FACTORS INFLUENCING PREDICTION OF BROMODICHLOROMETHANE (BDCM) IN EXHALED BREATH

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Background

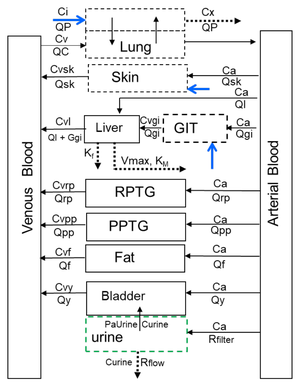
- Confidence in the predictive capability of a physiologically based pharmacokinetic (PBPK) model is increased when the model is demonstrated to predict multiple pharmacokinetic outcomes under differing exposure conditions.
- We previously showed that our multi-route human BDCM PBPK model adequately predicts both blood and urine BDCM concentrations from human exposure studies; activities in these studies included drinking, bathing, showering and swimming.
- Exhaled breath BDCM concentration (ExBr) was adequately predicted in subjects actively swimming.
- However, ExBr BDCM was over-predicted by 5 to 9-fold when compared to median experimentally measured ExBr BDCM for unmoving subjects immersed in pool water in two different studies.

OBJECTIVE

Use the BDCM PBPK model to explore possible physiological explanations for over-prediction of exBDCM in unmoving subjects immersed in pool water.

PBPK Model

BDCM Multi-Route Human Model

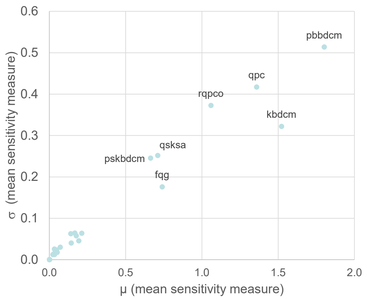


Original BDCM PBPK model (Kenyon *et al.*, 2016) modified with bladder tissue and urinary excretion added, and kidney compartment removed. Urinary excretion of BDCM occurs via glomerular filtration. GIT is GI tissue. RPTG and PPTG are richly and poorly perfused tissues, respectively.

Global Sensitivity Analysis

Activity: Water Immersion, Non-moving (dermal + inhalation)

Response: Exhaled Breath



Morris screening level GSA for non-moving water-immersed subjects for 40 min with 1.5 hr total simulation time. Water (13 μg/l) and air (22 μg/m^3) BDCM concentrations selected to reflect typical conditions reported in available studies. The sensitivity indices, μ and σ (averaged over simulation time), are plotted for all input parameters; only select points are annotated due to space limitations.

Approach

- Identify most influential parameters using global sensitivity analysis (GSA) for pool water immersion scenario with subject not actively swimming.
- Use the BDCM PBPK model to sequentially explore possible physiological explanations for this observation based on parameter ranking from GSA and literature review,
- Results of literature review identified temperature-dependence for parameters such as cardiac output, alveolar ventilation rate, apparent skin permeability and skin blood flow.
- Parameters were assessed in order of approximate increasing impact based on GSA: blood:air partition coefficient (pbbdcm), alveolar ventilation rate (qpc), cardiac output (rqpco), skin permeability (kbdcm), and skin blood flow (qsksa).

Table 1. Studies reporting exhaled breath BDCM used in current analysis

Study[1]	Study Description
Font-Ribera et al., 2010	Adult swimmers at indoor chlorinated pool, aggregate data reporting with estimates of exercise intensity
Marco et al., 2015	Adult active and non-active swimmers at indoor chlorinated and brominated pools, aggregate data reporting with estimates of exercise intensity
Salas et al., 2017	Adult active and non-active swimmers at indoor chlorinated pool, aggregate data reporting with subject characteristics and estimates of exercise intensity

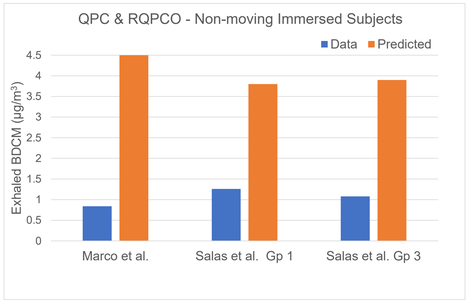
[1]All studies included measurements of both water and ambient air trihalomethanes with measurement of ExBr at end of activity (swimming, non-moving water immersion). Subjects were not professional/elite swimmers.

Table 2 Impact of Changing Blood Air Partition Coefficient (pbbdcm) on Model-Predicted ExBr BDCM

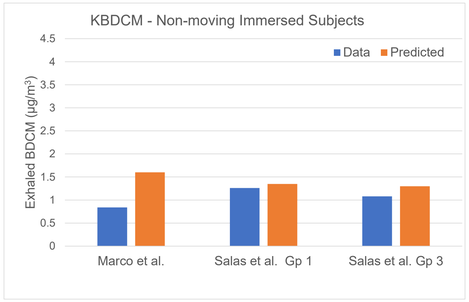
Study	Exposure Group	Measured ExBr (μg/m^3)	Predicted ExBr (μg/m^3)[d]	
			pbbdcm 15.97	pbbdcm 26.6
Font-Ribera et al., 2010[a]	Swimmers	1.8 (0.7 – 3.2)	2.5	1.9
Marco et al., 2015[a,b]	Swimmers, Cl pool	1.55 (0.5 – 2.8)	2.3	1.6
	Swimmers, Br pool	0.14 (0.07 – 0.25)	0.17	0.13
	Bathers, Cl pool	0.84 (0.59 – 1.2)	7.1	4.6
Salas et al., 2017[c]	Group 1 Non-swimming	1.26 [1.04, 1.45]	6.5	4.2
	Group 2 Swimming	1.61 [1.38, 1.82]	1.6	1.2
	Group 3 Non-swimming	1.08 [1.04, 1.11]	6.5	4.2
	Group 3 Swimming	2.09 [1.61, 2.65]	2.2	1.7

[a] Data reported are mean and range of exhaled breath at end of swimming for 40 minutes.
[b] Swimmers were actively swimming at capacity the entire 40 minutes; for bathing exposure subjects were immersed in pool water but not actively moving.
[c] Data reported are median, P25 and P75 for exhaled breath at end of swimming for 40 minutes. Non-swimming groups were immersed in water, but not actively moving.
[d] Original pbbdcm (15.97) was measured at US EPA (Kenyon et al., 2016) and alternate ppbdcm was reported in Batterman et al. (2002).

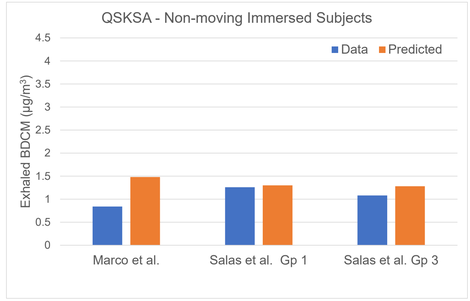
Impact of Changing Alveolar Ventilation Rate and Cardiac Output on Model-Predicted ExBr BDCM



Impact of Decreasing Skin Permeability on Model-Predicted ExBr BDCM



Impact of Decreasing Skin Blood Flow on Model-Predicted ExBr BDCM



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Summary

- Using an alternative pbbdcm from the literature (Batterman et al., 2002), while keeping other parameters at original values, decreased predicted ExBr, bringing it closer to measured data for immersed non-moving subjects and keeping predicted ExBr generally within range of data for swimmers.
- Subsequent simulations focused on non-moving water immersed subjects. Individual parameters were sequentially changed, keeping the same previously revised values.
- Increasing cardiac output and alveolar ventilation rate from default resting values to values more consistent with those estimated for non-moving (non-hypothermic) water-immersed subjects decreased over-prediction of exBr BDCM to 3- to 5-fold above median measured values for exhaled breath.
- Decreasing skin permeability by 75% resulted in over-prediction of exBr BDCM that was less than 2-fold compared to median data values.
- Decreased apparent skin permeability with decreasing water temperature has been reported for chloroform (83% decrease between 40 °C and 30 °C in male subjects). Chloroform and BDCM are both trihalomethanes (Corley et al., 2000).
- Decreasing skin blood flow by 50% resulted in predicted exBR BDCM that was within the range of the data for all groups of water-immersed non-moving subjects.
- Relative decreases in skin blood flow on the order of 3-fold have been documented in the literature when water temperature is decreased from 40-34 °C. In studies where water temperature has been reported, the typical range for showering is 38-40 °C, whereas pool water is more typically in the range of 26-28 °C.
- The net effect of decreased skin permeability and decreased skin blood flow is to decrease dermal absorption.
- The impact of water immersion on alveolar ventilation rate, cardiac output and skin blood flow is temperature-dependent, complex and an important source of uncertainty in model predictions for exhaled breath.
- These results illustrate the utility of a PBPK model for simulation of unique and complex physiology.

Citations for references available upon request.