Case Study Summary: Risk Assessment of Exposure to Trihalomethane Drinking Water Disinfection By-Products. Use of Biomonitoring Equivalents and Biomonitoring Data from NHANES

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1. **Method:** This case study explores the application of the Biomonitoring Equivalents (BE) paradigm and population-representative biomonitoring data for trihalomethanes (THMs) in blood from the National Health and Nutrition Examination Survey (NHANES) to risk assessment of non-cancer endpoints for THMs. Alternative approaches for low-exposure extrapolation of risk of non-cancer hepatic outcomes from THM exposure in the general US population based on the NHANES biomonitoring data and the BE approach are explored. Because THMs are rapidly absorbed and eliminated, issues in interpretation of biomonitoring data associated with the transience of the biomarker are discussed.

   Briefly, BE values for the THM compounds were derived using an internal dose-based risk assessment approach; the derivation is described in detail in Aylward et al. (2008). The current USEPA RfD derivations were reviewed and summarized. Fatty liver degeneration (or a related effect, hepatic vacuolization for tribromomethane) was the critical endpoint for all four compounds. Based on this information, hepatic area under the curve (AUC) of the parent compound was selected as a relevant dose metric for each compound.

   Previously-published PBPK models were used to estimate the hepatic AUC at the $BMDL_{10}$ for each THM (calculated by USEPA) in the relevant species. The hepatic AUC in the rodent or dog was extrapolated to a corresponding human-equivalent POD hepatic AUC by application of the interspecies uncertainty factor component for toxicodynamic extrapolation as used in the EPA RfD derivation ($10^{0.5}$). The toxicokinetic component of the interspecies UF was replaced by the use of a relevant internal dose metric. The human version of the PBPK model for each compound was used to estimate the steady-state average blood concentration consistent with the identified human-equivalent POD hepatic AUC. This quantity is termed the BE_{POD}. This estimate was dependent upon what route of exposure was assumed in the PBPK modeling. Assumption of 100% oral exposure produced the most conservative estimates of average blood concentration consistent with the target human-equivalent POD hepatic AUC for each compound; assumption of 100% inhalation exposure would have resulted in BE_{POD} values approximately 6-fold higher, with assumption of mixed exposure routes resulting in intermediate values. Finally, BE_{RfD} values were estimated via application of

the toxicodynamic portion of the intraspecies UF and any database UFs applied in the RfD derivation.

Biomonitoring data from NHANES was then compared to the BE_{RfD} through calculation of hazard quotients and hazard indices to aid in interpreting the biomonitoring data in the context of the risk assessments on both a chemical-specific and a cumulative basis across THMs.

The critical effect in the risk assessments for all four THM compounds was increased incidence of fatty liver. Non-alcoholic fatty liver disease (NAFLD) is prevalent in adults in the US, occurring in approximately 10% of the population. Two alternative approaches to extrapolation of risk of fatty liver in relationship to THM blood levels below the BE_{POD} in humans were explored. In the first approach, the BE_{RfD} was taken to represent a threshold below which the risk of NAFLD was zero and risks were estimated as a linear function of measured blood concentration from 10% risk at the BE_{POD} to zero at the BE_{RfD}. In the second approach, the risk was assumed to decline linearly from 10% at the BE_{POD} to zero at zero dose. Estimated increased risk of fatty liver was estimated in the general population based on THM blood levels under both approaches and compared to empirically observed prevalence of NAFLD. The impact of mode of action considerations on selection of low-dose extrapolation approach, uncertainties associated with the risk assessment, BE derivation, and transience of biomarkers, and issues associated with the quantification of fatty liver in the bioassays as quantal rather than continuous endpoints are discussed.

2. **Problem Formulation:** How can the current USEPA THM non-cancer risk assessments be used to interpret human biomonitoring data for trihalomethanes (THMs)? How do alternative approaches to low-exposure extrapolation compare to the conventional Hazard Quotient approach for assessing non-cancer risks based on internal dose-response assessment in conjunction with the biomonitoring data? Assessment of these approaches and issues would be useful in the assessment and comparison of costs/risks and benefits of drinking water disinfection measures and assessment of regulatory options to reduce THM disinfectant byproducts (DBPs).

3. **Generalizability of the Method:** The method is generalizable for chemicals with appropriate pharmacokinetic data. BEs are translations of exposure guidance values from external dose units to biomarker concentrations, and BE values have been published for more than 80 chemicals. The method allows evaluation of biomonitoring data in the context of existing or new risk assessments. Low dose extrapolation can be conducted based on a variety of approaches and allows the evaluation of the distribution of biomonitored chemical concentrations in a risk assessment context.

4. **Overall strengths and weaknesses:** The overall strengths of the method include ability to incorporate valuable biomonitoring data into the risk assessment paradigm, reducing the need to rely upon estimated external doses. The BE method provides a translational tool that allow these real-world exposure data to be evaluated in the context of the existing risk assessments. The biomonitoring data directly reflect distributions of exposure levels as well intraspecies differences in pharmacokinetics, and the data allow assessment of real-world cumulative exposures across compounds of interest. The method limitations include the need for pharmacokinetic data or models of various types, which are not available for all chemicals. Biomonitoring data and the BE method have limitations when applied to biologically transient compounds due to issues associated with the limited representativeness of spot biomarker concentrations for long-term average exposures. Another limitation of the method to date is that it is applied to existing risk assessments, which may not provide appropriate data for low dose risk evaluation and distributional risk analyses.

5. **Minimum data requirements:** Some data on compound distribution or pharmacokinetics in the relevant laboratory species or humans are required in order to translate exposure guidance values into corresponding biomarker concentrations (see Hays et al. 2008).

Does this case study:

A. **Describe the dose-response relationship in the dose range relevant to human exposure?**

The biomonitoring data suggest that human exposures are not reaching blood concentrations consistent with the $BMDL_{10}$ values used in the derivation of reference doses for the THM values. We explore alternative methods for extrapolation below the $BMDL_{10}$; however, the toxicological data sets do not provide non-quantal data that would be more appropriate for such extrapolations.

B. **Address human variability and sensitive populations?**

Human exposure and toxicokinetic variability is explicitly addressed by use of the biomonitoring data. While sensitive populations exist for the endpoint of interest (non-alcoholic fatty liver disease), the toxicological data are not presented in a way that allows extrapolation to these populations.

C. **Address background exposures or responses?**

The method explicitly addresses background exposures through use of population-representative biomonitoring data for exposure characterization.

D. Address incorporation of existing biological understanding of the likely mode of action?

We discuss mode of action for THM-induced fatty liver; however, the appropriate use of the toxicological data for low dose extrapolation based on this mode of action is unclear.

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation?

The method relies upon estimation and interspecies extrapolation of a biologically relevant internal dose metric, and the biomonitoring data provide exposure data that are directly interpretable in terms of the relevant internal dose metrics.

F. Address uncertainty?

The method requires consideration of numerous sources of uncertainty as well as variability.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

Because in this case the evaluation is based on a $BMDL_{10}$ as a point of departure, risk estimation in the low dose region is possible and approaches to that are explored in this case study.

H. Work practically? If the method still requires development, how close is it to practical implementation?

The method can be used in practice. BE values have been derived for more than 80 chemicals and biomonitoring data for these chemicals have been generated by the US CDC.