BETTER EXPOSURE-DOSE MODELS FOR PESTICIDES

Emerging Technologies

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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 exposure-dose model. Establish a tractable relationship between the tissue enzyme content and metabolic activity in the model .
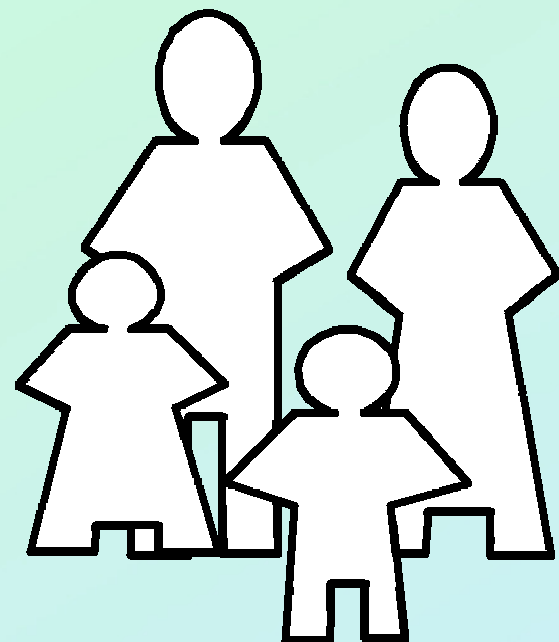
METHODOLOGY

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

2. Determine the specific content of CYP isozymes in human liver microsomes (*pmol* / 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

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

$$NR = \left[\frac{\frac{pmol}{min}}{pmolCYP} \right] \times \left[\frac{pmolCYP}{mg\ MSP} \right] \cdots$$

PBPK Model for Parathion

Described in model: cytochrome P450 isozymes (CYPs) located in the liver catalyze 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.
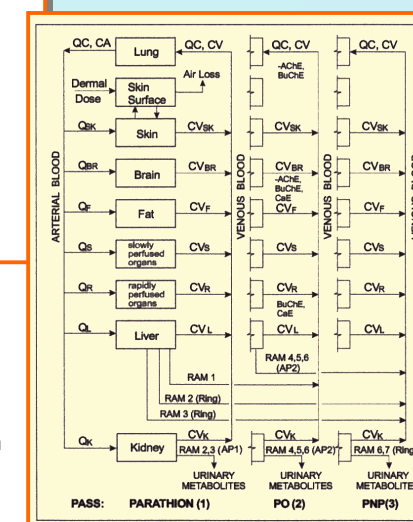
4. As we gain more information on the variability of CYPs (and other enzymes) within subpopulations we improve the quality of exposure-dose models in risk assessment and decision-making.