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# A FEASIBILITY STUDY OF CUMULATIVE RISK ASSESSMENT METHODS FOR DRINKING WATER DISINFECTION BY-PRODUCT MIXTURES

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*Humans are exposed daily to complex mixtures of chemicals, including drinking water disinfection by-products (DBPs) via oral, dermal, and inhalation routes. Some positive epidemiological and toxicological studies suggest reproductive and developmental effects and cancer are associated with consumption of chlorinated drinking water. Thus, the U.S. Environmental Protection Agency (EPA) conducted research to examine the feasibility of evaluating simultaneous exposures to multiple DBPs via all three exposure routes. A cumulative risk assessment approach was developed for DBP mixtures by combining exposure modeling and physiologically based pharmacokinetic modeling results with a new mixtures risk assessment method, the cumulative relative potency factors (CRPF) approach. Internal doses were estimated for an adult female and an adult male, each of reproductive age, and for a child (age 6 yr) inclusive of oral, dermal, and inhalation exposures. Estimates of the daily internal doses were made for 13 major DBPs, accounting for activity patterns that affect the amount of human contact time with drinking water (e.g., tap water consumed, time spent showering), building characteristics (e.g., household air volumes), and physicochemical properties of the DBPs (e.g., inhalation rates, skin permeability rates, blood:air partition coefficients). A novel cumulative risk assessment method, the CRPF approach, is advanced that integrates the principles of dose addition and response addition to produce multiple-route, chemical mixture risk estimates using total absorbed doses. Research needs to improve this approach are presented.*

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 the mix of DBPs may vary considerably with geographic location and water treatment process. Furthermore, for the more volatile

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DBPs, inhalation exposures may be high; for 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 (summarized in U.S. EPA, 2000a), often via gavage in a vehicle that may alter the pharmacokinetic (PK) profile of absorption and tissue distribution. 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 public drinking water. The first issue is to evaluate the association between DBP mixture exposures and human health outcomes and thereby evaluate the potential for human health risks. As new drinking-water regulations are promulgated and others posed with the goal of controlling levels of DBPs in the drinking water (e.g., U.S. EPA, 1979, 1994, 1998), 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 is to examine the potential toxicity of unidentified total organic halide material, comprising approximately 50% of the DBP mass (Weinberg, 1999). By comparing whole-mixture toxicity data with qualitative and quantitative data on DBP mixture components, the contribution of the unknown fraction to the toxicity of the complex DBP mixture can be evaluated assuming additivity.

The U.S. Environmental Protection Agency (EPA) National Center for Environmental Assessment has conducted research on how to assess DBP health risks and has concluded it is appropriate to evaluate DBP mixtures using a cumulative risk assessment (CRA) approach, defined as multiple chemical exposures via multiple exposure routes over time (U.S. EPA, 2000a). This evaluation of human health risks as a CRA problem requires consideration of the following factors:

- Exposure to multiple chemicals.
- Knowledge of toxic mode of action (MOA) and judgment regarding similarity of MOA among DBPs.
- Extrapolation of animal bioassay results from typically high to low doses.
- Dermal, oral, and inhalation routes of exposure.
- Measures of internal 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.
- Sensitive subpopulations.

Incorporating many of these factors, new research has been conducted to develop human exposure estimates for individual DBPs from multiple exposure

routes; whole-body (e.g., blood concentrations) and organ-specific internal doses are estimated based on exposures to all three routes for each selected DBP. This article describes a feasibility study of how these data can be developed and then used to assess DBP risks using a newly developed risk assessment method, the cumulative relative potency factors (CRPF) approach.

Two different mathematical models are employed to evaluate human exposures for use as an input for risk assessment. An *exposure assessment model* employs human activity and water use patterns and information on DBP concentrations in water to generate estimates of exposures at the body boundaries through human contact with the media. A *physiologically based pharmacokinetic (PBPK) model* incorporates information on organ volumes, organ-specific blood flows, and metabolic capacity with an assumption of no pharmacokinetic interactions among mixture components to predict doses of DBPs experienced by relevant organs or target tissues. Four different measures of dose are presented with respect to possible application of the CRPF approach (Figure 1):

1. *Route-specific exposures*. The amount of a chemical available prior to going through the exchange boundaries (e.g., skin, lungs, intestinal tract).
2. *Route-specific absorbed doses*. The amount of a contaminant that is absorbed from a single exposure route through the portal of entry for that route.

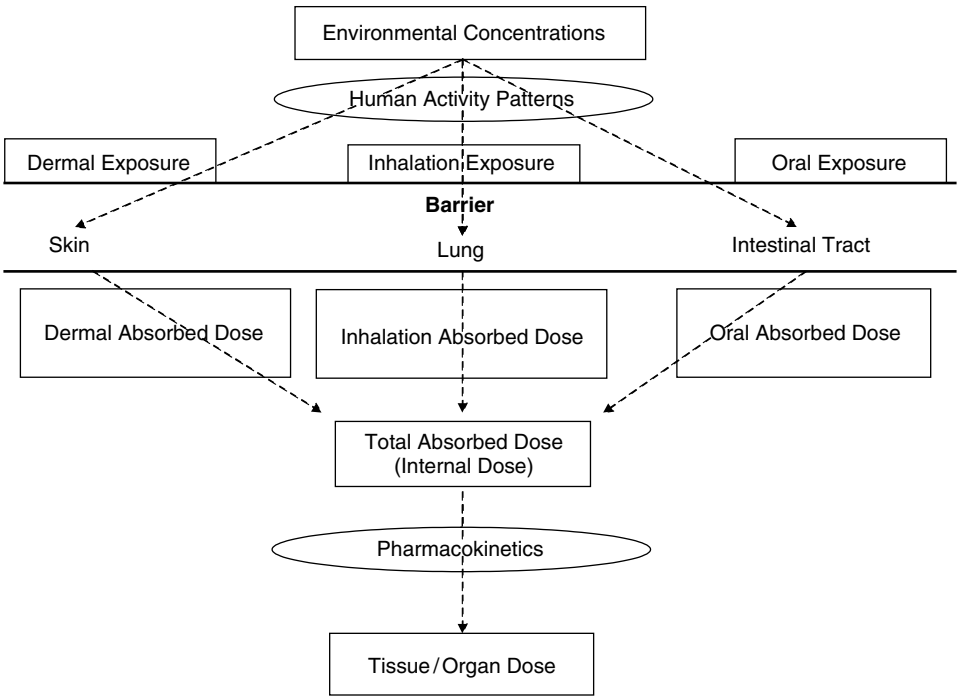


**FIGURE 1.** Dose metrics for environmental contaminants.

3. *Total absorbed doses*. The amount of a contaminant that is absorbed from all exposure routes without regard to specific absorption processes (e.g., blood concentrations).
4. *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 toxicity data. For risk assessment purposes, the choice of dose and dose expression depends on several factors. When the available toxicity information warrant, a decision can be made to identify either parent chemical or metabolite(s) as the toxicologically active moiety. Information from additional studies may also inform the choice between peak concentration and average concentration as most related to toxicity.

Exposure estimates must be combined with dose-response information to develop a DBP mixtures risk characterization. Toxicity data for animals exposed orally is available for most of the major DBPs identified in the drinking water for cancer, developmental and reproductive effects, and a number of systemic effects. Because dermal and inhalation dose-response animal data are relatively sparse, the CRPF approach, based primarily on the use of oral dose-response information, is suggested as a plausible research direction.

This article examines the feasibility of conducting a CRA for drinking-water DBP mixtures by combining exposure and PBPK modeling results with the CRPF risk assessment approach. Discussions include presentation of the CRPF approach; examples of exposure and PBPK modeling results that provide multiple route human internal dose 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 CRA for DBP mixtures. A complete description of this research and its results can be found in U.S. EPA report, *The Feasibility of Performing Cumulative Risk Assessments for Mixtures of Disinfection By-Products in Drinking Water* (U.S. EPA, 2002a).

## THEORY OF THE CRPF APPROACH

Humans are exposed to chemical mixtures daily, and the components of these mixtures may produce the same toxic effect by similar or dissimilar modes of action (MOA).* For a common effect, (1) the risk from exposure to multiple chemicals acting via a common MOA may be assessed using the

*The terms *mechanism of toxicity* (or *mechanism of toxic action*) and *mode of action* represent a continuum of understanding regarding a toxicodynamic process (U.S. EPA, 2002a). A toxicologic outcome is considered to be damaging to the organism at any level of biological organization (i.e., molecular, cellular, tissue, etc.). 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. Knowledge of a chemical's *mode of action* implies a general understanding of key toxicodynamic events, but not a detailed description of these events. Mode of action is defined as the set of key biological events leading to a toxicologic outcome.

summed doses of the individual chemicals scaled for relative potency (dose addition), or (2) the risk from multiple chemicals acting via independent MOA may be assessed by summing the probabilistic risks of response from exposure to the individual chemicals (response addition) (U.S. EPA, 2000a). Thus, approaches for assessing the toxicity(ies) of chemical mixtures must be flexible enough to address these complexities.

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, 2002a). (Using two subclasses, Sets A and C, Figure 2 illustrates how the CRPF approach estimates risk from exposure to the mixture.) The CRPF approach uses information on MOA to assign chemicals to common MOA subclasses. These subclasses differ with respect to MOA, but the toxicological endpoint (or outcome) is the same. For each subclass, an index chemical (a mixture component with high-quality dose-response data that acts [or is judged to act] through the same MOA as the other members of the subclass for the effect and route of concern) is selected, 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 and 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.

The RPF approach has been proposed for characterizing health risks associated with mixtures of chemicals 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 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. The component ICEDs are then summed within the subclass to generate a subclass ICED. The risk posed by the subclass can be estimated using the dose-response information for the index chemical. For each subclass, the RPF approach uses dose addition to estimate risk for the toxicologic outcome common across the subclasses. However, because each subclass differs in MOA, their risks are independent of each other (i.e., the toxicity caused by one subclass does not influence the toxicity caused by the other subclass). This condition

*The ICED has the same mathematical interpretation as the dioxin toxicity equivalents (TEQ). TEQ refers to the quantification of dioxin concentrations based on the congeners' equivalent 2,3,7,8-TCDD toxicity (U.S. EPA, 1989). ICED is applied to mixtures other than dioxins.

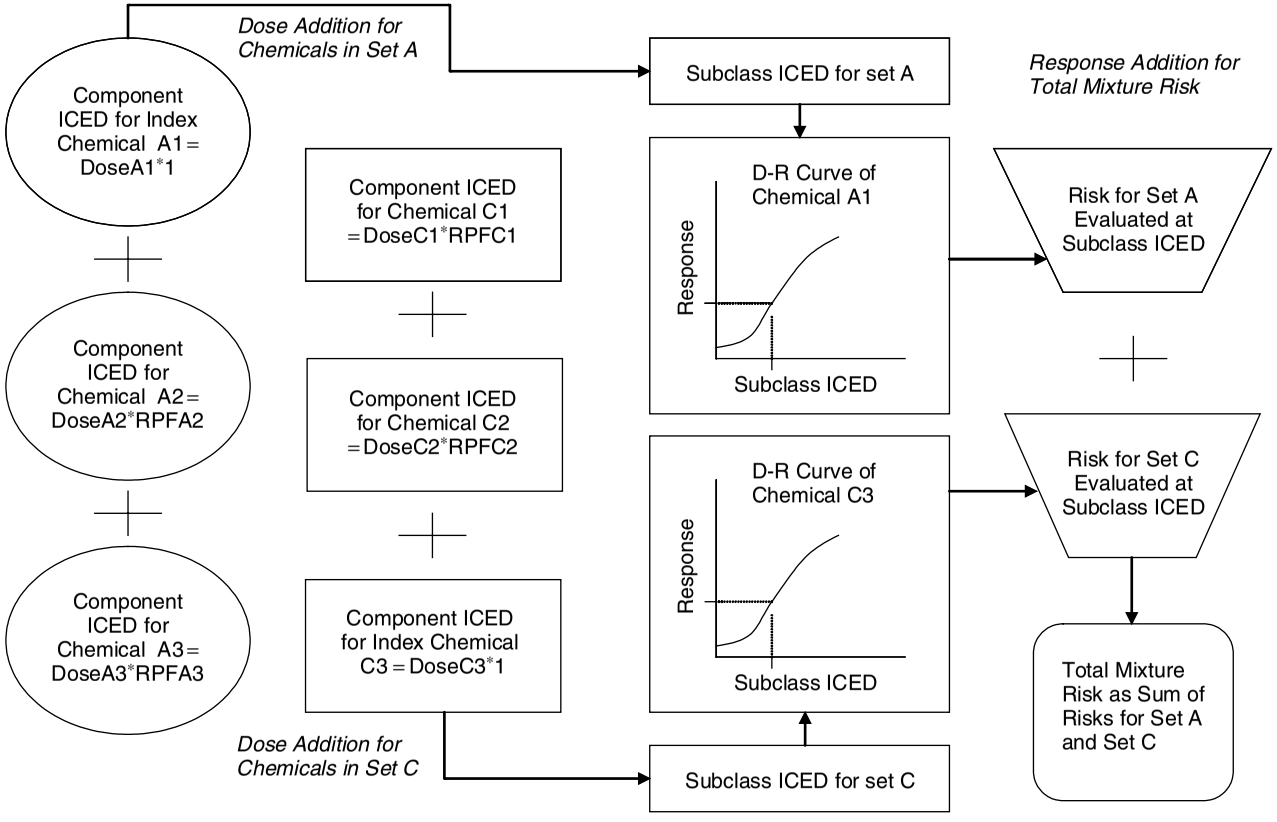


**FIGURE 2.** CRPF approach: integration of dose addition and response addition to estimate mixture risk.

meets 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 1. Their co-occurrence in finished drinking water has been evaluated previously (Krasner et al., 1989; Richardson, 1998; U.S. EPA, 2000c), and the analysis here is based on such information. Given the scope of the present feasibility study, the interdependence of DBP concentrations was not evaluated. In the final modeling exercise, data were insufficient to estimate chemical properties for bromochloroacetonitrile 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 yr) and children (age 6 yr). The water concentrations chosen for use in this study, presented in Table 1, were selected based on data presented in the "Stage 2 Occurrence and Exposure Assessment for Disinfectants and Disinfection Byproducts (D/DBPs)" (Cadmus Group, Inc., 2001). For each chemical, the value was selected based on the 90th percentile concentration for surface water supply systems.

Models selected for this effort were the total exposure model (TEM) (Wilkes, 1998) and the exposure related dose estimating model (ERDEM) (U.S. EPA, 2002b). Combining these two models into one analysis provided the ability

**TABLE 1.** List of Chemicals for Exposure and Internal Dose Assessment

| DBP subclass | Chemical name | CAS number | Water concentration (mg/L) |
|---|---|---|---|
| Trihalomethanes (THMs) | Chloroform ($CHCl_3$) | 67-66-3 | 0.070 |
| | Bromodichloromethane (BDCM) | 75-27-4 | 0.023 |
| | Dibromochloromethane (DBCM) | 124-48-1 | 0.015 |
| | Bromoform ($CHBr_3$) | 75-25-2 | 0.0077 |
| Haloacetic acids (HAAs) | Chloroacetic acid (CAA) | 79-11-8 | 0.0051 |
| | Dichloroacetic acid (DCA) | 79-43-6 | 0.032 |
| | Trichloroacetic acid (TCA) | 76-03-9 | 0.034 |
| | Bromoacetic acid (MBA) | 79-08-3 | 0.01 |
| | Dibromoacetic acid (DBA) | 631-64-1 | 0.0043 |
| | Bromochloroacetic acid (BCA) | 5589-96-8 | 0.0091 |
| Haloacetonitriles (HANs) | Dichloroacetonitrile (DCAN) | 3018-12-0 | 0.0020 |
| | Trichloroacetonitrile (TCAN) | 545-06-2 | 0.00014 |
| | Bromochloroacetonitrile (BCAN) | 83463-62-1 | 0.0011 |
| | Dibromoacetonitrile (DBAN) | 3252-43-5 | 0.00081 |
| Miscellaneous | Bromate | 15541-45-4 | 0.0074 |

to estimate organ and target tissue doses (estimated using ERDEM) as a function of external measures (estimated using TEM), such as human behaviors, environmental factors, and other exposure-related parameters. Figures 3, 4, and 5 illustrate the flow of information in and out of the two models. Of particular note is that TEM is used to develop 24-h 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.

Exposure to contaminants 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. The exposure model, TEM, assembles 24-h activity and water-use patterns based on sampling activity pattern databases and a variety of defined representative distributions. TEM then models the 24-h period, estimating emissions, air and water concentrations, exposure, and uptake resulting from the sampled water-use and location activities. This process was repeated to estimate the distribution of exposures and doses for each population group.

For this study, TEM was initialized to represent a three-person family occupying a typical household based on an analysis of U.S. housing stock having DBP concentrations in the water supply as specified in Table 1. Each of the three occupant's water-use activities, locations, and other relevant behavioral characteristics have been developed based on the data presented in the National Human Activity Patterns Survey (NHAPS; Tsang & Klepeis, 1996), the Residential End Use Water Survey (REUWS; Mayer et al., 1998), the Residential Energy Consumption Survey (RECS; U.S. Department of Energy, 1997), appliance manufacturer data, and supplemented, as necessary, by best judgment. The volume of consumed water was sampled from lognormal distributions for each occupant, developed consistent with their respective population groups (i.e., adult male, adult female and 6-yr-old child) based on an analysis of the 1994–1996 Continuing Survey of Food Intake by Individuals (CSFII; Jacobs et al., 2000). The geometric means for direct consumption (plain water used in or as a beverage) used in this study were 389.5 ml/d, 394.3 ml/d, and 189 ml/d for the adult male, adult female, and child, respectively. The geometric means for indirect consumption (water used in food preparation) used in this study were 419 ml/d, 384.8 ml/d, and 97.4 ml/d for the adult male, adult female, and child, respectively. The values for other model input parameters were developed or estimated based on available data to be representative of the behavior or characteristics of the population group being modeled. For a complete description of model parameters, refer to U.S. EPA (2002c). TEM results include distributions of absorbed dose estimates for the dermal, ingestion and inhalation exposure routes and total absorbed dose. Absorbed doses for a 24-h period as a function of route, population group, and percentile of the population

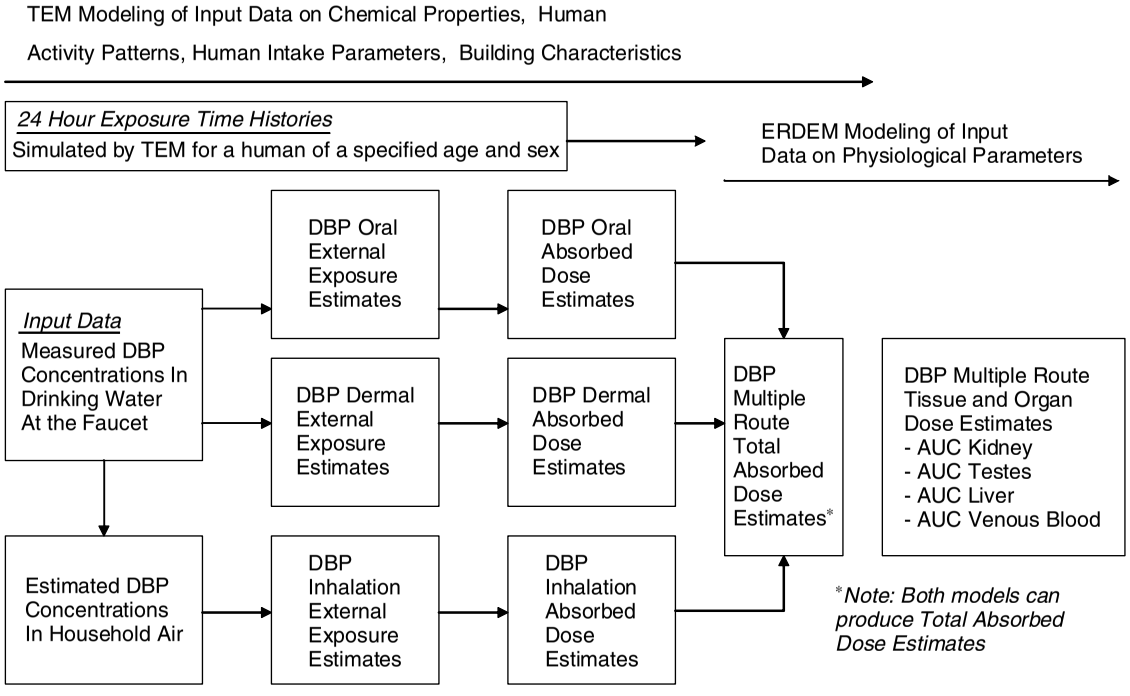


**FIGURE 3.** Linking TEM exposure assessment modeling with ERDEM PBPK modeling.

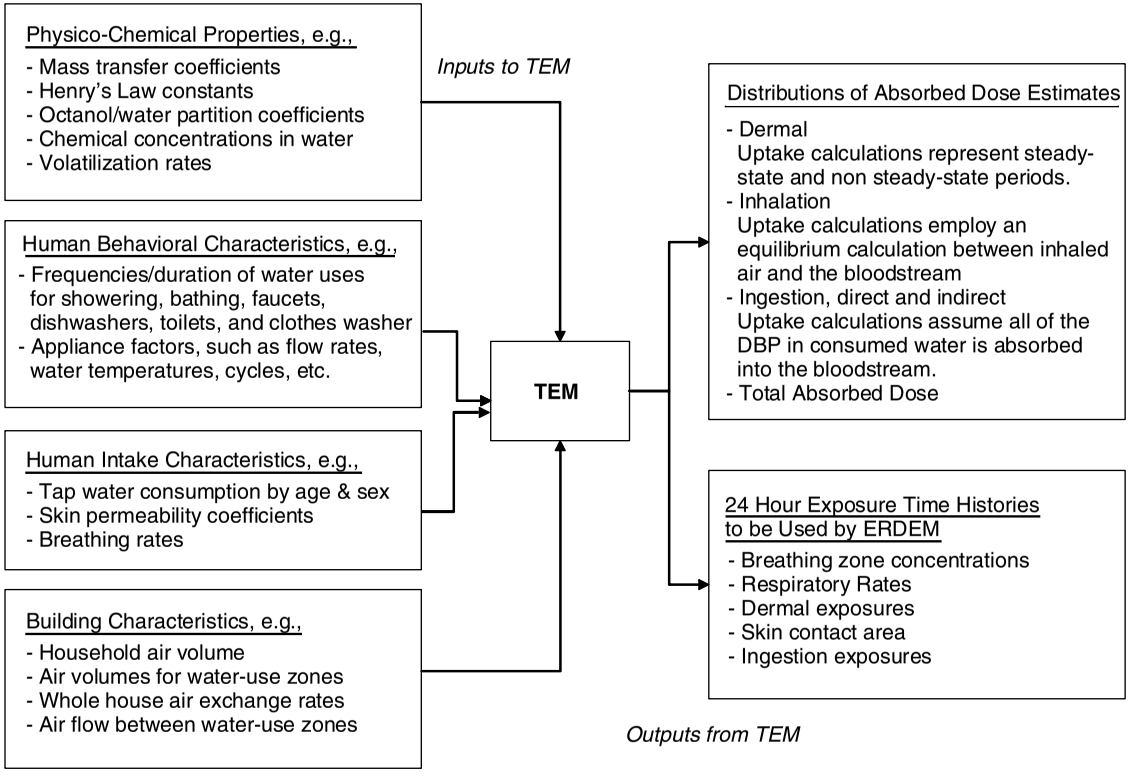


**FIGURE 4.** TEM modeling of indoor air concentrations, exposure, and absorbed dose estimates.

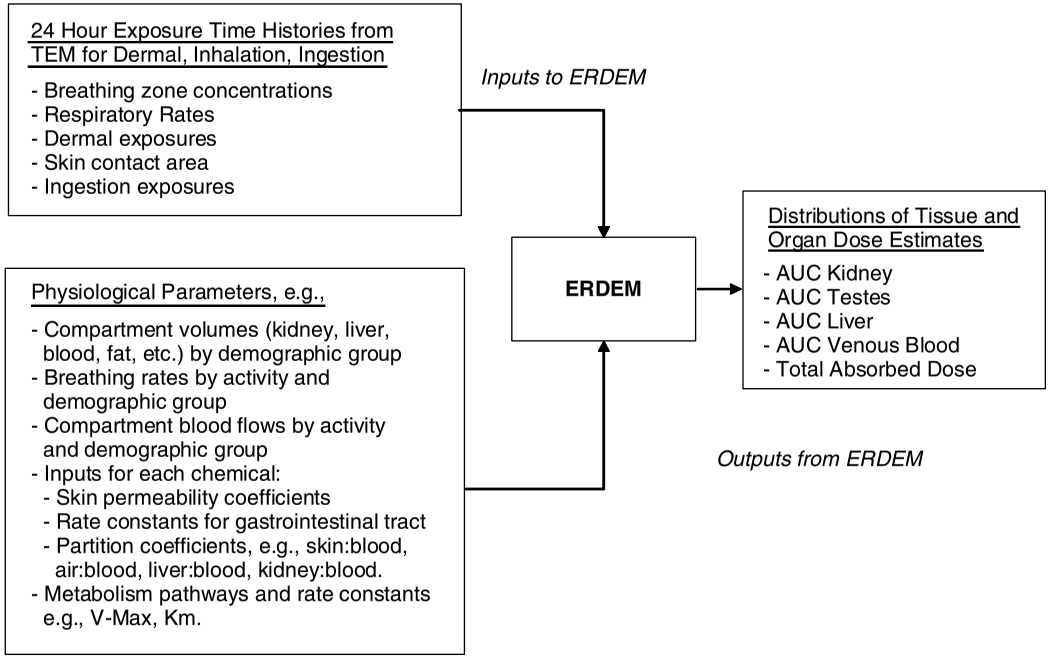


**FIGURE 5.** ERDEM modeling of tissue- and organ-level absorbed dose estimates.

were produced for each of the 13 DBPs. Table 2 shows an example of the distribution of absorbed dose estimates for BDCM. Table 3 shows the 50th percentile absorbed dose estimates for all 13 DBPs.

The results of the uptake modeling provide information for comparing and contrasting uptake as a function of the chemical, the population group

**TABLE 2.** TEM Output for BDCM: Absorbed Dose Estimates (mg) for a 24-h Exposure

| | | | Ingestion | | | |
|---|---|---|---|---|---|---|
| Percentile | Total[a] | Dermal | Direct | Indirect | Total[a] | Inhalation |
| Female, age 15–45 yr | | | | | | |
| 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 yr | | | | | | |
| 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 |
| Child, age 6 yr | | | | | | |
| 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.** 50th Percentile 24-h Absorbed Dose Estimates (mg) Output by TEM

| | | | Ingestion | | | |
|---|---|---|---|---|---|---|
| Chemical | Total[a] | Dermal | Direct | Indirect | Total[a] | Inhalation |
| Female, age 15–45 yr | | | | | | |
| $CHCl_3$ | 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 yr | | | | | | |
| $CHCl_3$ | 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 |
| 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 yr | | | | | | |
| $CHCl_3$ | 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.

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 skin permeability rates are generally poorly quantified. 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.

Exposure patterns simulated by TEM were used as input values upon which ERDEM based the exposure scenarios for simulating tissue doses. The estimation of tissue doses was accomplished by programming and operating a previously validated, single-chemical, PBPK model for bromodichloromethane (BDCM), $CHCl_3$, dichloroacetic acid (DCA), and trichloroacetic acid (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 48 h.* Table 4 shows the ERDEM results for BDCM for 3 different age-dependent models: the adult male, the adult female, and the 6-yr-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 are useful tools in extrapolating tissue dosimetry across different exposure routes.

The available information on toxicity and the results of exposure modeling for the 13 DBPs examined have been successfully combined. The following steps are identified to be followed when conducting a CRPF-based assessment.

### Group Chemicals 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

*Note that the TEM and ERDEM modeling results were done for different time periods, 24 and 48 h, respectively. Given this was a feasibility study, these efforts were conducted independently; the time periods were therefore not coordinated to be the same.

**TABLE 4.** 48-h PBPK Modeled Absorbed Doses for BDCM for the Adult Male, Adult Female and Male Child

| Demographic group endpoint | Average | Standard deviation | Skewness | Maximum | Minimum | 5th | 10th | 50th | 90th | 95th |
|---|---|---|---|---|---|---|---|---|---|---|
| Adult male | | | | | | | | | | |
| AUC kidney (mg/L·h) | 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·h) | 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·h) | 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·h) | 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·h) | 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·h) | 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 |
| Child male | | | | | | | | | | |
| AUC Kidney (mg/L·h) | 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·h) | 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·h) | 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 |

*Note*. AUC, area under the curve.

(i.e., route specific exposures, total absorbed doses, organ/tissue doses); identify component subclasses, 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).

### Develop Human Internal Dose Dose-Response Models for Each Chemical (Figure 6)

For each chemical, make two adjustments to the animal toxicology data: (1) Adjust 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. Using these data and assuming the animal and human responses are the same, develop human internal dose dose-response curves for each chemical; reevaluate subclass groupings based on similarly shaped dose-response curves (at least look for similarity within the exposure region of interest).

### Develop RPF Estimates for Each Subclass

For each subclass, evaluate the strength and completeness of the components' toxicity data to identify an index chemical; using the human internal dose dose-response curves, estimate component RPFs; multiply each component dose by its RPF to obtain the component ICED; sum the component ICEDs to generate subclass ICEDs.

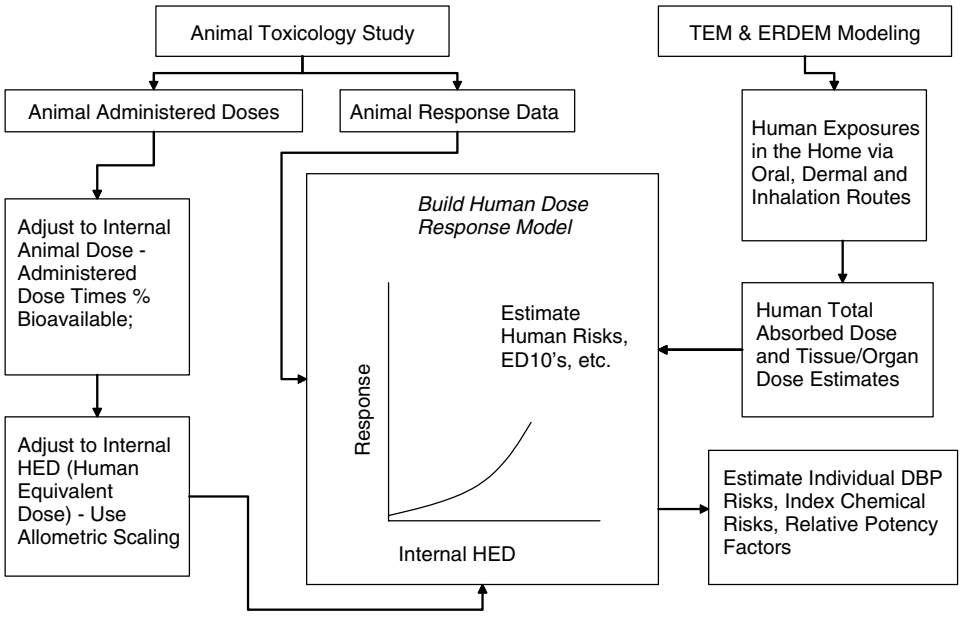


**FIGURE 6.** Dose-response development, human risk estimates, and RPF calculations for each single DBP.

### Develop the Risk Characterization for the Whole Mixture Using the CRPF Approach

Use the dose-response curve for each index chemical to estimate risk for its subclass; sum the subclass risks under response addition to estimate the total mixture risk; develop a full risk characterization for the analysis, including an analysis of uncertainty.

## CRPF ILLUSTRATION FOR DBPS

The CRPF approach is illustrated here, addressing the cancer endpoint only, utilizing two DBP subclasses, simplified for illustration of the method. Carcinogens are divided into those thought to be genotoxic or non-genotoxic. The basic schematic for this illustration is shown in Figure 7 the calculations for the illustration are shown in Table 5.

For each subclass, an index chemical is chosen. (Figure 7 indicates that BDCM and DCA were selected as the index chemicals for the genotoxic subclass and nongenotoxic subclasses, respectively. In an actual analysis, additional details regarding the MOA would be needed to evaluate if the subclasses and the selected index chemicals are appropriate.) 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 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 relationship for the index chemical is used to estimate the subclass risk at the subclass ICED.

Table 5 provides an illustration of the central tendency estimates of cancer risk calculations for a 70-kg adult male by combining dose-response information with the TEM total absorbed dose estimates shown in Table 3. The 50th percentile doses (mg/d) from Table 3 are converted to mg/kg/d doses (dividing by 70 kg) and then multiplied by the RPF for each DBP to obtain component ICEDs. The sum of the component ICEDs forms each subclass ICED. The product of the subclass ICEDs and the maximum likelihood estimate (MLE) of the slope factor for the subclass index chemical provides an central tendency estimate of cancer risk for that subclass (see footnote *a* of Table 5). The subclass risks are then added to obtain the final total central tendency estimate of 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 (or other chemical mixtures) for which fewer toxicity data exist. For example, other genotoxic carcinogens exhibiting similar MOA to BDCM may

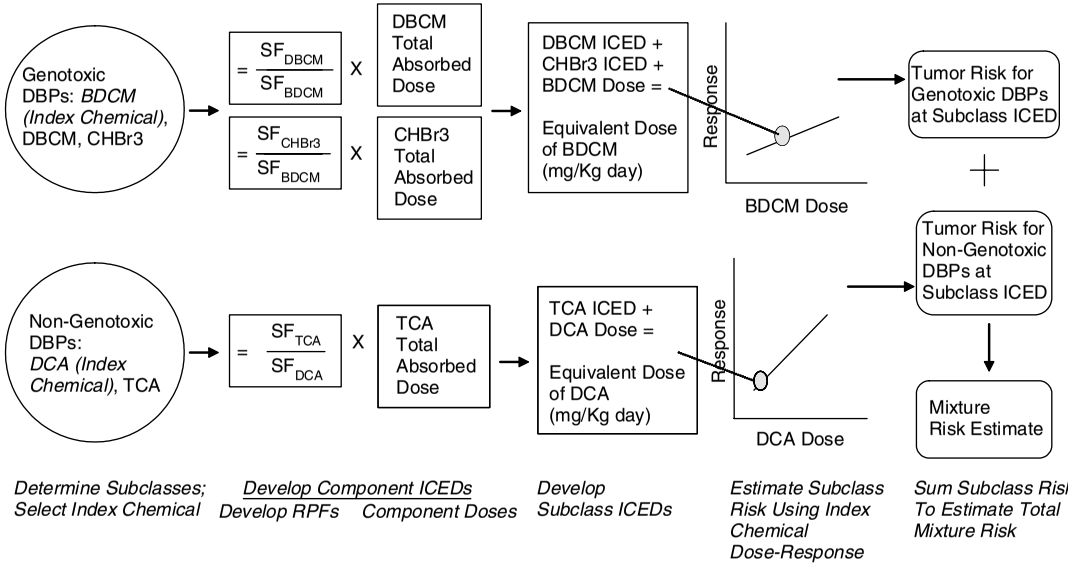


**FIGURE 7.** Schematic of CRPF approach for illustration of DBP mixture cancer risk.

**TABLE 5.** Illustration of CRPF Approach for Central Tendency Cancer Risk Estimates (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/d) | Subclass ICED (mg/kg/d) | Subclass risk, MLE slope factor times subclass ICED |
|---|---|---|---|---|---|---|---|
| | | | 50% (mg/d) | 50% (mg/kg/d) | | | |
| 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 | | |
| Nongenotoxic 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 U.S. EPA peer-reviewed, endorsed values. This illustration assumes exposures below the $CHCl_3$ reference dose (RfD) of 0.01 mg/kg/d 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]Nongenotoxic subclass index chemical, MLE SF = 1.4E–3.

be present in drinking water. 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 1990s (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 dose–vehicle effects, nonlinear 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 to reduce uncertainty in the dermal estimates. 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, such as Henry's law constant, $K_{ow}$, boiling point, vapor pressure, and liquid and gas-phase diffusivities. This is an 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, including those that vary with age. 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 to the liver and kidney, volume of the liver, metabolic capacity of the liver, volume of 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), and toxicokinetic and toxicodynamic differences among individuals.
9. Approximately 50% of DBPs in the finished drinking water consists of unidentified material. The U.S. 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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