Physiologically-Based Pharmacokinetic/Pharmacodynamic Modeling and Cumulative Risk Assessment:

Case Study for the N-Methyl Carbamate Pesticides

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Healthy Communities and Ecosystems

Issues: (ORD-66)

While most human health risk assessments are developed for exposure to single agents, real world exposures are generally to multiple agents.

In recognition of this fact, The Food Quality Protection Act requires EPA to consider the potential cumulative risks resulting from aggregate exposure to pesticides acting through a common mechanism of toxicity.

In 2001, EPA established the N-methyl carbamate insecticides as a common mechanism group based on their structural characteristics and their shared ability to inhibit acetylcholinesterase (AChE).

Strategy:

If agents act by a common mechanism of action, then their combined toxicities should be predicted according to relative potency factors (RPFs).

While conventional RPF-based assessments will be done as part of the of cumulative assessment for N-methyl carbamates, PBPK/PD models will aid in these analyses by accounting for anatomical, physiological and biochemical processes that lead to tissue dose and effect (AChE Inhibtion).

This will allow for more accurate and precise estimates of RPFs.

Goals:

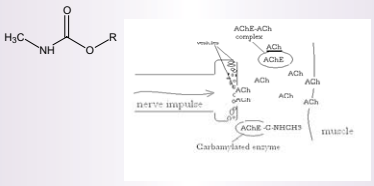
The overall goal of this project is to develop improved methodologies for evaluating and incorporating dose-response information in the cumulative risk assessment of pesticides, particularly N-methyl carbamate insecticides.

These methodologies specifically involve the development of physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models to evaluate the time dependant relationship between exposure and effect, resulting from multi-chemical, multi-pathway exposure.

This research is a collaborative effort between the Office of Pesticide Programs (OPP), The Office of Research and Development (ORD), and CIIT Centers for Health Research.

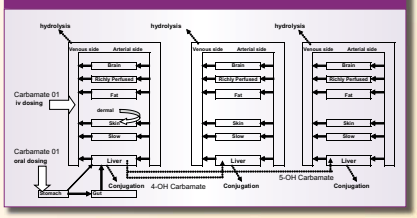
N-Methyl Carbamates

N-Methyl Carbamates

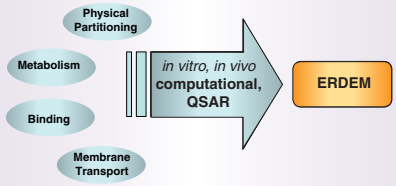


N-methyl carbamates are effective insecticides by virtue of their ability to inhibit AChE in the nervous system. AChE catalyzes the hydrolysis of the neurotransmitter acetylcholine (Ach) to choline and acetic acid.

ERDEM Dose Modeling of the N-Methyl Carbamates for the Cumulative Risk Assessment



Model Parameterization



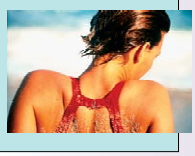
Dermal Absorption

Partition coefficients are used in PBPK/PD models to indicate the transfer of materials (distribution) between skin and blood.

Permeability rate constants, Kp (cm/h) can be determined from the measurement of flux according to following rate equation:

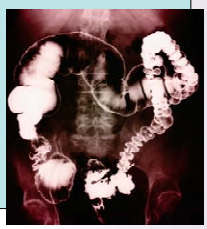
$$Flux = DPC/l = KpC$$

Where C is the concentration gradient of the chemical in skin (g/cm³), l is the thickness of the path length (cm), P is the partition coefficient of the chemical in skin (unitless), D is the diffusion coefficient (cm²/h), and Kp is the permeability constant (cm/h)



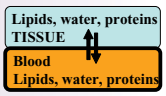
Gastrointestinal Absorption

First order rate constants for the absorption (h^{-1}) of pesticides from the gastrointestinal tract using a two-compartment model describing absorption from the stomach (KaS, h^{-1}) and the intestinal tract (Kal, h^{-1})



Computational approach: tissue:blood partition coefficients

Physical Partitioning

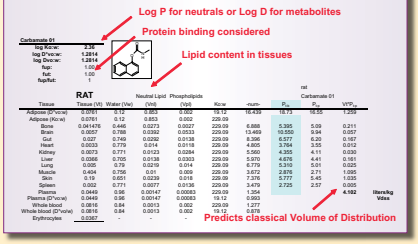


Equilibrium

- Based on LogP (octanol:water)
- Based on distribution of lipids and water in tissues

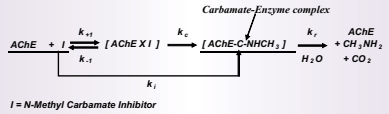
Computational approach: tissue/blood partition coefficients

Physical Partitioning



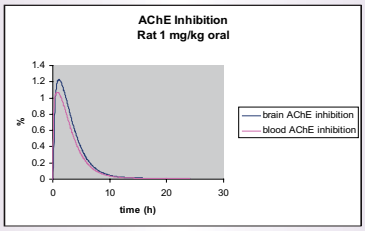
Pharmacodynamic modeling of N-Methyl Carbamates

- N-methyl carbamates inhibit AChE reversibly, so the time component of exposure is relatively more important.
- PBPK/PD models will relate projected exposures to n-methyl carbamates in food, water, and through residential use to AChE inhibition.
- Bimolecular rate constants ki (pM-1 h-1) are used to describe inhibition of the acetylcholinesterase (AChE) by N-methyl carbamates. The rate constants are derived from the reactions of N-Methyl Carbamates (I) with AChE.

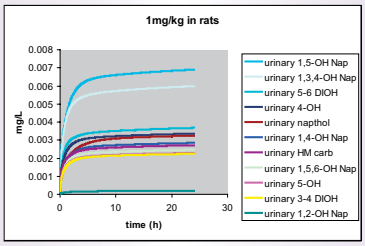


I = N-Methyl Carbamate Inhibitor

ERDEM predicts inhibition of AChE in blood and brain following oral ingestion of an N-methyl carbamate



ERDEM simulates the chemicals in excretion pathways, allowing for interpretation of dose-excretion studies



Summary:

- The goal of this work is to extend our understanding of single and multi-chemical kinetics to improve our understanding and characterization of cumulative risk.
- This research will evaluate assumptions of dose-additivity and potential interactions among n-methyl carbamates through processes such as competition for metabolism (oxidation, hydrolysis) or inhibition of AChE.

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