

Impact of Interindividual Differences for Human Health Risk Assessment: Hepatic Bioactivation of Chloroform

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Chloroform is a volatile disinfection byproduct in drinking water. The Office of Water (OW) has the lead for conducting risk assessment from exposure to chloroform. The oral risk assessment is complete, and the current task is the assessment via inhalation route. Similar to the mode of action by the oral route (see IRIS on chloroform assessment), a nonlinear approach is taken. This includes developing the inhalation Reference Concentration. Because of the expertise in the area of pharmacokinetic modeling, dose extrapolation, and metabolic studies, the Office of Research and Development was sought as a partner in this endeavor. The study was designed to compare the doses attained within the liver of experimental animals and humans to refine the RfC determination. The original work was conducted under Agency guidance using both extramural and internal resources including the IAGs, contracts, cooperative agreements, and collaborations within EPA. ORD/NHEERL collaborated with ORD/NCEA to examine chloroform metabolism in human samples. The work recognized and addressed differences in chloroform-metabolizing enzyme content among adults, differences in the distribution of blood flow among humans, and differences in critical biochemical parameters between human infants, juveniles, and adults. Specific investigations used tissues and samples taken from human donors. The results from these investigations were combined in a physiologically based pharmacokinetic (PBPK) model specifically developed for chloroform and tailored to each human developmental age.

A separate model was used to examine chloroform doses in the mouse. The mouse model converts an external inhalation exposure to the concentration of the toxic metabolite in liver. Metabolic, toxicokinetic differences between animals and humans and among humans, respectively, serve as the basis for developing uncertainty factors used in the assessment. This represents a significant advance in risk assessment practice. It involves the use of chloroform-specific data from animal and human tissues/preparations. The resulting scientific findings and their application in quantitative risk assessment demonstrate the applicability of chemical-specific data in the development of non-default values for dose extrapolation and the determination of uncertainty factors useful in risk assessment. This should encourage organizations to plan additional well-targeted biochemical research to develop more chemical-specific data for risk assessment.