Science Forum Partnering to Protect Human Health and the Environment

BETTER EXPOSURE-DOSE MODELS FOR PESTICIDES

James B. Knaak¹, Rogelio Tornero-Velez², Fred Power², Jerry N. Blancato², Curtis C. Dary² ¹State University of New York at Buffalo, NY. ²U.S. EPA, Human Exposure and Atmospheric Sciences Division, Las Vegas, NV

Accounting for Human Variability in the Metabolism of Pesticides: Use of Specific Content of Tissue Enzymes in Exposure-Dose Models

OBJECTIVE

Reduce uncertainties in risk assessment through improved exposure-dose models.

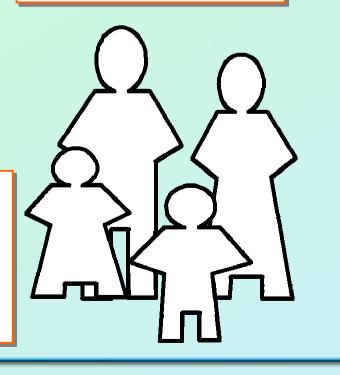
To address this need. physiologically-based pharmacokinetic (PBPK) models are increasingly being used in the evaluation of chemical exposures on human health.

PROBLEM

PBPK models require metabolism parameters to properly estimate tissue dose; however, no single parameter value is universal to all people due to population variability in enzyme levels.

SOLUTION

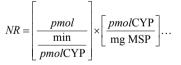
Account for human variability in metabolism in exposuredose model. Establish a tractable relationship between the tissue enzyme content and metabolic activity in the model .



METHODOLOGY

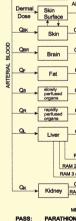
1. Determine the specific metabolic activity (V_{max}, K_m) for each isozyme (e.g., CYPs, PON1).

3. Employ normalized metabolism parameter, based on content of individual CYP isozvmes in the PBPK model.



PBPK Model for Parathion

Described in model: cytochrome P450 isozymes (CYPs) located in the liver catalvze the activation of parathion to paraoxon, the toxic cholinesterase (ChE) inhibiting agent. A-esterases oxonases (PON1), located in brain catalyze the hydrolysis of paraoxon to nontoxic hydrolysis products.



QC, CA Lung

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2.	Determine the specific content of
	CYP isozymes in human liver
	microsomes (<i>pmol</i> / mg MSP).

CYP	HLM-3	HLM-23	HLM-24	HLM-34	HLM-43	HLM-56	AVE
1A2*	7	50	85	77	23	35	46.2
2A6	83	20	56	54	70	30	52.2
2B6*	18	2	7	10	53	4	15.6
2C9	42	74	56	42	80	51	50.5
2C19	9	15	17	8	6	47	17.0
2D6	13	12	16	29	10	4	14.0
2E1	83	52	41	84	28	22	51.6
3A4*	95	38	85	79	306	94	116
3A5	0.9	0.5	0.72	1.00	1.1	0.7	0.82

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4. As we gain more information on the variability of CYPs (and other enzymes) within subpopulations we improve the quality of exposure-dose models in risk assessment and decision-making.

