Liter-Equivalence Extrapolation for Four Trihalomethanes (THMs): What Drink Would It Take to Get the Same Internal Dose?

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Background

- Disinfection byproducts (DBPs) are formed when oxidizing disinfectants react with inorganic and organic matter in water.
- EPA regulates 4 trihalomethane (THM) DBPs in drinking water: chloroform (TCM), bromodichloromethane (BDCM), dibromo-chloromethane (DBCM), and bromoform (TBM) as a group.
- Environmental exposure studies and physiologically based pharmacokinetic (PBPK) model analyses demonstrate that, compared to oral exposure, dermal and inhalation exposure to water containing BDCM results in more BDCM being delivered to the systemic circulation and thus available for biotransformation in extra hepatic tissues.
- Recent epidemiology findings indicate an association between exposure to disinfected tap water and bladder cancer.
- Mechanistic data suggest target tissue metabolism via the glutathione pathway is likely to be important for some types of BDCM-induced toxicity, including carcinogenicity. Thus, systemic circulating dose is an important determinant of potential adverse effects in extra-hepatic target tissues such as the urinary bladder.

Objective & Approach

Use liter equivalency analysis to evaluate the impact of route of exposure: oral vs. inhalation and dermal (via bathing or showering) on two measures of internal dose - area under the curve in venous blood (AUCv) and amount metabolized in liver. We simulated showering for 10 minutes or bathing for 20 with water containing 8.2, 12.2, 13.5, and 8.7 µg/L for TCM, BDCM, DBCM and TBM, respectively. These are measured drinking water concentrations from a system with predominantly brominated species of THMs (Gulf coast TX, Lynberg et al., 2001).

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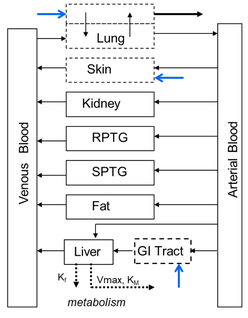
What is Liter Equivalency?

The concentration (µg/L) of each THM required to be consumed orally in one liter of water to achieve the same values for specific internal dose measures when showering or bathing under particular exposure scenarios.

THM PBPK Model



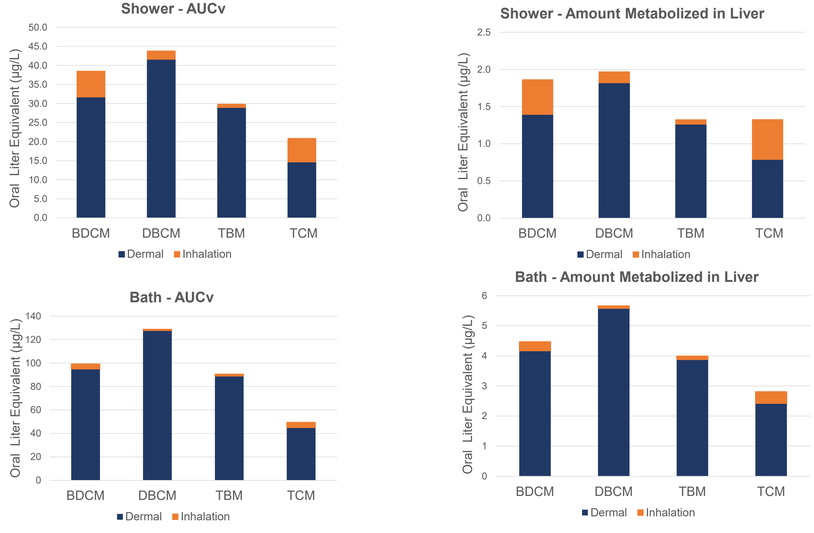
Blue arrows are routes of exposure. Kf refers to glutathione metabolism pathway, active for brominated, but not chlorinated, THMs. Vmax and Km refer to oxidative (CYP) metabolic pathway.

RPTG and SPTG are rapidly and slowly perfused tissue groups, respectively.

Model Parameters

- Model structure, assumptions and physiological parameters are the same as the published BDCM model (Kenyon et al., 2016), repeated for each of the THMs.
- Partition coefficients and metabolism parameters are matched for species source (rodent vs. human) to avoid mis-interpretation when comparing THMs.
- Blood:air partition coefficients were derived from humans and were divided by rodent tissue:air partition coefficients to calculate tissue:blood partition coefficients.
- Metabolism parameters for the oxidative pathway were derived from rodent studies.

Liter Equivalency - Showering & Bathing



Liter Equivalency Analysis - ingested water concentration (assuming 1 liter of water consumed) required to produce the same value for the dose metrics, area under curve in venous blood (AUCv) and amount metabolized in liver for 4 THMs resulting from a 10 minute shower or 20 minute bath with water containing 8.2, 12.2, 13.5, and 8.7 µg/L for TCM, BDCM, DBCM and TBM, respectively. The individual contributions of inhalation and dermal routes of exposure are represented as stacked bars.

The Methodology

TCM 8.2 BDCM 12.2 DBCM 13.5 TBM 8.7 µg /L

1. Run model for 10-minute shower or 20 minute bath.

   Dermal, Inhalation Exposures

2. Determine dose menrics
   - AUC for venous blood
   - Amount metabolized in liver.

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3. "Bootstrap" the model to determine Liter Equivalent needed to reach these dose metrics.

   Oral exposure concentration required in 1 liter of water.

Summary and Future Work

- This analysis suggests a large contribution for dermal and inhalation exposure routes during showering or bathing to internal dose of all THMs reaching the systemic circulation (AUCv).
- Dermal uptake was relatively greater compared to inhalation uptake for both AUCv and amount metabolized in liver following showering and bathing (TCM < BDCM < DBCM < TBM), reflecting decreasing volatility across chemicals which results in lower air concentrations.
- The contribution of inhalation exposure was relatively greater during showering compared to bathing because of greater volatilization during showering compared to bathing.
- Consideration of multiple routes of exposure when evaluating risks from water-borne THMs provides for a comprehensive basis to assess human health risk.
- Future work will focus on
  - Target tissue biotransformation (bladder) to eventually evaluate metabolic interactions
  - Impact of variability in physiological parameters on measures of internal dose
  - Monte Carlo analysis (using input water concentrations) to assess impact of variability in water concentrations on measures of internal dose