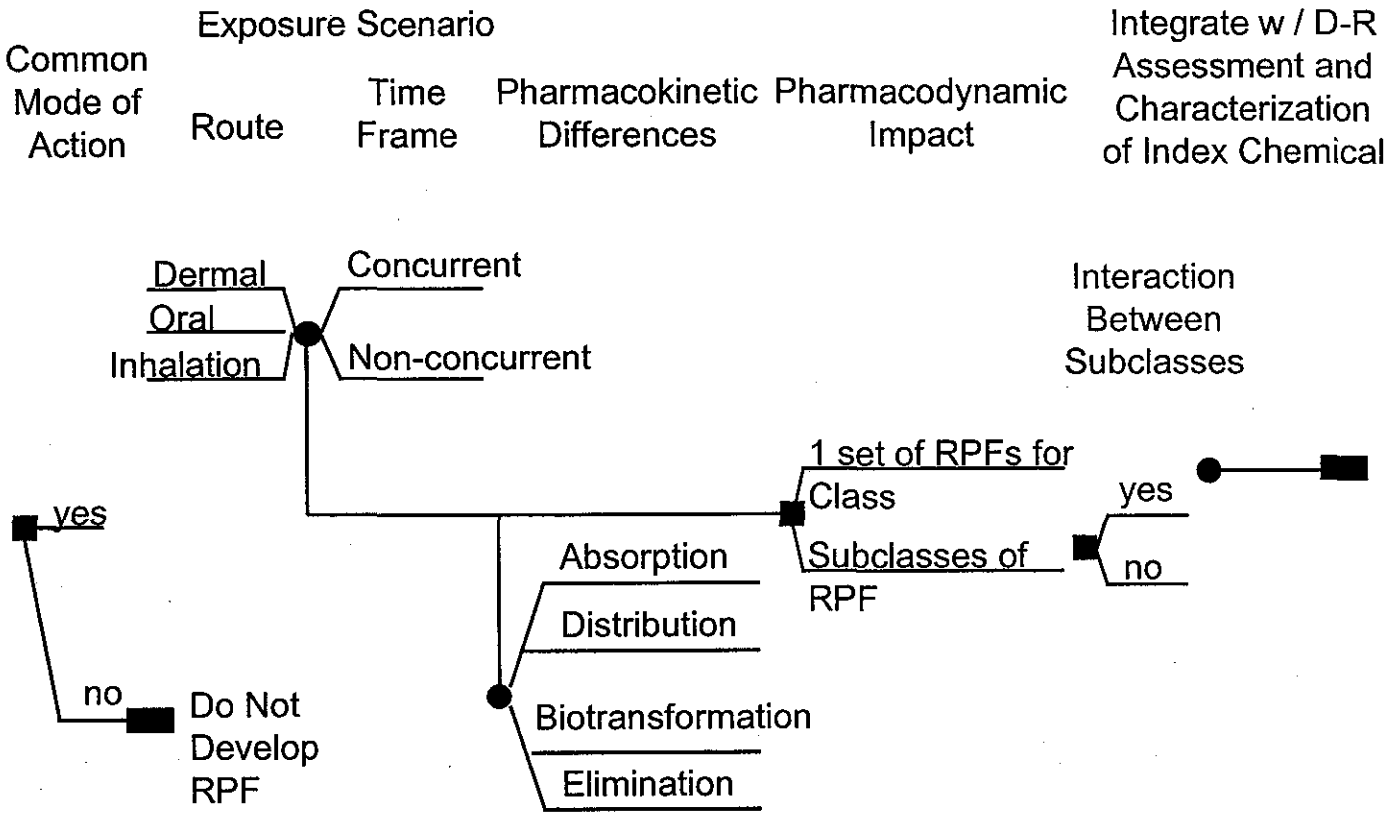


FIGURE 10

Schematic of CRPF Decision Process

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 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, 2000b). 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, 2000b). 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 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 ith chemical's ED_{01} provide an RPF_i for that chemical. The measured concentration, C_i, of the ith chemical is then

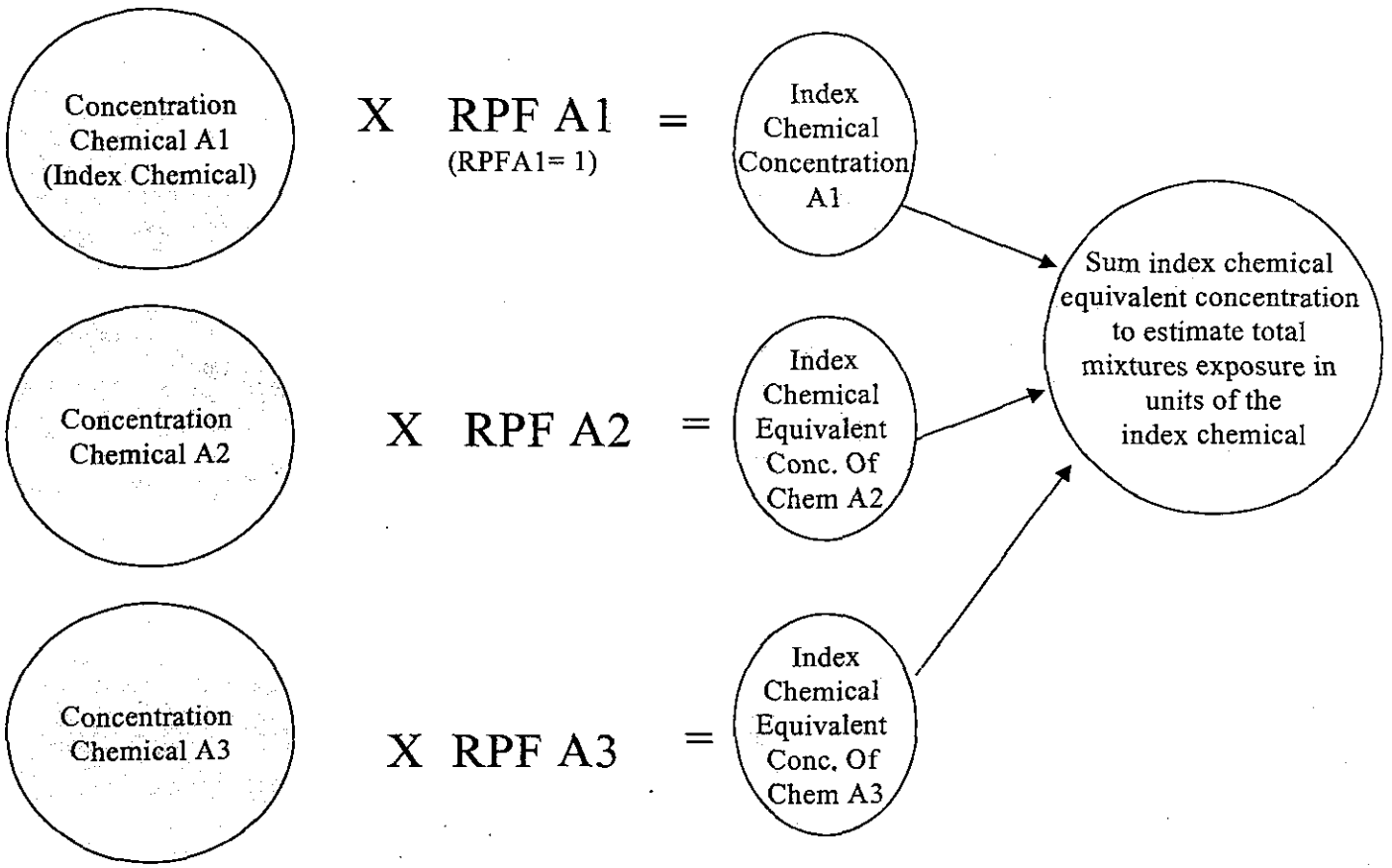


FIGURE 11

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

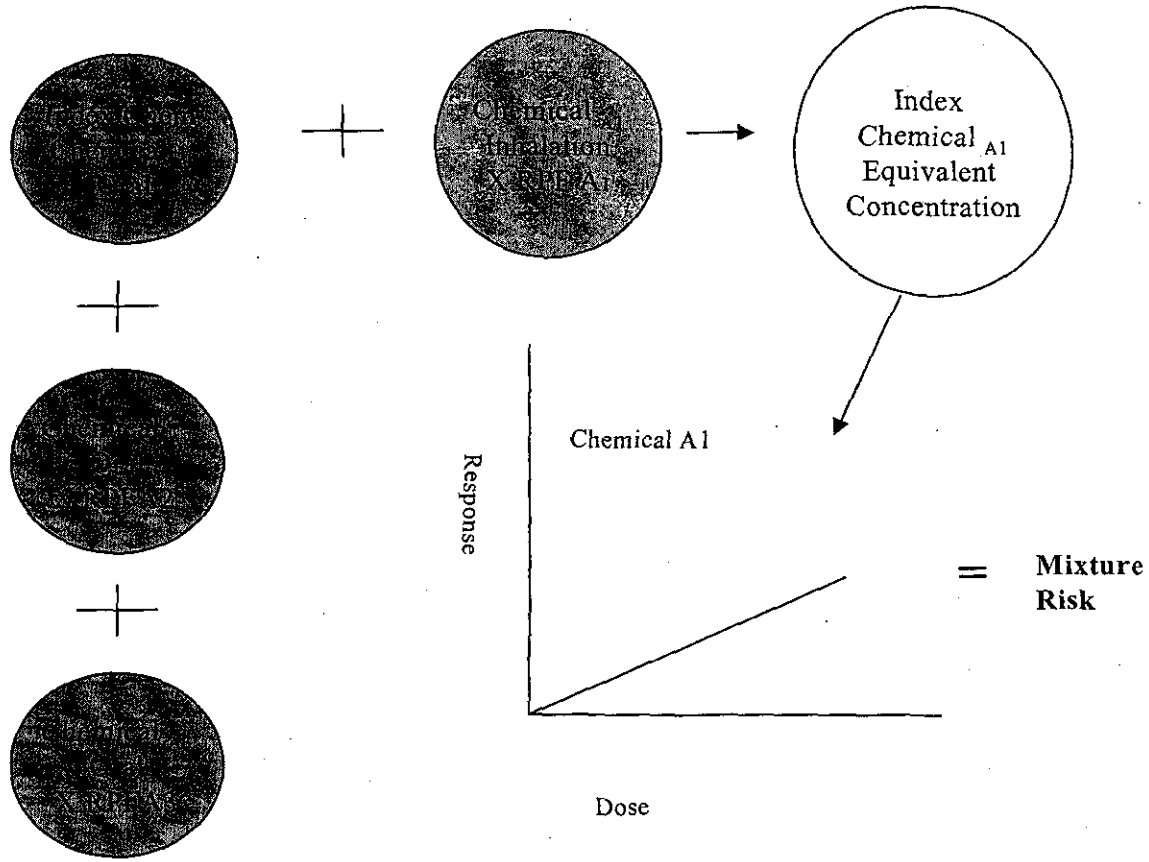


FIGURE 12

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 Cancer Risk [R_m] from Exposure to DBP_1 Equivalent Concentration (DBP_1 Unit Risk = 2.4 E-6 per µg/L)			62% 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.

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 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.

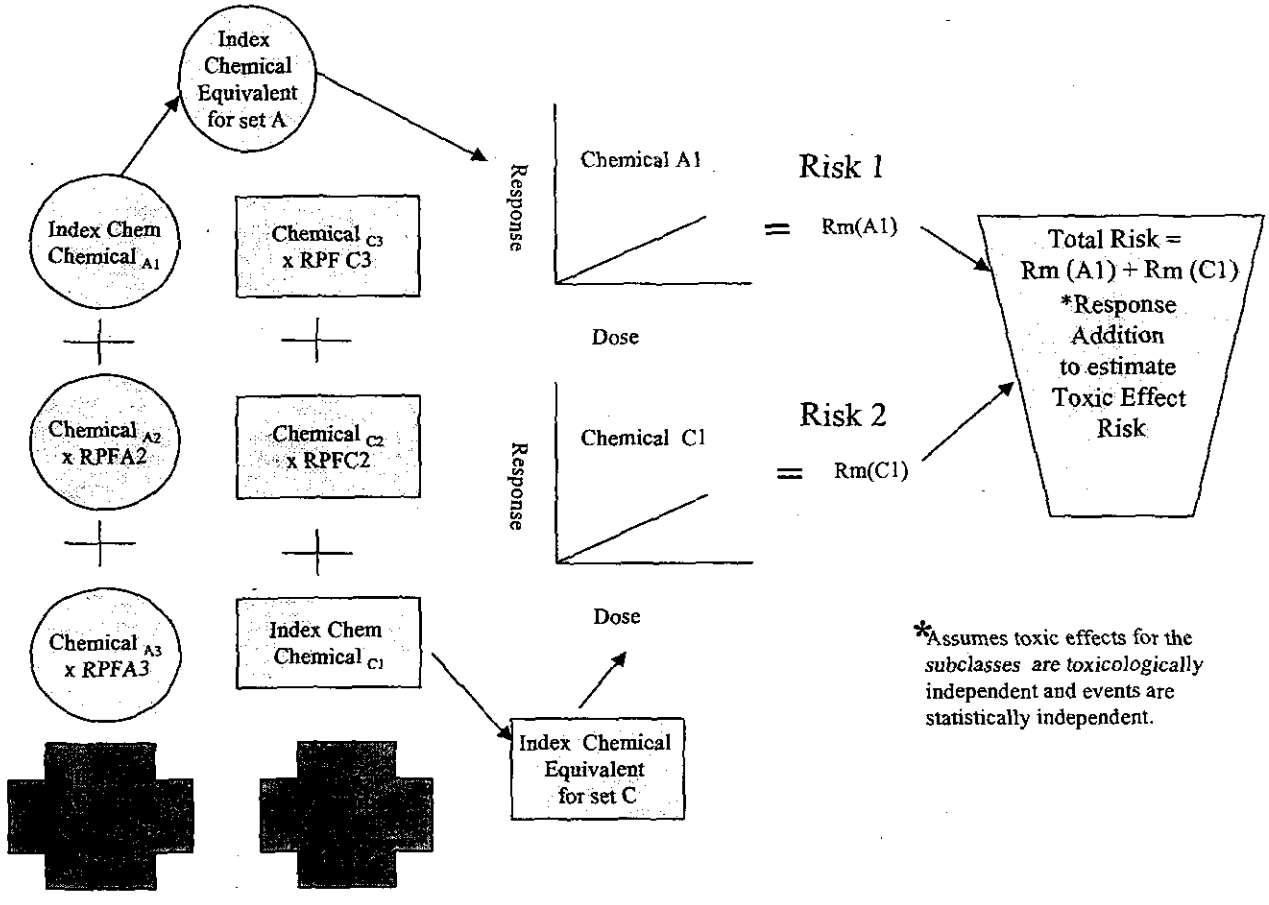


FIGURE 13

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

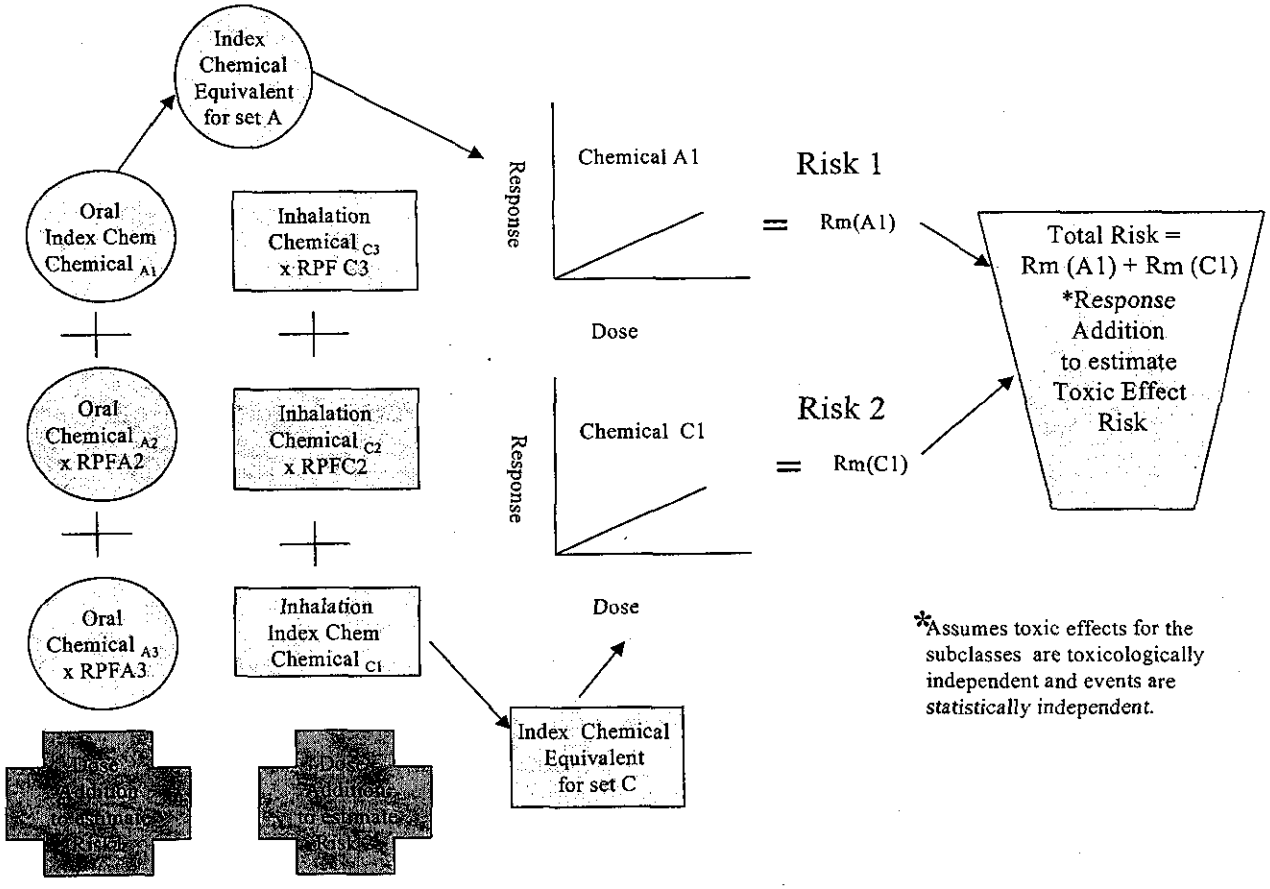


FIGURE 14

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

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 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-5 +

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 $(µg/L)^{-1}$	62%	9.5E-5	Oral	Liver Cancer
DBP_q	27.3 (µg/L) 1.8E-6 $(µg/L)^{-1}$	69%	4.9E-5	Oral	Kidney Cancer
DBP_r	1.7 $(µg/m^3)$ 1.3E-5 $(µg/m^3)^{-1}$	55%	2.2E-5	Inhalation	Kidney Cancer

4.9E-5 + 2.2E-5 = 1.7E-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.

4.2.3. Unidentified DBPs. The initial response addition assessment 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. 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 the Workshop Pre-meeting Report (U.S. EPA, 2000a), 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 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.

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