PROJECT SUMMARY
THE APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING TO DETERMINE ROUTE-SPECIFIC CONTRIBUTIONS TO TISSUE DOSIMETRY OF TRIHALOMETHANES IN DRINKING WATER

September 2008

SUMMARY:

This project summary describes an improved approach for estimating route-specific exposures and tissue doses for trihalomethane (THM) compounds found in drinking water. The development of drinking water disinfection procedures has had a positive impact on public health through the eradication of microbially induced diseases, such as cholera, but it may also have some potentially negative consequences. Several drinking water disinfection byproducts (DBPs) have been demonstrated to be toxic and/or carcinogenic in experimental animals and these findings have raised concern for potential adverse effects in humans. Initial epidemiologic investigations suggest a potential link between the consumption of DBPs and adverse pregnancy outcomes (e.g., spontaneous abortions). A mixture of DBPs occurs in finished drinking water, with four trihalomethane (THM) compounds representing the highest concentrations: chloroform, bromodichloromethane (BDCM), chlorodibromomethane (CDBM) and bromoform. These THM compounds are regulated as a group and co-occur in drinking water as a mixture whose constituents and concentrations vary by season, drinking water source and disinfectant type. While their summed concentration is regulated, specific consideration to their individual concentrations or proportions of the mixture is not required. Due to the uncertainty surrounding the quantification of actual exposures in these initial epidemiologic investigations, more recent investigations have attempted to refine the assessment of exposure and to further delineate critical periods of exposure (see Hinckley et al., 2005; Savitz et al., 2006).

The goals of this investigation are to characterize route-specific contributions to THM absorbed and target-tissue THM doses, to estimate whether metabolic interactions were likely to occur at these exposure levels, and to examine the population distribution of exposure. The approach comprises six principle efforts:

(1) *To determine the feasibility of linking exposure modeling with pharmacokinetic modeling*.

(2)*To ascertain the concentrations of individual THMs in finished drinking water in the United States.*

(3) *To estimate indoor air concentrations of THMs by evaluating human water use and household activity patterns.*

(4) *To characterize human exposures to waterborne THMs by overlaying human activity patterns (the activity, the location and the duration) with water use behavior.*

(5) *To link an exposure model (the Total Exposure Model; TEM) to a simplified pharmacokinetic model to estimate route-specific and total absorbed doses.*

(6) *To translate the measures of absorbed dose, as determined by the TEM, into measures of exposure for target organs of interest via physiologically based pharmacokinetic (PBPK) modeling simulating the adult male, the adult female and the child.*

This collection of publications has been developed collaboratively among scientists within the U.S. EPA's Office of Research and Development and under contracts with Anteon Corporation and Wilkes Technologies.

The citations for the publications and abstracts that comprise this project include the following:

Peer-Reviewed Publications:

Teuschler, L.K., G.E. Rice, C.R.Wilkes, J.C. Lipscomb and F.W. Power. 2004. A feasibility study of cumulative risk assessment methods for drinking water disinfection by-product mixtures. *J. Toxicol. Environ. Health*. 67:755–777.

U.S. EPA (Environmental Protection Agency). 2006a. Exposures and Internal Doses of Trihalomethanes in Humans: Multi-Route Contributions from Drinking Water ORD/NCEA, Cincinnati, OH. EPA/600/R-06/087.

Abstracts:

Kedderis, G.L., C.R. and J.C. Lipscomb. 2006. Internal doses of trihalomethanes in humans resulting from drinking water use (M4.P106). Society for Risk Analysis Annual Meeting, Baltimore, MD. December, 2006. Available at: http://birenheide.com/sra/2006AM/program/singlesession.php3?sessid=P

Rice, G.E., L.K. Teuschler, C.R. Wilkes, et al. 2003. A cumulative risk assessment method to evaluate multiple-route exposures to chemical mixtures in drinking water (W6.3). Society for Risk Analysis Annual Meeting, Baltimore, MD. December, 2003. Available at: http://www.birenheide.com/sra/2003AM/program/singlesession.php3?sessid=W6

Wilkes, C.R., J.C. Lipscomb and G.L. Kedderis. 2006. Exposures to trihalomethanes in humans resulting from drinking water exposures (M4.P105). Society for Risk Analysis Annual Meeting, Baltimore, MD. December, 2006. Available at: http://birenheide.com/sra/2006AM/program/singlesession.php3?sessid=P

Wilkes, C.R., L.K. Teuschler, G. E. Rice, J.C. Lipscomb and F.W. Power. 2003. Estimating multi-chemical, multi-route cumulative exposure to disinfection by products in drinking water (W18.3). Society for Risk Analysis Annual Meeting, Baltimore, MD. December, 2003. Available at: http://www.birenheide.com/sra/2003AM/program/singlesession.php3?sessid=W18

Development of risk assessment methods is a major component of the work done by U.S. EPA's National Center for Environmental Assessment, NCEA, which provides guidance and risk assessments aimed at protecting human health and the environment. The Safe Drinking Water Act and Amendments of 1996 charge the U.S. EPA with providing the U.S. public with drinking water free from hazards. Part of this calls for the development of new methods to characterize the hazards of mixtures of drinking water contaminants. This project focuses on the trihalomethane (THM) disinfection byproducts (DBPs), whose concentration in drinking water is regulated as the summed concentration of four THM compounds, rather than on the basis of their individual concentrations. Given their structural, toxicological and metabolic similarities, and their multi-route exposures, some questions have arisen about the toxic responses that can arise from chemical interactions among the THM class of DBPs. By expressing dose as tissue concentration for use in advanced risk assessments as in this project, more accurate estimates of exposure and response can be developed. This approach has the benefits of developing population-based estimates of exposure and fostering exposure- and dose-response assessments that will reduce some uncertainties inherent in the risk assessment process.

BACKGROUND:

Humans are exposed daily to complex mixtures of DBPs via oral, dermal, and inhalation routes. Human health risk estimates made using animal data based only on oral exposures do not reflect the same magnitude of risks found in positive epidemiologic studies. Thus, research was conducted to evaluate whether this difference can be accounted for by assessing simultaneous exposures to multiple DBPs via all three exposure routes. Several of these THM compounds share a metabolic pathway catalyzed by CYP2E1, a metabolic enzyme highly expressed in animal and human liver. Because of this commonality, some competition between them for metabolism may occur, though the exposure conditions necessary for such competition have not yet been determined. Because THM-specific oxidative metabolites may be differentially toxic, the conditions under which competition for metabolism may occur are of importance for risk assessment of THM mixtures. The ORD's National Center for Environmental Assessment (NCEA) develops methods and approaches to assess the risks of exposure to chemicals, either individually or in mixtures. These approaches are applied by risk assessors in NCEA and throughout the U.S. EPA. Drinking water disinfection byproducts (DBPs) occur as complex mixtures, and several DBP chemicals are regulated by approaches based on chemical class (a mixture of chemicals sharing molecular attributes). The U.S. EPA's Office of Water (OW) develops such regulations based on several factors—including the results of risk assessments. The uncertainty in risk assessment and regulatory approaches

using data from studies using single-chemical exposures can be reduced by employing mixtures-based approaches. We have developed an approach to refine estimates of internal exposures and characterize the likelihood of toxicological interactions for the THM compounds. The approach was applied to data from the US EPA's Information Collection Rule data for THM compounds.

Several factors determine human exposure to THMs present in drinking water. The most obvious is their concentration in finished drinking water. Another obvious factor is the amount of water ingested through drinking and consumption of prepared foods. Some factors that are not so obvious include dermal exposures via hand washing, showering, bathing, etc., and inhalation exposures resulting from water use activities. Inhalation exposures are especially relevant for more volatile water contaminants, like the THMs. Because in humans the doses to target organs result from multiple exposure routes, human exposure assessments for volatile compounds likely to occur in confined environments can be improved by assessing exposure via the anticipated routes.

Several findings are evidenced in the results. Available technology supports the linking of exposure modeling software and pharmacokinetic modeling software; available data support estimations of internal doses (target tissue concentrations) of drinking water contaminants including route-specific contributions to total dose (U.S. EPA, 2003; Teuschler et al., 2004). For the volatile THM compounds, exposure via the inhalation pathway was a key determinant of internal dose, especially at the upper portion of the total dose distribution (U.S. EPA, 2006a). This means that the individuals most exposed to THMs were those experiencing higher levels of inhalation exposure. While the absorbed dose from any route may be compared to standards for human exposure, because route of exposure can impact toxic outcome, analysis of tissue dosimetry should accompany such comparisons of absorbed dose.

The characterization of population-based probabilistic measures of route-dependent external or absorbed doses was successful (U.S. EPA, 2006a). This approach for linking population-based route-specific measures of exposure to THM compounds with PBPK modeling has been successful (see U.S. EPA, 2006a), which confirmed and extended earlier findings with DBPs (U.S. EPA, 2003; Teuschler et al., 2004). Because target tissue dose is the most appropriate measure of dose for dose-response analysis and exposure characterization, this represents a significant advance in characterizing exposures for risk assessment of indoor THM exposures. The PBPK model used in this investigation was adapted from a well accepted model, for chloroform (Corley et al., 1990), that has been previously used in many other risk assessment applications. The new model includes compartments specific for known THM toxicities (liver, kidney, gonads) and has been further modified to include capability to assess competitive metabolic interactions of THMs in the liver. Some generalizations can be inferred about population distributions of internal target tissue exposures. With respect to population distributions of kidney dosimetry (for parent THM compounds), the distribution of exposure may be slightly different than for the adult, with a higher fraction of the child population receiving higher tissue doses (U.S. EPA, 2006a). The same pattern is evident for gonads. For liver dosimetry (CM_{24}, the metabolite), the distribution of exposure may

be slightly different than for the adult, with a higher fraction of the child population receiving lower tissue doses. Because the models were parameterized with point values, rather than with ranges of values for key (sensitive) physiological (e.g., blood flows) and biochemical parameters (e.g., metabolic rate constants), the variability in dosimetry represents only variability resulting from human exposure patterns (contacted or absorbed dose estimated by TEM), rather than also including variability in dosimetry influenced by variability in values for parameters (e.g., liver blood flow, metabolic rate) in the pharmacokinetic models employed.

Finally, evaluation of the competitive metabolic interactions of the THMs in the liver provided useful information. The responsible enzyme, CYP2E1, has a relatively high capacity to metabolize chemicals. Under the conditions simulated (e.g., THMs present in drinking water at the 95th percentile of their distributions), the extent of metabolic interaction (competitive inhibition) reached a maximum of 0.0001% for BDCM; no inhibition of the metabolism of other compounds is indicated. Because these chemicals are not expected to compete against one another for metabolism to toxicologically active chemical species, tissue distribution data generated from single-chemical exposures may be appropriate for application in mixtures risk assessment. Secondly, the PBPK model was also parameterized to simulate lower levels of CYP2E1 activity, which could result from under-expression of the enzyme or as a consequence of reduced enzymatic activity (due to exposure to other chemicals which may reduce enzymatic capacity either through competition or suicide inhibition. Under the conditions evaluated, a one million-fold reduction of enzymatic activity resulted in only a 0.2% competitive inhibition (U.S. EPA, 2006a).

Together, these results demonstrate the value of linking exposure modeling with PBPK modeling for the purposes of both exposure assessment and dose-response evaluation. This approach will be applicable and valuable to the assessment of risks from single chemicals and defined chemical mixtures. These results demonstrate (1) that the THM compounds will not alter the tissue dosimetry and oxidative metabolism of one another, when encountered under the near-extreme exposure conditions simulated here, and (2) that variations in the activity and liver concentrations of CYP2E1 will not increase risk in affected individuals. On the basis of these findings, data from studies in which test animals were exposed to a single THM compound provide data that can form a reliable basis for a THM mixture risk assessment.

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Corley, R.A., A.L. Mendrala, F.A. Smith et al. 1990. Development of a physiologically based pharmacokinetic model for chloroform. *Toxicol. Appl. Pharmacol*. 103:512-527.

Hinckley, A.F., A.M. Bachand and J.S. Reif. 2005. Late pregnancy exposures to disinfection by-products and growth-related birth outcomes. *Environ Health Perspect.* 113:1808–1813.

Savitz, D.A., P.C. Singer, A.H. Herring, et al. 2006. Exposure to drinking water disinfection by-products and pregnancy loss. *Am J Epidemiol.* 164:1043–1051.

Teuschler, L.K., G.E. Rice, C.R.Wilkes, J.C. Lipscomb and F.W. Power. 2004. A feasibility study of cumulative risk assessment methods for drinking water disinfection by-product mixtures. *J. Toxicol. Environ. Health*. 67:755–777.

U.S. EPA (Environmental Protection Agency). 2006a. Exposures and Internal Doses of Trihalomethanes in Humans: Multi-Route Contributions from Drinking Water ORD/NCEA, Cincinnati, OH. EPA/600/R-06/087.

RELATED LINKS AND DOWNLOADS:

U.S. EPA (Environmental Protection Agency). 2003. The Feasibility of Performing Cumulative Risk Assessments for Mixtures of Disinfection By-Products in Drinking Water. ORD/NCEA Cincinnati, OH. EPA/600/R-03/051. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=56834

U.S. EPA (Environmental Protection Agency). 2006b. Stage 2 Disinfectants and Disinfection Byproducts Rule; Final Rule. Federal Register, 71(2):388-493. Available at: http://www.epa.gov/fedrgstr/EPA-WATER/2006/January/Day-04/w03.pdf

U.S. EPA (Environmental Protection Agency). 2006c. Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment (Final Report). U.S. Environmental Protection Agency, Washington, D.C., EPA/600/R-05/043F. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=151384

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