UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

January 19, 2005

MEMORANDUM

Subject: Transmission of Background Materials and Charge to the Panel for
the **Session 1** of February 15-18, 2005 FIFRA Scientific Advisory
Panel on the N-methyl carbamate cumulative risk assessment:
"*Cumulative Hazard Assessment: Issues for the FIFRA SAP*"

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A meeting of the FIFRA SAP is scheduled for February 15-18. This meeting will
focus on issues related to the N-methyl carbamate cumulative risk assessment.
Session 1 (February 15) of this meeting will focus on the paper entitled
"Cumulative Hazard Assessment: Issues for the FIFRA SAP" and associated
appendices.

This memo contains the questions and issues posed by EPA to the panel for discussion. In addition to this memo, several documents and/or supporting files are provided:

1. "Background document for the FIFRA Scientific Advisory Panel: N-Methyl Carbamate Cumulative Risk Assessment: Pilot analysis"
2. "Cumulative Hazard Assessment: Issues for the FIFRA SAP"
3. Appendix 1. General Protocol for the Acute Time Course and Dose-Response Studies of the Individual Carbamate Pesticides in Adult Male Rats
4. Appendix 2. Time course and dose-response plots for seven *N*-methyl carbamates
5. Appendix 3. Computational details for the empirical dose-time-response and simple PK risk assessment models
6. Appendix 4. R Source code for the simple pharmacokinetic risk assessment model example
7. Executable file: CarbUtils_1.0
8. Executable file : RAexample1.R

CHARGE AND QUESTIONS TO THE PANEL:

Issue 1.1:   Laboratory method for measuring cholinesterase inhibition

As discussed in the paper (Cumulative Hazard Assessment: Issues for the FIFRA SAP), in toxicology studies performed for pesticide registration, typically, acetylcholinesterase (AChE) inhibition is measured used modified Ellman, spectrophotometric methods (Ellman et al, 1961). Scientists at EPA's National Health and Environmental Effects Research Laboratory (NHEERL) have performed a series of time course and dose-response studies (Appendices 1 and 2) with seven *N*-methyl carbamate pesticides. These studies have compared radiometric and spectrophotometric methods following acute dosing in rats. EPA has provided plots of these studies along with plots of dose-response data from single dosing rat studies submitted for pesticide registration (Appendix 2). Prior to the completion of these studies, there was a concern that studies submitted to EPA for pesticide registration may underestimate relative potency. Specifically, using spectrophotometric methods, recovery of inhibition can occur prior to analysis if the proper precautions are not taken in the laboratory.

Statistical analyses evaluating results of the radiometric data generated by EPA and the spectrophotometric data reported by registration studies have not been performed. However, in general, based on visual observation of these plots (Appendix 2), there appears to be good concordance, particularly at doses at or near 10% inhibition, between the results of studies submitted for registration purposes where spectrophotometric methods were used and the results of studies performed by EPA where radiometric analyses performed. Nostrandt *et al.* (1993) have previously shown that modified Ellman assay gave answers comparable to the radiometric assay if some special precautions were taken. EPA does not know the exact conditions used in various laboratories performing registration studies. However, it appears that the AChE data provided in the registration studies are sufficient quality for evaluating relative potency. .

Question 1.1 Please comment on EPA's observations regarding the results of radiometric studies conducted by NHEERL and the results of studies submitted for pesticide registration.

Issue 1.2: **Empirical modeling of AChE Data**

Part A. Benchmark dose calculations:

In the EPA's cumulative risk assessment of the organophosphorus pesticides (OPs), a decreasing exponential model was used to develop benchmark dose estimates. The FIFRA SAP previously endorsed this approach (FIFRA SAP, 2001 & 2002). EPA plans to use again use a decreasing exponential model in its benchmark dose estimates for the *N*-methyl carbamate pesticides, with the addition of a component to model the time course of AChE inhibition. This model was provided in the Eqs. 1 – 4 and the associated text (See Cumulative Hazard Assessment: Issues for the FIFRA SAP and Appendices 3-4).

Question 1.2a. Please comment on the appropriateness of using the model provided in Equations 1 – 4 to calculate benchmark dose estimates based on cholinesterase inhibition for the N-methyl carbamate pesticides.

Part B. Simple pharmacokinetic model

As discussed in the background document prepared for the FIFRA SAP, EPA is committed to improving methodologies and approaches for conducting cumulative risk assessments. To this end, EPA has begun development a simple, pharmacokinetic (PK) based approach for incorporating recovery of cholinesterase inhibition in risk estimates. The simple PK model is more sophisticated than conventional relative potency approaches but less data-intensive than physiologically-based pharmacokinetic/ pharmacodynamic approaches and thus provides a pragmatic method for considering PK and/or mechanistic information in risk estimates. There are still, however, limitations to the application of this approach for the *N*-methyl carbamate cumulative risk assessment—namely, the capability for cumulative exposure models to output distributions of exposure (in mg/kg or similar units) to individuals. Given this limitation, EPA continues to pursue practical methods for improving risk assessment methods. It is unclear at this time the degree to which this simple PK approach may be used in the cumulative risk assessment for the *N*-methyl carbamate pesticides. However, as EPA continues to work towards to improving its risk assessment methods, EPA is requesting comment from the FIFRA SAP regarding aspects of the development and application this simple PK approach.

Question 1.2.b Please comment on the simplifying assumptions used in the simple PK approach to predicting cholinesterase inhibition. Please include in your comments whether these assumptions tend to underestimate or overestimate potential risk. These assumptions are:.

- *The inhibitor is cleared quickly from the target tissue, so that recovery time mostly depends upon the rate of decarbamylation of AChE.*
- *Competition among multiple inhibitors for AChE or clearance pathways is quantitatively insignificant.*
- *Inhibitors do not modify the affinity of AChE for other inhibitors (e.g., by binding to a site on the AChE molecule that has allosteric effects), or such effects are quantitatively insignificant.*
- *It is appropriate to ignore resynthesis of new AChE molecules in the time frame of interest (1 – 6 hours).*
- *The model for effects in humans can be calibrated by scaling parameters of models fit to rodent data.*

Question 1.2c EPA historically has utilized (default) uncertainty factors for interspecies and intraspecies extrapolation. EPA's issue paper (and related appendices 3-4) suggests that application of the simple, PK approach to estimation of risk provides an opportunity to consider probabilistic methods in uncertainty analysis for cumulative hazard assessment. Please comment on biological and quantitative factors which may be important for consideration in the event probabilistic methods were to be used to perform uncertainty analysis in cumulative hazard assessment.