# ORD Research in Support of the *N*-Methyl Carbamate Cumulative Risk Assessment


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Contributing Organizations: ORD: NHEERL, NCCT, NERL; OPPTS: Office of Pesticide Programs




LTG 2 Poster 04

## Science Question

How do we estimate cumulative risk from aggregate exposures to *N*-methyl carbamate pesticides?

## Research Goals

The Food Quality Protection Act of 1996 introduced the requirement that the Agency conduct joint assessments for pesticides with a common mode of action. Both organophosphates (OPs) and *N*-methyl carbamates (NMCs) inhibit the acetylcholinesterase (AChE) enzyme, thereby disrupting cholinergic nervous system transmission. This action is considered a key step in the toxicity of both classes of pesticides, although the time-course characteristics for these pesticide classes are quite different. EPA/OPP completed its first cumulative risk assessment (CRA) with the OP pesticides in 2002 (reported in the 2005 HHRP BOSC review). The next class of pesticides evaluated was the NMCs (10 pesticides currently on the market). OPP and ORD built on the experience gained with the OP CRA, and as before, ORD provided valuable research and guidance informing OPP's final risk assessment.

The goal and ultimate outcome of this endeavor is a cumulative risk assessment that incorporates the best-possible estimates of risk, employing advanced computational modeling of exposure and dose-response data. In addition, experimental tests of NMC mixtures were included to assess the default assumption of additivity.

NMCs in Cumulative Risk Assessment

| | |
|---|---|
| Aldicarb | Carbaryl |
| Carbofuran | Formetanate HCl |
| Methiocarb | Methomyl |
| Oxamyl | Pirimicarb |
| Propoxur | Thiodicarb |

## Findings and Conclusions

Brain AChE inhibition was selected as the target endpoint for determining relative potency. All NMCs inhibited brain AChE in a dose-related fashion with peak effects ½ to 2 hr after dosing and recovery at 24 hr. While the magnitude of AChE inhibition correlates with functional/behavioral changes, a 10% decrease is expected to be protective.

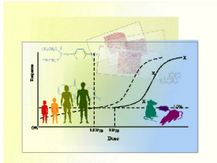
Dose-time-response modeling, which took into account different peak times, indicated greater than 100-fold difference in potencies. When converted as a function of oxamyl (index chemical) dose, a cumulative dose-response based on dose-additivity was determined.

The default assumption of additivity holds for a mixture of 7 NMCs combined on the basis of relative potency. For brain AChE, this is the case following both acute and repeated dosing; motor activity showed less effect with repeated dosing, indicative of tolerance development.

The young are more sensitive to acute effects of certain carbamates, including carbaryl, carbofuran, and aldicarb. This impacts both the individual risk assessments as well as the CRA.

ORD collaborated closely with OPP to produce sophisticated dietary risk assessments that improved the multi-media and multi-pathway exposure and risk assessments for individual chemicals as well as the CRA. Using data for 3 NMCs, ORD demonstrated the use of a composite PBPK/PD model linked to an exposure model, such as SHEDS, for modeling human population risk assessment.

## Methods/Approach

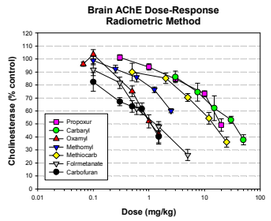


Hazard/RPF Characterization → Cumulative Risk Estimation, Assumptions of Additivity → FQPA 10X Factor → Final Cumulative Risk Assessment

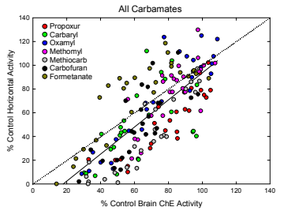
Exposure Characterization → Cumulative Risk Estimation, Assumptions of Additivity

### Experimental Dose-Response Data Informing the Use of Brain AChE for Risk Assessment

- Because rapid reversal of AChE inhibition could underestimate *in vivo* potency, parallel assays were conducted and compared to the registrant-submitted data. For some chemicals, only the EPA dose-response data were sufficient for modeling.

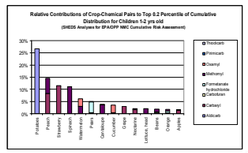


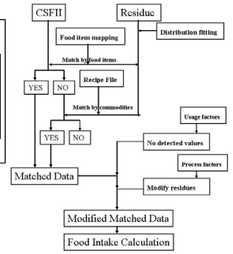

- ORD studies linking AChE inhibition and functional changes – here, decreases in spontaneous motor activity – indicated a clear correlation with brain AChE inhibition.




### Analysis of Dietary and Hand-to-Mouth Exposure Estimates

- ORD's Stochastic Human Exposure and Dose Simulation (SHEDS) model allowed OPP to explore and investigate important longitudinal aspects of dietary consumption. This provided timely dietary exposure sensitivity analyses for OPP risk managers.
- The SHEDS dietary module, which included analyses of eating occasions and food contributors, assisted OPP's aldicarb risk assessment and the NMC CRA.
- Refinements of OPP's children hand-to-mouth exposure algorithm were used to evaluate more realistically exposures from both indoor and outdoor residential uses.

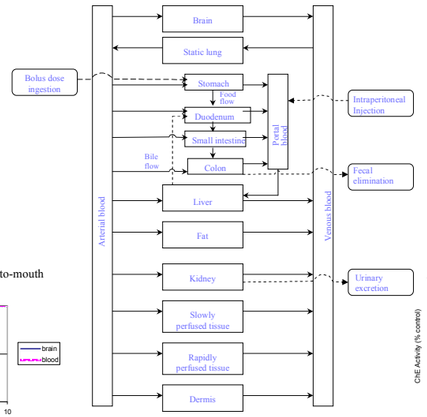



SHEDS dietary module flowchart

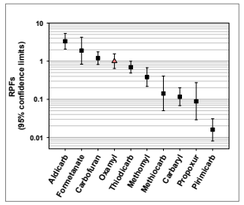
### Cumulative Risk Estimation Using Exposure and Dose Models

- SHEDs models provided population estimates with the exposure timelines for single and multiple days. These estimated potential exposures were used as inputs to a multiple-chemical PBPK/PD model for carbaryl, carbofuran, and aldicarb and 4 related metabolites in a 16-compartment model using ORD's Exposure Related Dose Estimating Model (ERDEM).
- Predictions of RBC and brain AChE activities showed >99.99% of control values for all age and gender groups at the 95th percentile.
- Urinary biomarker concentrations were predicted only at trace levels.
- The PBPK/PD model approach showed an advantage in that exposure scenarios were simulated in a more pharmacologically representative fashion, thus avoiding overestimating cumulative risk from probabilistic exposures.

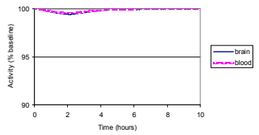



### Dose-Time-Response Modeling of Combined Datasets

- A generalized exponential dose-response model was used to estimate benchmark doses.
- The time course model tested the assumption that inhibition decays exponentially, with half-life independent of dose. When rejected, separate half-lives were estimated for different dose levels.
- Hierarchical modeling was used to combine datasets when possible, and the resulting BMD estimates represent the median of the distribution of BMDs among studies, and the uncertainty incorporates any variation among studies.
- Oxamyl was chosen as the index chemical, based on its robust and high-quality database. Relative potency factors (RPFs) were established for each chemical based on their BMD estimates.

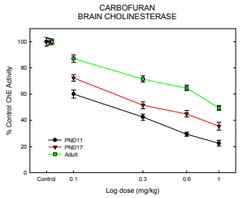



AChE inhibition for the oral hand-to-mouth scenario of carbaryl exposure.



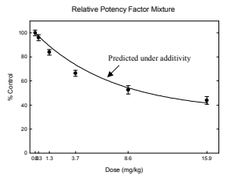

### FQPA 10X Factor for Protection of Infants and Children

- Comparing acute responses of preweanling and adult rats for individual pesticides showed up to about 3-fold increase in sensitivity for aldicarb, carbaryl, and carbofuran.

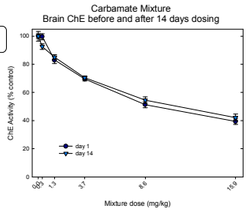


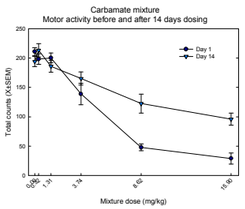

### Testing the Assumption of Dose-Additivity of NMC Mixtures

- A mixture of 7 carbamates combined on the basis of relative potencies showed additivity for brain AChE inhibition (right) as well as motor activity.




- After repeated dosing for 14 days, there was no change in AChE inhibition when compared to the response after a single dose. In contrast, there was less motor activity depression after 14 days.




## Impact and Outcomes

The enhanced science and products of this research helped to reduce uncertainty in risk assessment/ management decisions by:

- Providing OPP with *in vivo* data answering key questions about registrant submitted NMC data, and substantially improving the datasets used for RPF assessments. Dose-time-response modeling of all available data allowed transparent and unambiguous estimates of RPFs and the point of departure and their associated uncertainties.
- Providing OPP with the results of correlative studies supporting the Agency's choice of the point of departure, and confirming the additivity of the RPF mixture of 7 carbamates.
- Providing OPP with dietary data generated by probabilistic analyses of NMC exposures informing the importance of human activities in exposure estimates.
- Providing OPP with age-related data to inform and allow refinement of the FQPA Factor.
- Collaborating with OPP in the establishment of the NMC CRA; the most recent version was issued for public comment in fall 2007 and final revisions are being made.

## Future Directions

- Additional studies have been conducted evaluating the nature of interaction when the NMCs are combined in a ratio that reflects environmental usage, as well as studies to test the assumption of additivity in preweanling rats. Approaches described in poster LTG2-02 and 2-03 are being used to statistically analyze those data.
- The methods and models used in this CRA are being advanced further in the pyrethroid CRA (see posters LTG2-05 and 2-06). Explicit linkages between the SHEDS and PBPK models are being developed to predict target tissue dose, and both *in vivo* and *in vitro* studies are conducted to link tissue dose to effect.

## Researchers Involved

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Cumulative Risk


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