Assessing the impact of human metabolic variability on the health risks of occupational and environmental exposures to chloroform

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Approximately 15,000 Canadians are occupationally exposed to chloroform, primarily in the recreational sector. Non-occupational exposures can also occur when people ingest drinking water or shower in water containing chloroform that is formed during the chlorination process. Occupational and environmental exposure limits have been derived to protect workers and the general public from the adverse effects of chloroform. Several of these exposure limits are designed to prevent liver toxicity and tumours resulting from sustained cytotoxicity, for which the toxic moiety is likely a metabolite (e.g., phosgene). Others are designed to prevent neurological effects, which are thought to result from the parent compound (i.e., unmetabolized chloroform). Because chloroform is primarily metabolized by the 2E1 isoform of cytochrome P450 (CYP2E1), variability in the levels of the enzyme in the human population could influence susceptibility to the compound. High metabolizers might be more susceptible to liver toxicity due to the generation of higher levels of the toxic metabolite, whereas low metabolizers might be at greater risk for neurotoxicity because more of the unmetabolized compound could reach the brain. The objective of this research was to investigate the effect of interindividual variability in CYP2E1 activity on the health risks of chloroform and to identify whether existing exposure limits sufficiently account for these differences. To estimate the rate of metabolism and levels of parent compound and metabolites in the body, a human physiologically based pharmacokinetic (PBPK) model for chloroform was developed in Berkeley-Madonna software. The model allowed for the simulation of chloroform in the lungs, liver, kidneys, fat, other slowly perfused tissues and other rapidly perfused tissues, with exposure via inhalation and oral ingestion. Equations for metabolic activity were included for liver and kidneys. The model was based on an existing chloroform model (Corley et al., 1990), but updated with newer physiological data (Brown et al., 1997; Environment Canada and Health Canada, 2001), and was validated against results from other models (Corley et al., 1990; Reitz et al., 1990) and experimental studies in humans. Data from human donors on the concentrations of CYP2E1 in human liver microsomes and of microsomes in liver were obtained from the literature (Lipscomb et al., 2003a, 2003b). Microsomal CYP2E1 concentrations had ten-fold variability (11□130 pmol CYP2E1/mg microsomal protein; n=75), and four-fold variability was measured for hepatic microsome concentrations (27□108 mg microsomal protein/g liver; n=20). To allow for the adjustment of CYP2E1 and microsomal concentrations in the PBPK model, an equation was developed for VMAX using these variables, the specific activity of CYP2E1 for chloroform (from Lipscomb et al., 2004) and a default value for liver volume. The PBPK model was run to simulate exposure scenarios for selected occupational and environmental exposure limits for 5th percentile, average and 95th percentile metabolizers. The first scenario considered the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) and the National Institute of Occupational Safety and Health (NIOSH) Recommended Exposure Limit (REL), which were both 8-hour time-weighted average (TWA) values of 10 ppm. Because the basis of

both values was hepatic effects, the amount of the metabolite that binds to liver macromolecules was considered of greatest relevance. Using an exposure scheme of 8 hours per day, 5 days per week, for 40 years, average liver macromolecular binding (MMB) levels at steady state for 5th percentile, average and 95th percentile metabolizers were 23.7, 25.6 and 26.1 mg/d, respectively. An environmental exposure scenario in which the model was run for 70 years at the Health Canada Guideline for Canadian Drinking Water Quality for total trihalomethanes (based on hepatic effects of chloroform) of 0.1 mg/L had similar results, with average liver MMB values of 0.28943, 0.28958 and 0.28964 mg/d in 5th percentile, average and 95th percentile metabolizers, respectively. A second occupational exposure scenario investigated the NIOSH REL and Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (PEL), a ceiling value of 50 ppm, at daily 30-minute periods, 5 days per week, for 10 years. The dose metric considered in this scenario was the peak concentration of chloroform in blood—a proxy for brain concentration in the absence of a brain compartment in the model—because the ceiling value was based on neurological effects. Arterial concentrations for 5th percentile, average and 95th percentile metabolizers were 0.31, 0.28 and 0.25 mg/L, respectively. To ensure that occupational and environmental exposure limits are protective for a sufficiently broad segment of the population, the potential for pharmacokinetic differences must be adequately considered during the derivation of the values. These differences should be addressed either by using a study that is based on a sufficiently broad human population or by applying uncertainty (or safety) factors to reflect these differences. As expected, the 5th percentile group metabolized less chloroform, resulting in higher blood chloroform concentrations. Likewise, the 95th percentile metabolizers had higher levels of metabolism and liver MMB. However, the differences amongst the groups were less than 2-fold, despite much higher variability levels for CYP2E1 and microsome concentrations; therefore, these factors only have a minor impact on the risks of liver toxicity and acute neurological effects within the population. Although variability due to CYP2E1 and microsomal concentrations has been adequately addressed in selected exposure guidelines, other physiological differences (e.g., in inhalation or blood flow rates) could also impact this variability. Moreover, pharmacodynamic differences (e.g., the potential for differing susceptibility to hepatocellular damage from the same liver dose of toxic metabolites) also need to be sufficiently considered. When evaluating exposure levels for compounds, industrial hygienists and public health risk managers should assess whether human variability was sufficiently addressed in relevant exposure limits. This evaluation is particularly important if exposure levels for a chemical are close to the exposure limits.