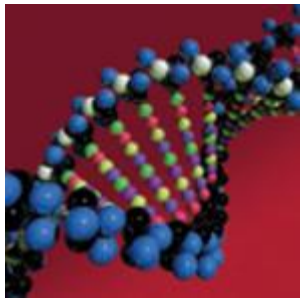
A Regional Model of Lung Metabolism for Improving Species Dependent Descriptions of 1,3-Butadiene and its Metabolites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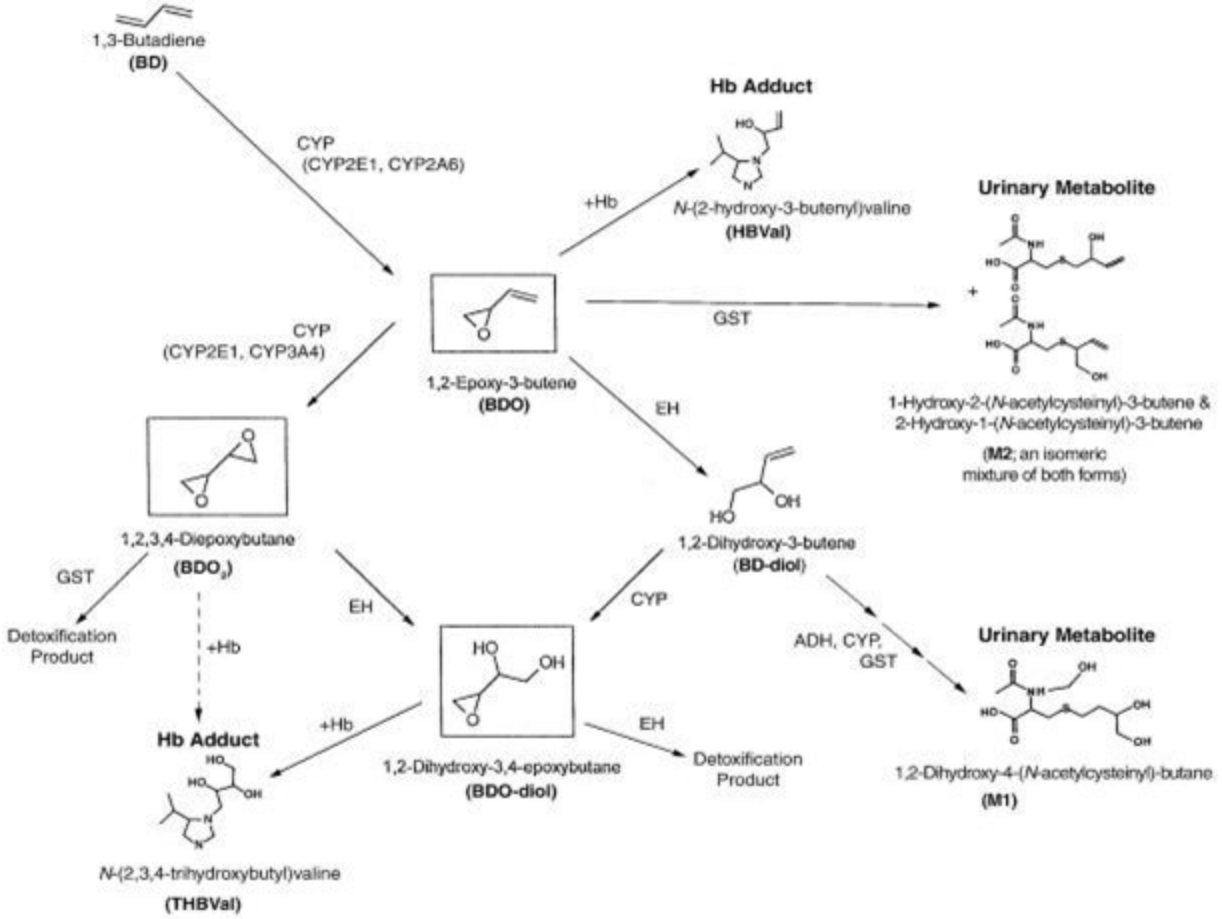
Multi-species inhalation PBPK model for Butadiene (BD)

Goals:

- To provide a description of regional inhalation dosimetry through inclusion of lung compartment specific transport and metabolism
  - Based on modeling approach developed for styrene (Sarangapani et al. 2002)
- To expand the model to include a description of metabolite excretion
  - To enable consideration of available urinary biomarker data in animals and humans during model calibration.

BD Metabolism



A simplified metabolic scheme for BD showing the metabolism modeled - Adapted from Albertinin et al. (2003)
A box around the chemical structure indicates it is a reactive epoxide metabolite, and broken lines indicate future additions to the model. Note that there are multiple urinary metabolites that are not referenced in this simplified scheme.

EH-epoxide hydrolase, GST – glutathione transferase, P450 – cytochrome P450

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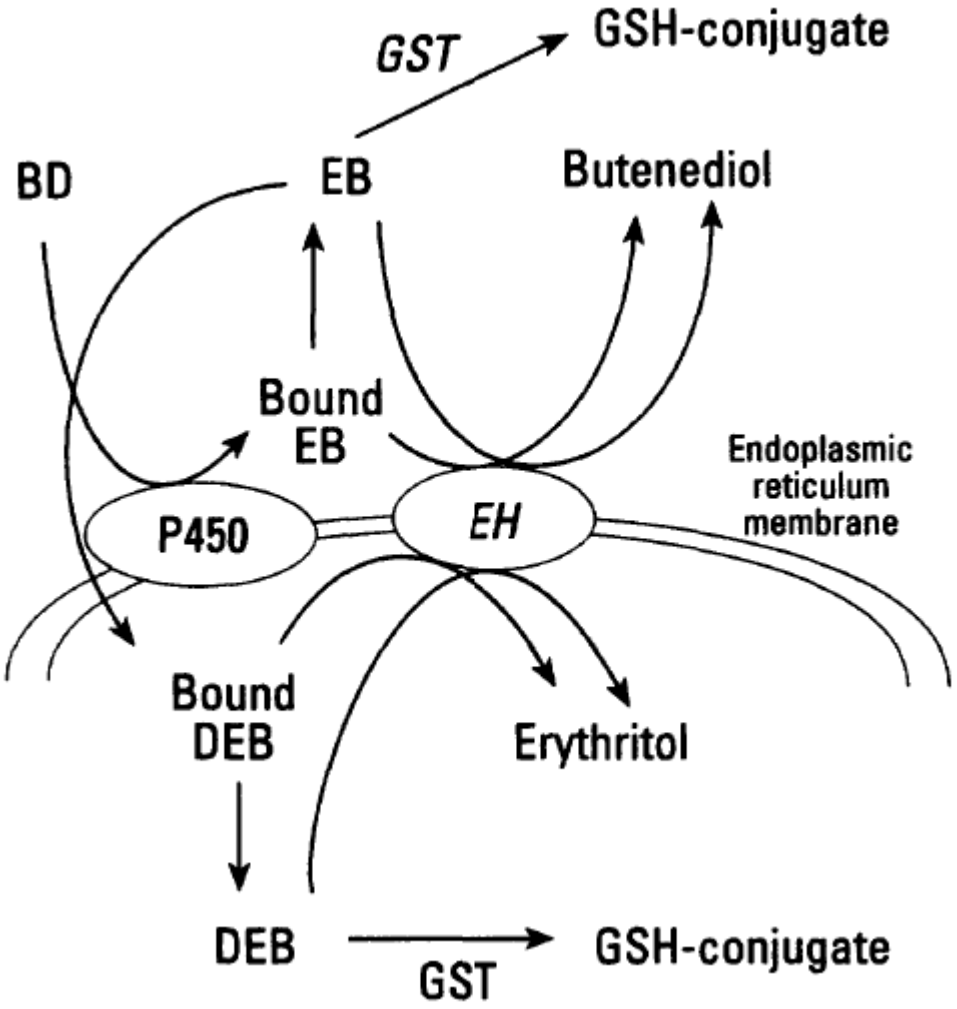
PBPK modeling of butadiene

Primary Existing Models		
Original publication	Subsequent published updates	Notable model features
Johanson and Filser, 1993	Johanson and Filser, 1996; Csanady et al. 1996	- BD and EB sub-models, with simple distributed DEB sub-model -Saturable metabolism in liver compartment only -Intraphepatic first pass metabolism of EB (to describe the lower-than-expected EB concentrations in blood) -Epoxide-GSH conjugation described with ping-pong kinetics
Kohn and Melnick, 1993	Kohn and Melnick 1996; 1997; 2000; 2001	-BD, EB, DEB sub-models -Blood compartment divided into arterial, venous and tissue capillary beds -Saturable metabolism in liver, lung, and kidney -Privileged access enzyme channeling between P450 and epoxide hydrolase resulting in enhanced hydrolysis of epoxide metabolites -Epoxide-GSH conjugation described with bi-bi kinetics
Medinsky et al. 1994	Bond et al. 1996; Sweeney et al. 1996; 1997; 2001; Jackson et al. 2000	-BD, EB, DEB sub-models -Saturable metabolism in liver and lung -Non-enzymatic elimination of EB and DEB -BD metabolism occurs by multiple enzymes (EB-producing and other)
Bois et al. 1999	Brochot et al. 2007; Beaudouin et al. 2010	-Human lifetime model with 22-41 compartments (non-pregnant vs. pregnant) -First order metabolism in liver, lung, gut, placenta -Pulmonary, fecal, urinary, and lactational excretion

“Privileged Access” Metabolism of EB (Kohn and Melnick, 2000)



Problem: metabolic Parameters from closed chamber exposures to EB don’t predict kinetics of EB following BD exposure

Explanation: faster clearance of EB produced from BD than when dosed directly

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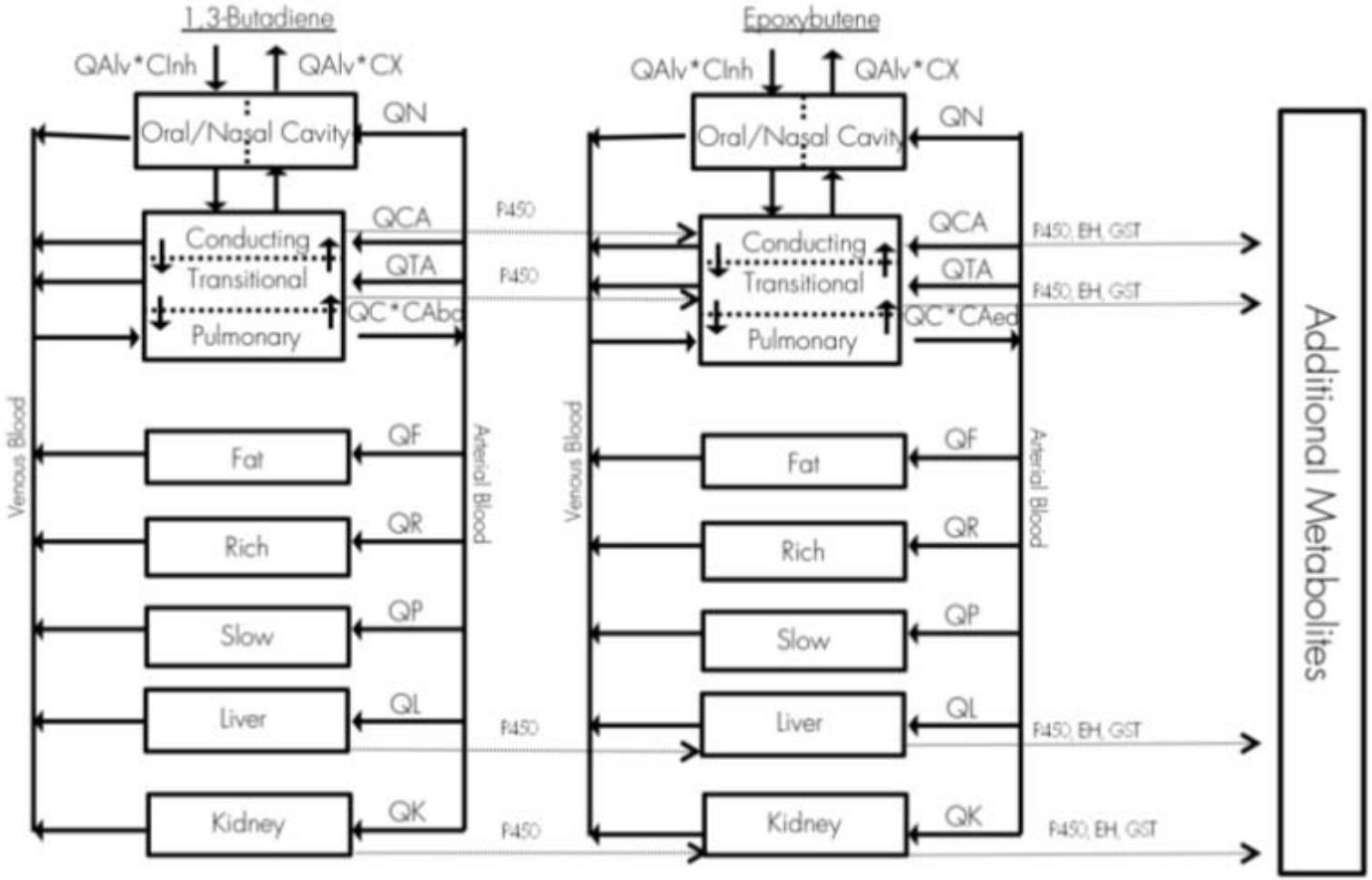
PBPK Model Structure



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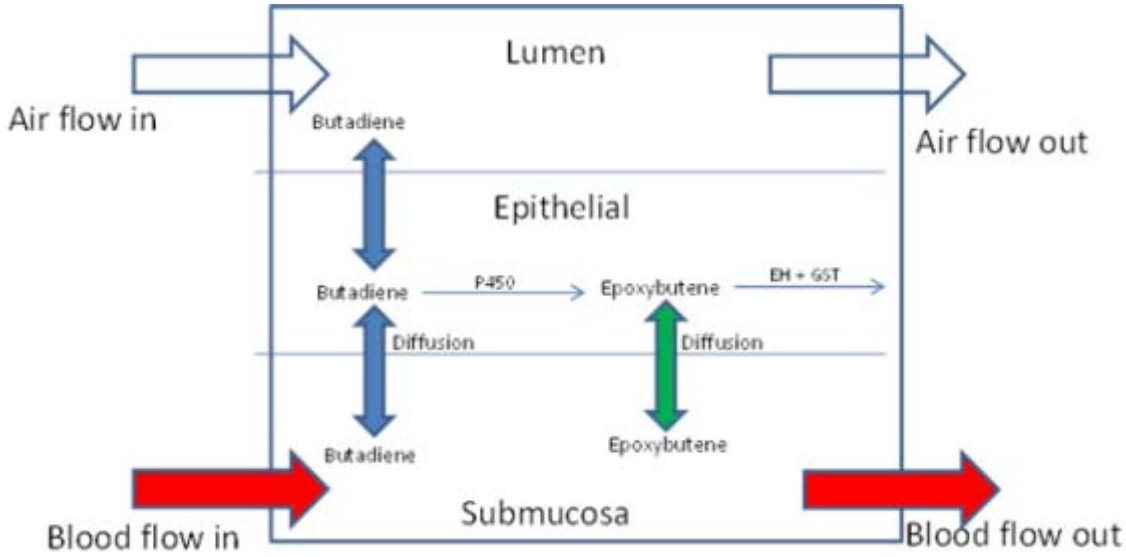
PBPK Model Structure

- Model contains compartments representing blood, liver, kidney, fat, richly and slowly perfused tissues and a multi-compartment lung.
- Sub-models were included to track the metabolism of two major metabolites of BD
  - EB
  - B-diol
- Pulmonary metabolism was distributed among four compartment regions with distinct physiological and metabolic features:
  - Oral/nasal passages
  - Conducting airways (traches, bronchi and anterior bronchioles)
  - Transitional airways (terminal bronchioles)
  - Alveolar gas exchange regions

PBPK Model Structure

- Metabolism in the pulmonary region is based on species-specific information on the distribution and density of metabolically active Clara cells.
- The lung compartments are based on the styrene model of Sarangapani et al. 2002.



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PBPK model structure

- BD metabolism in the liver, lung and kidney compartments follows a saturable oxidative metabolism (V_{max} and K_m) by cytochrome P450 to form EB
- A metabolically active kidney compartment was added to account for renal metabolism as well as for elimination of M1 and M2 urinary biomarkers
- A BD-Diol sub-model was included to better account for the metabolism of BD to the urinary metabolites M1 and M2 (Kohn and Melnick 2001; Sweeney et al. 2001)

BD Metabolite Modeling

- EB metabolism occurs by multiple pathways in the liver, lung and kidney compartments
  - Saturable oxidative metabolism by CYP450 to form DEB
  - Saturable hydrolysis by EH to form BD-Diol
    - "privileged access" (Kohn and Melnick 2001)
  - Conjugation via GST to produce the M2 urinary metabolite
- BD-Diol metabolism is modeled in the liver, lung and kidney compartments
  - Saturable oxidation by CYP450 to form the intermediate hydroxymethylvinyl ketone (HMVK)
  - HMVK conjugated via GST to produce the M1 urinary metabolite

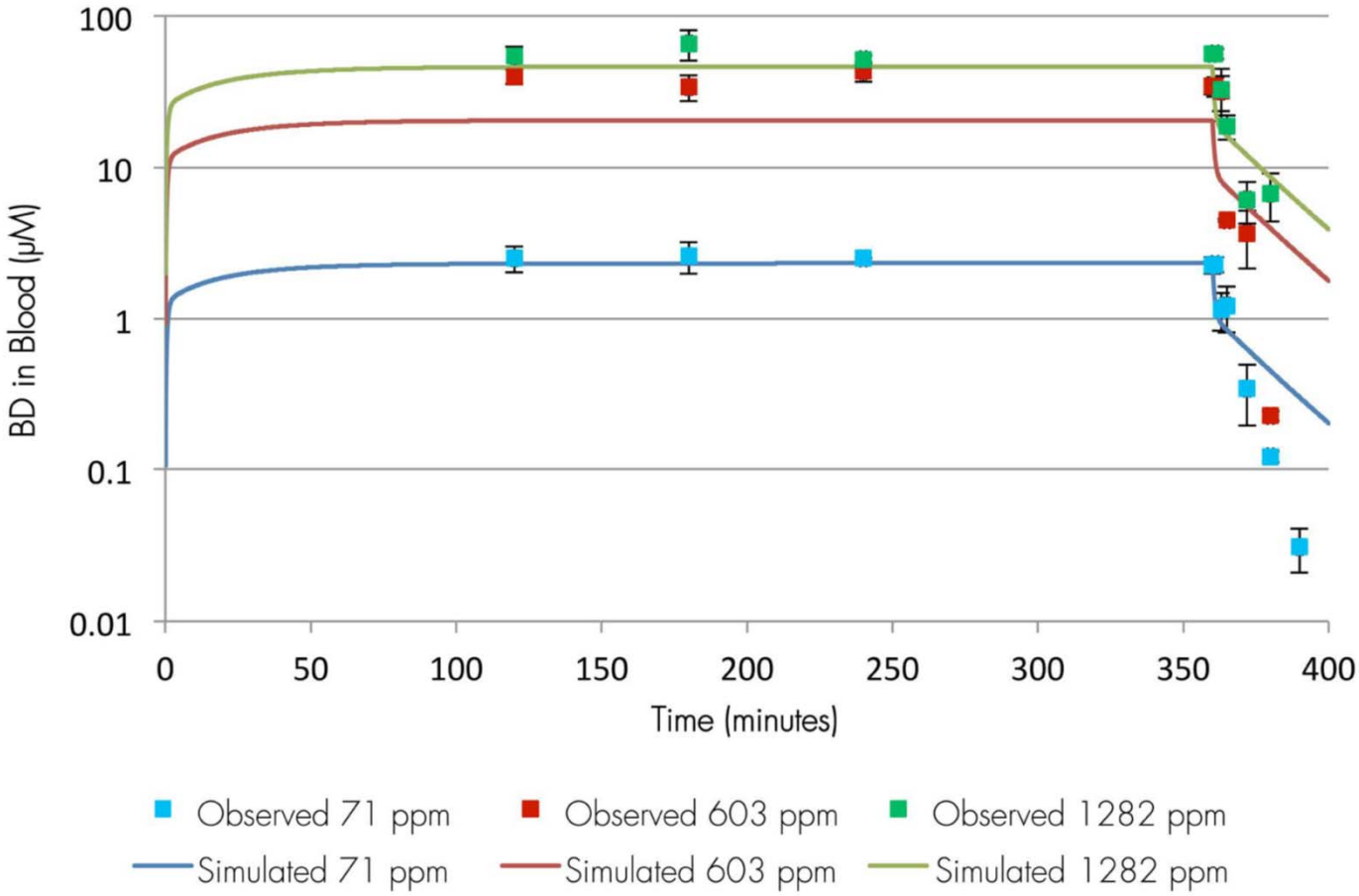
Lung Metabolism

- CYP450 metabolism only occurs in certain epithelial cells (Type1, Type II and Clara cells)
- Clara cells comprise the majority of the metabolic activity (Plopper et al. 1980; Plopper 1993)
- In mice Clara cells are found through out the respiratory tract, but they are only found in the transitional airway of rats and humans (Parent 1992; Plopper et al. 1992; Mercer et al 1994).
- Metabolic constants for the lung were scaled from measured whole lung homogenate
  - Experimental measurements of metabolic rate constants for BD and metabolites have not been measured yet in Clara cells

Sources for Parameters Estimates

Parameters	References
Blood Flow	Bogdanffy *et al.* 1999; Bogdanffy *et al.* 1998; Menache *et al*. 1997; Estimated
Surface Areas	Hinderliter *et al.* 2005; Bogdanffy *et al.* 1999; Bogdanffy *et al.* 1998; ICRP 1994; Oldham *et al.* 1994; Sarangapani and Teeguarden 2002; EPA 1994
Tissue Thicknesses	Plowchalk *et al.* 1997; Hinderliter *et al.* 2005; Bogdanffy *et al.* 1998; Mariassy 1992; Plopper *et al.* 1980; Pinkerton *et al.* 1992
Blood Exchange Region Thicknesses	Sarangapani and Teeguarden 2002
%Diffusivity Constants	Sarangapani and Teeguarden 2002
Partition Coefficients	
Butadiene	Bois *et al.* 1999; Johanson and Filser 1993; Sweeney *et al.* 1997; Filser *et al.* 1993
Epoxybutene	Csanady *et al.* 1996; Johanson and Filser 1993; Sweeney *et al.* 1997
Butenediol	Kohn and Melnick 2001
Gas Phase Mass Transfer Coefficients	Hinderliter *et al.* 2005; Bogdanffy *et al.* 1999; Bogdanffy *et al.* 1998; Sarangapani and Teeguarden 2002
Maximum Metabolic Rates	Csanady *et al.* 1992; Kohn and Melnick 2001; EPA 2002; Sweeney *et al.* 2001
Affinity Constants	Kreuzer *et al.* 1991; Csanady *et al.* 1992; Kohn and Melnick 2001; Sweeney *et al.* 2001
GSH Production and Elimination Rates	Johanson and Filser 1993
Initial GSH Tissue Concentrations	Sarangapani and Teeguarden 2002; Potter and Tran 1993

BD concentrations in the blood of B63CF1 mice during and following six hours of inhalation exposure to 71, 603 or 1282 ppm of BD



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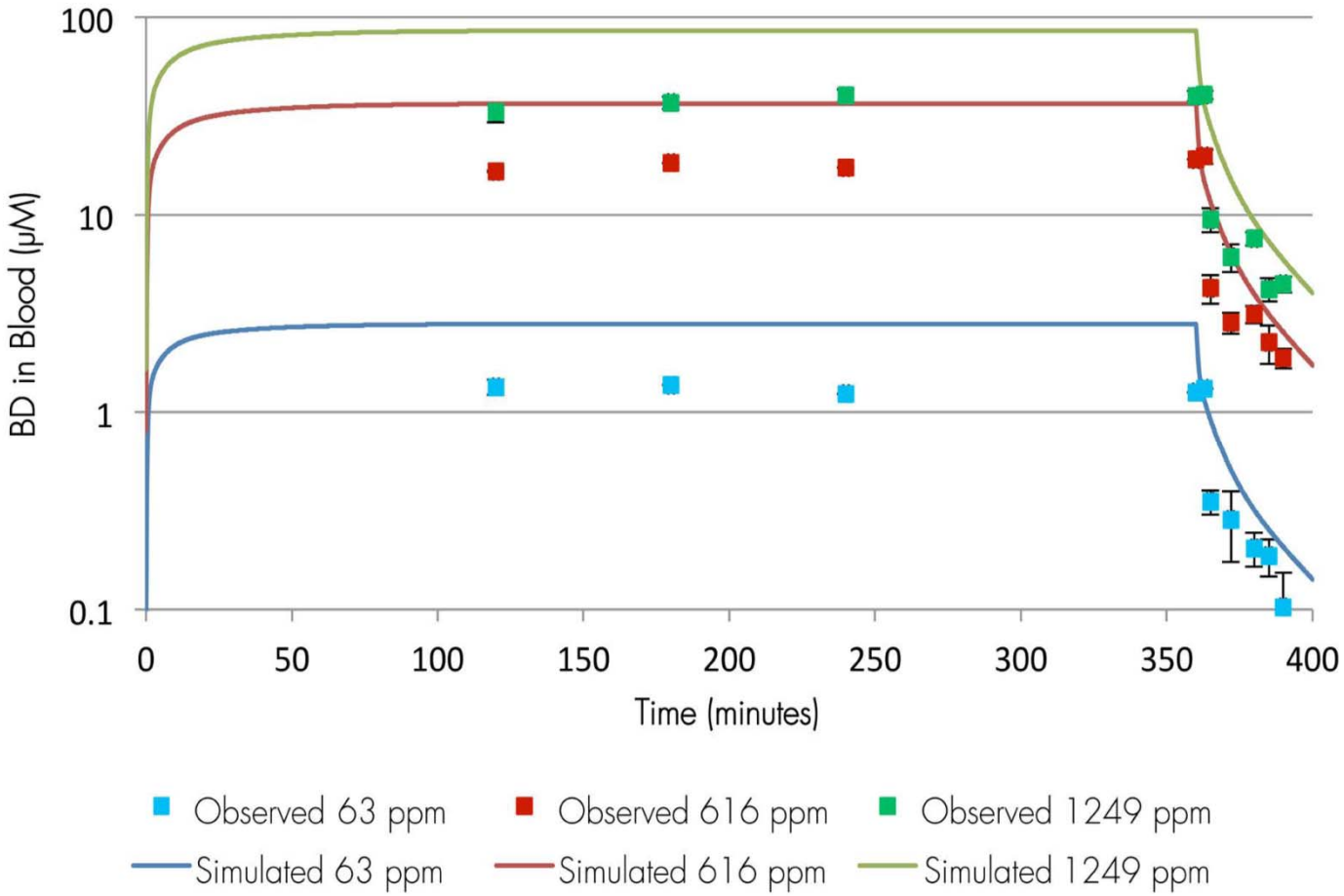
BD concentrations in the blood of Sprague-Dawley rats during and following six hours of inhalation exposure to 63, 616 or 1249 ppm of BD



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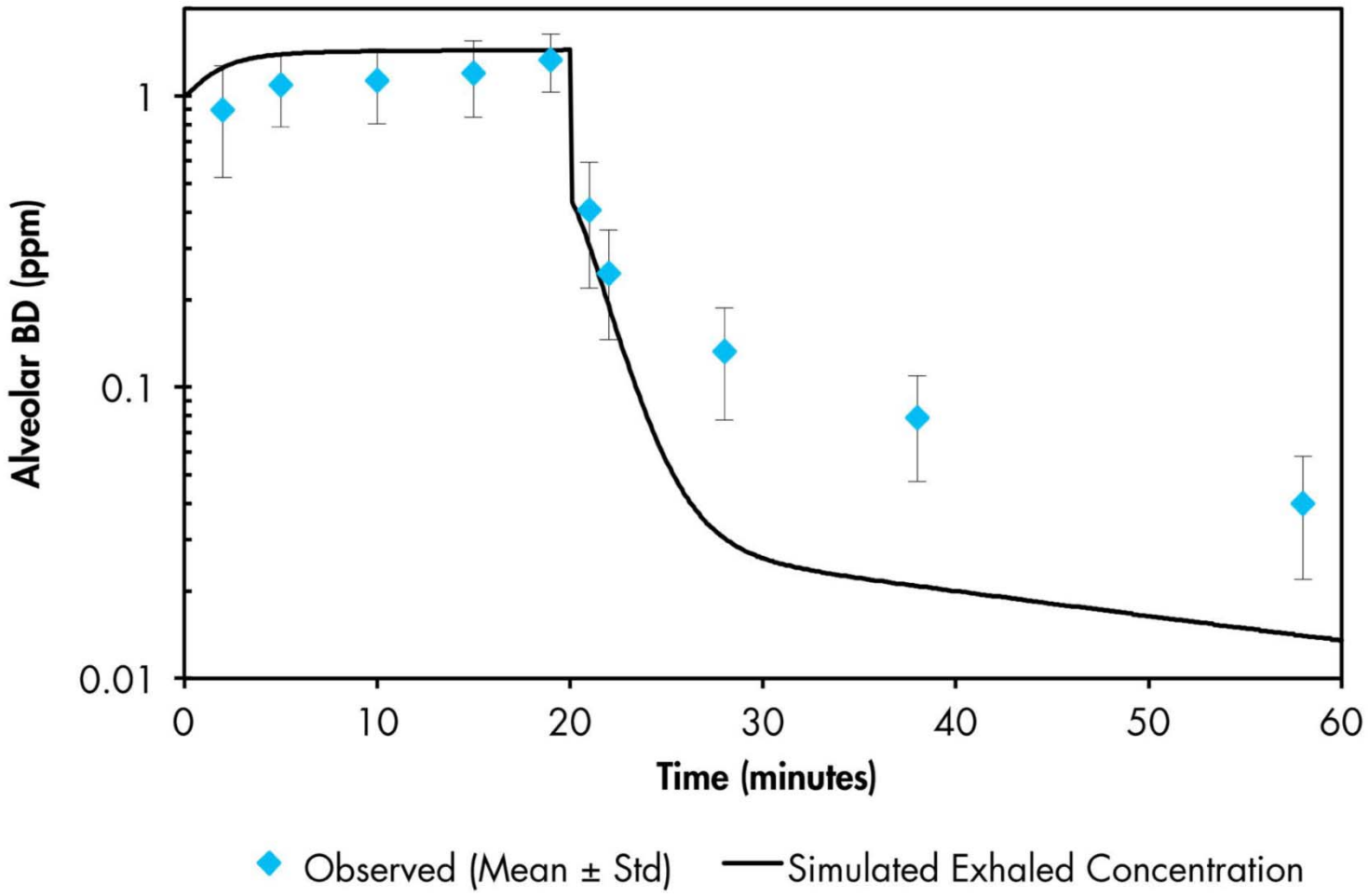
Exhaled concentrations of BD in human subjects (Lin et al. 2001)



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Discussion

- A PBPK model for BD in mice, rats and humans has been developed that includes regional generation of reactive metabolites in the lung as well as in the kidney and liver
- Specific metabolic rate constants for BD and its metabolites measured in enriched Clara cell cultures are needed to refine the pulmonary metabolism parameters
- Additional metabolic pathways of EB are being added to the model to provide a comprehensive description of metabolite concentrations in the blood and tissues and to characterize the urinary metabolites
- Time-course information on BD metabolite concentrations in rodent and human urine will be used to further refine the parameterization and to evaluate model predictions of BD and metabolite dosimetry for long-term exposures

References

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