Technical Comment on PBPK Model and MOA RfD Derivation

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Commenting on behalf of the American Chemistry Council

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Acknowledgement

- Comments offered on behalf of the Chlorine Chemistry Division of the American Chemistry Council

Overview

- Need for detailed QA/QC on quantitative work presented in document
- Quantitative issues with PBPK model predictions
- Interspecies sensitivity differences for consideration in MOA analysis

Annotated Table 5-21

These rows were added to review to document some of the intermediate steps in the review of values.		These columns were added present rat whole blood concentrations corresponding to NO(A)EL, LO(A)EL, and modeled BMDLs			Lifetime Human Equivalent Doses (HED) yielding lifetime (LT) and peak 5-yr (5YR) average blood concentrations (from Appendices C.4.1 and C.4.2, respectively) equal to rat whole blood concentrations from columns A, B, and C				
		Rat whole blood concentrations from BMD input Tables (Appendix H.1) and BMD results (Appendix H.2). Page references in italics.							
Key event	Endpoint and exposure duration	NO(A)EL (ng/kg) A	LO(A)EL (ng/kg) B	BMDL[a] (ng/kg) C	NO(A)ELHED (ng/kg-day)	LO(A)ELHED (ng/kg-day)	BMDLHED[a] (ng/kg-day)	RfD[b] (ng/kg-day)	Study
Liver tumors									
Changes in gene expression	CYP1A1 mRNA, 1 day	1E-02 *p. H-2*	1.1E-01 *p. H-2*	1.68E-01 *p. H-27* BMR in BMDS output does not correspond to 1 SD	1.8E-05 5.6E-05 (LT) 2.8E-05 (5YR)	3.4E-04 1.2E-03 (LT) 7.4E-04 (5YR)	2.3E-03 (Appendix H) 2.3E-03 (LT) 1.4E-03 (5YR) Lifetime model apparently used for 1 day rat study	8E-13[c,d]	Vanden Heuvel et al. (1994, 594318)
Changes in gene expression	Benzo(a)pyrene hydroxylase (BPH) activity (CYP1A1), 1 day	6E-02 *p. H-1*	2E-01 *p. H-1*	4.9E-01 *p. H-10*	9.2E-04 5.3E-04 (LT) 3.0E-04 (5YR)	6.0E-03 3.0E-03 (LT) 1.9E-03 (5YR)	4.6E-04[e,f] (Appendix H) 1.1E-02 (LT) 7.7E-03 (5YR)	3E-11[c,d]	Kitchin and Woods (1979, 198750)
	EROD (CYP1A1), 53 weeks Liver	none *p. H-2*	2.48 *p. H-2*	9.351E-02 *p. H-22*	none	1.4E-01 1.3E-01 (LT) 1.0E-01 (5YR)	9.5E-03[f] (Appendix H) 9.5E-04 (LT) 5.0E-04 (5YR) Footnote "c" indicates poor BMD fit, but Appendix H.2.5 does not support that.	3E-10[d]	NTP (2006, 197605)
Oxidative stress	DNA single-strand breaks, 90 days	none *p. H-1*	1.94 *p. H-1*	9.1655E-01 *p. H-7* SDs transcribed incorrectly from study into BMD Input Table H.1.1, so BMR does not correspond to 1 SD from study	none	3.3E-02 9.1E-02 (LT) 7.0E-02 (5YR)	2.2E-03 (Appendix H) 2.9E-02 (LT) 2.1E-02 (5YR) Footnote "c" indicates poor BMD fit, but Appendix H.2.2 does not support that.	7E-12	Hassoun et al. (2000, 197431)
	TBARS, 90 days	1.94 *p. H-1* Incorrectly noted as "LOAEL" in Table H.1.1	4.61 *p. H-1*	1.737E+00 *p. H-14* SDs transcribed incorrectly from study into BMD Input Table H.1.1, so BMR does not correspond to 1 SD from study	- 9.1E-02 (LT) 7.0E-02 (5YR)	- 3.4E-01 (LT) 2.7E-01 (5YR)	4.4E-02 (Appendix H) 7.7E-02 (LT) 5.9E-02 (5YR)	2E-09[f]	Hassoun et al. (2000, 197431)
	Cytochrome C reductase, 90 days	4.61 *p. H-1*	6.15 *p. H-1* LOAEL incorrectly identified in Table H.1.1	3.1E+00 *p. H-3* SDs transcribed incorrectly from study into BMD Input Table H.1.1, so BMR does not correspond to 1 SD from study	- 3.4E-01 (LT) 2.7E-01 (5YR)	- 7.8E-01 (LT) 6.3E-01 (5YR)	8.8E-02 (Appendix H) 1.9E-01 (LT) 1.5E-01 (5YR)	3E-09[f]	Hassoun et al. (2000, 197431)
Hepatotoxicity	Toxic hepatopathy, 2 years	none *p. E-10*	2.56 *p. E-10*	3.06 *p. E-195*	none	1.4E-01 1.4E-01 (LT) 1.1E-01 (5YR)	1.8E-01 (Appendix E) 1.8E-01 (LT) 1.4E-01 (5YR) Footnote "c" indicates poor BMD fit, but Appendix E.2.39 does not support that.	5E-09 5E-10 (UF of 30 was apparently applied instead of UF of 300 as indicated by footnote f)	NTP (2006, 197605)
	Hepatocyte hypertrophy, 31 weeks Modeled data are from 2 yr time point	none *p. E-10* All dose groups are significant.	2.56 *p. E-10*	7.9E-01 *p. E-191*	9.3E-02 none	3.3E-01 1.4E-01 (LT) 1.1E-01 (5YR)	8.8E-03 (Appendix E) 2.3E-02 (LT) 1.7E-02 (5YR) Appendix E.2.35 suggests model fit is inadequate so footnote "c" should be applied.	3E-10[f]	NTP (2006, 197605)
Hepatocellular proliferation	Labeling index, 31 weeks	none *p. H-2*	2.33 *p. H-2*	3.13 *p. H-33*	none	1.4E-01 1.2E-01 (LT) 9.4E-02 (5YR)	6.6E-02[f] (Appendix H) 1.9E-01 (LT) 1.5E-01 (5YR)	2E-09[f]	NTP (2006, 197605)
Lung tumors									
Metabolic enzyme induction	EROD (CYP1A1), 53 weeks Lung	none *p. H-2*	2.48 *p. H-2*	5.91E-02 *p. H-26*	none	1.4E-01 1.3E-01 (LT) 1.0E-01 (5YR)	2.6E-[illegible] (Appendix H) 5.2E-04 (LT) 2.9E-04 (5YR) Footnote "c" indicates poor BMD fit, but Appendix H.2 does not support that.	1E-11[f]	NTP (2006, 197605)
Retinoid homeostasis	Hepatic retinol and retinyl palmitate, 90 days	none *p. E-13*	7.20 *p. E-13*	3.38 (retinol) *p. E-234* 3.65E+01 (retinyl palmitate) *p. E-241*	none	1.1E+00 6.5E-01 (LT) 5.2E-01 (5YR)	1.7E-[illegible] (Appendix E) 2.1E-01 (LT) 1.7E-01 (5YR) (retinol) 6.1E+00 (LT) 5.0E+00 (5YR) (retinyl palmitate)	5E-09[f]	Van Bingelen et al. (1995, 197452)

Quantitative Issues with PBPK Model

- CYP1A2 Induction Dose-Response Curve
- Fat:Blood Partition Coefficient
- Comparison of Model Predictions to Key Data Set

CYP1A2 Induction Dose-Response

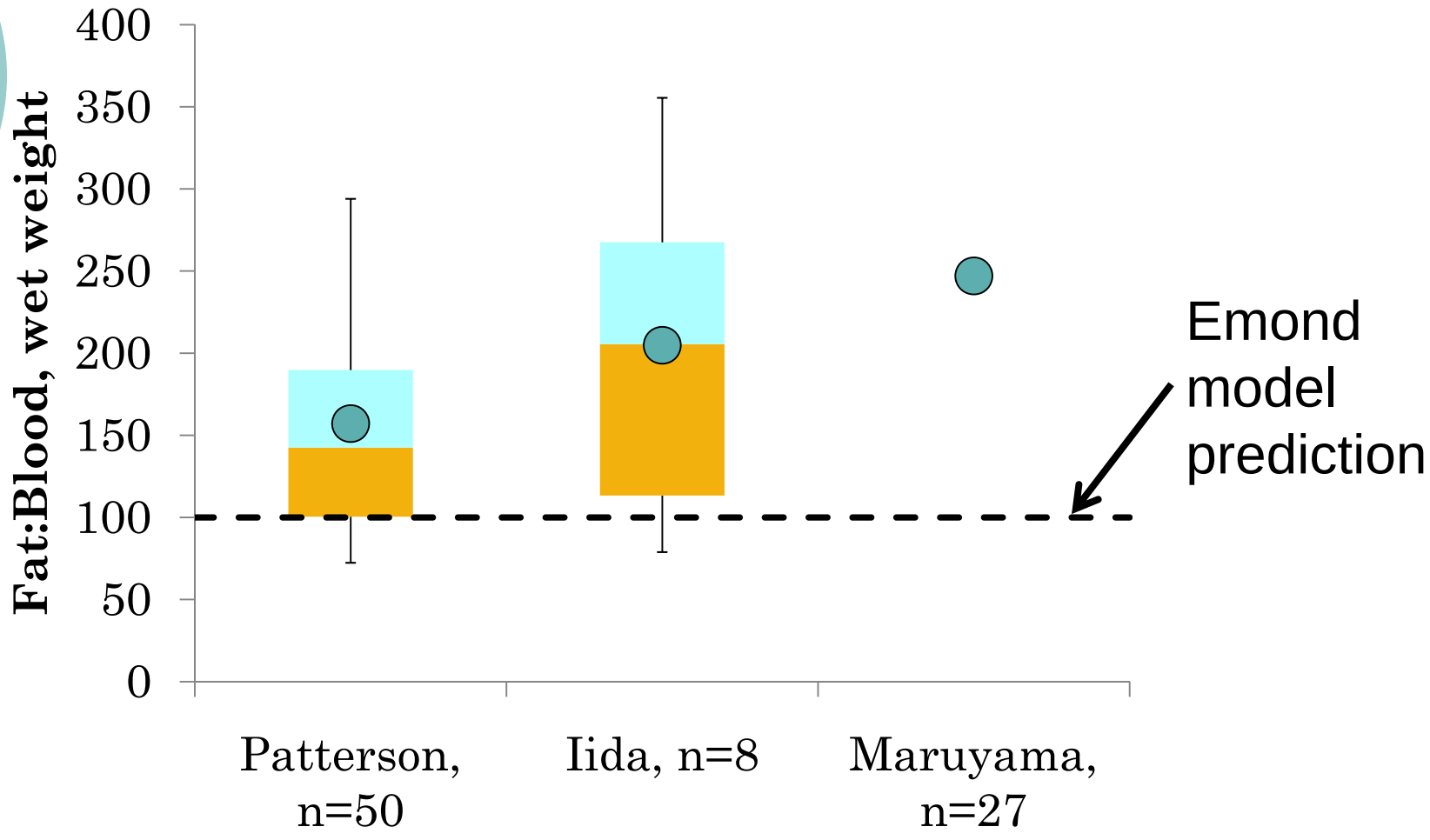
- As noted at July SAB meeting, Hill coefficient of 0.6 used in model without data support
- High quality *in vivo* dataset is available:

Characterization of the Dose–Response of CYP1B1, CYP1A1, and CYP1A2 in the Liver of Female Sprague–Dawley Rats Following Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

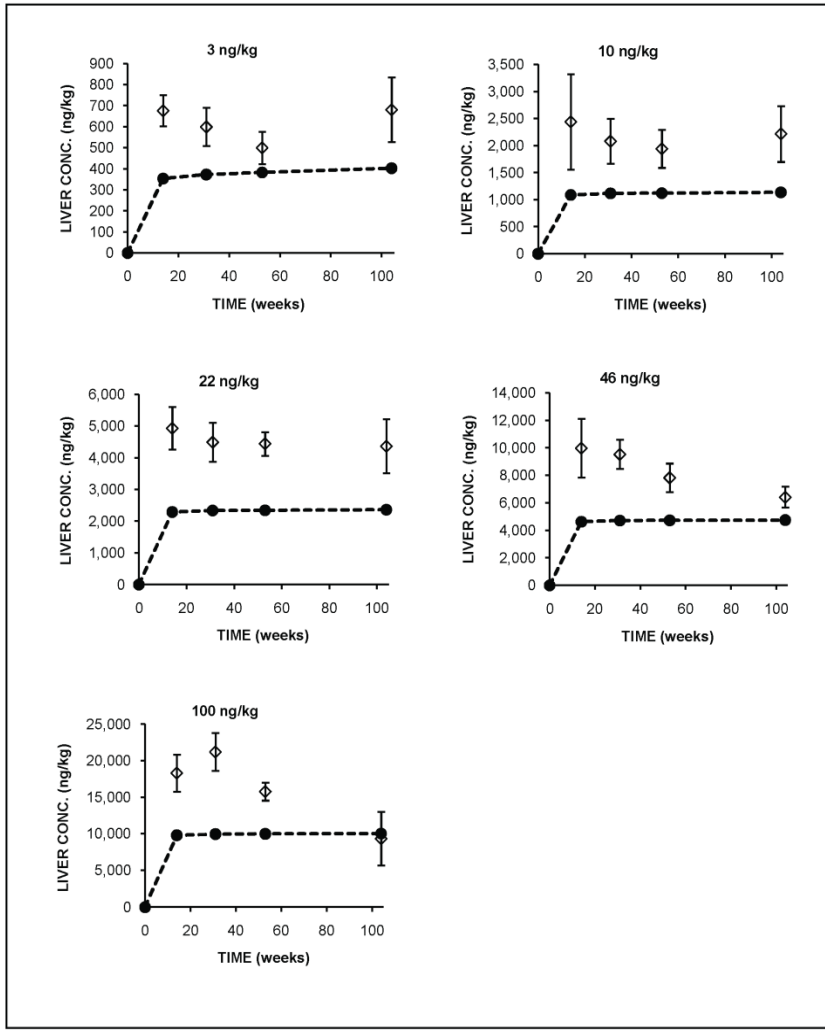
Nigel J. Walker,[*,1] Christopher. J. Portier,[*] Sigurd F. Lax,[†] Frances G. Crofts,[‡] Ying Li,[‡] George W. Lucier,[*] and Thomas R. Sutter[‡,1]

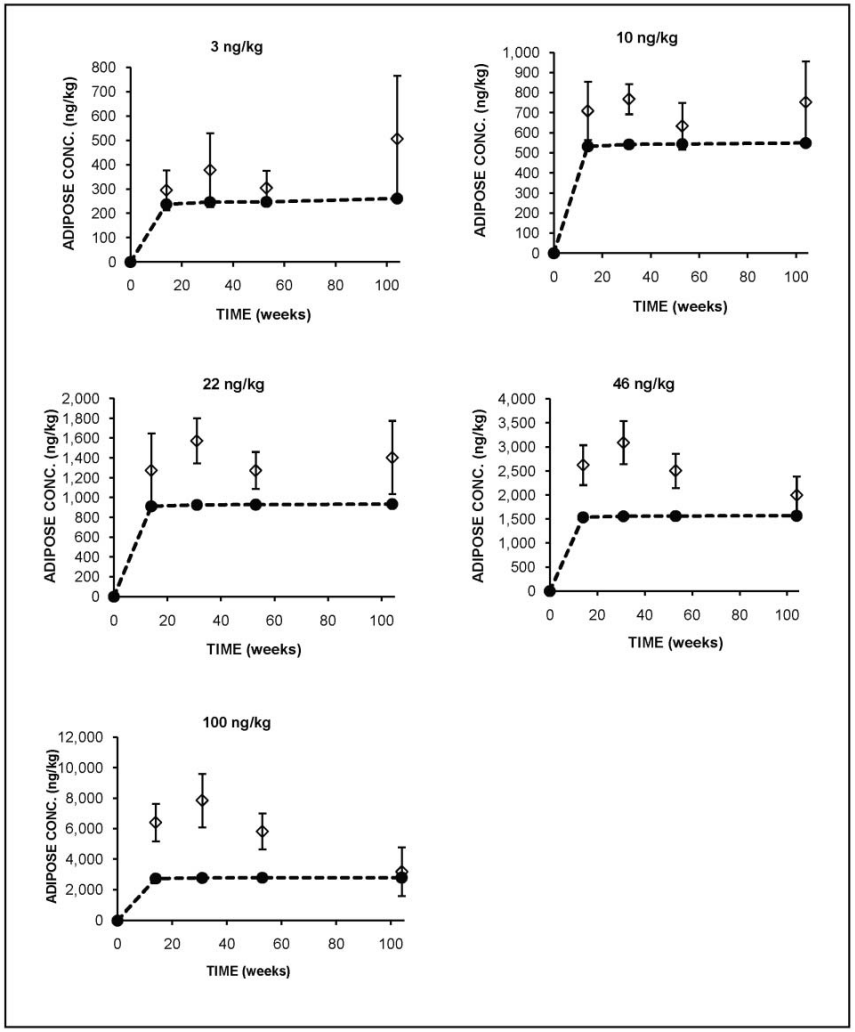
- Hill coefficient of 0.94 – affects behavior of model in key low-dose region

Ratio of Fat to Blood Concentrations: Data vs. Model



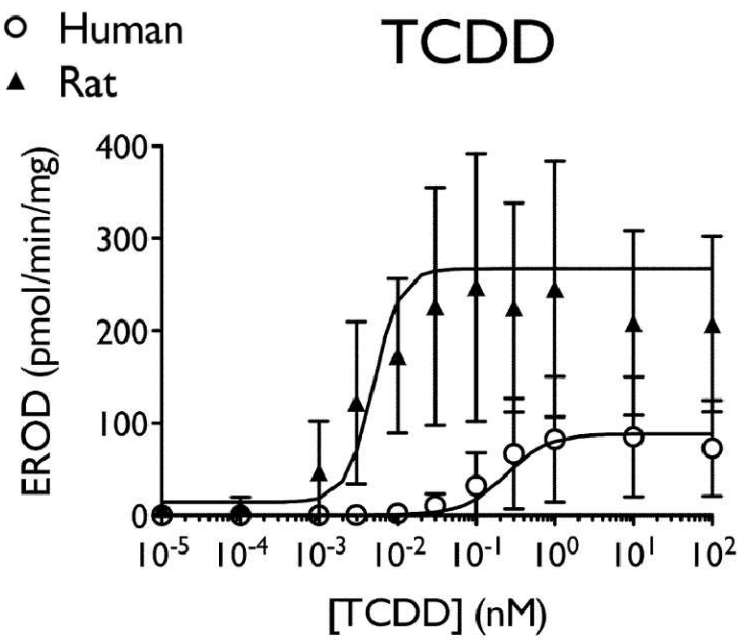
Model Underpredicts Tissue Concentrations in NTP Bioassay





Interspecies Sensitivity: Human Liver Cells Are Less Sensitive than Rat Liver Cells

- Many datasets and clear molecular biology basis (reviewed in Conner and Aylward 2006)
- For early key hepatic MOA events such as CYP1A1 induction, a data-derived interspecies UF_{TD} factor of 1 or less is justified



Budinsky et al. 2010

Thank you for the opportunity to offer comments