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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

January 19, 2005

MEMORANDUM

Subject: Transmission of Background Materials and Charge to the Panel for the February 18, 2005 (Session 4) FIFRA Scientific Advisory Panel Entitled "The *N*-methyl Carbamate Cumulative Exposure Assessment: A Case Study of 10 *N*-Methyl Carbamates"

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The February 15-18, 2005 FIFRA SAP meeting on the *N*-methyl Carbamate Cumulative Risk Assessment is the second in a series of SAP meetings planned by EPA to discuss various aspects of the *N*-methyl carbamate cumulative risk assessment. The first meeting held on December 4, 2004 involved the review of a white paper entitled "Designing Exposure Models that Support PBPK/PBPD

Models of Cumulative Risk" developed by the LifeLife Group Inc (LLG). This February 2005 meeting will highlight four important topics:

- **Session 1:** Hazard assessment: laboratory method for measuring acetylcholinesterase (AChE) inhibition and empirical modeling of AChE inhibition and recovery data

- **Session 2:** Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK/PD) modeling for carbaryl

- **Session 3**: Groundwater exposure models

- **Session 4**: Exposure assessment: Pilot case study of the *N*-methyl carbamate exposure assessment.

This transmittal letter concerns Session 4 of this FIFRA SAP meeting entitled "The *N*-methyl Carbamate Cumulative Exposure Assessment: A Case Study of 10 *N*-Methyl Carbamates." In support of this session scheduled for February 18, 2005, two documents in addition to this transmittal memorandum are being provided to members of FIFRA Scientific Advisory Panel

1. Background of EPA Activities Related to the *N*-Methyl Carbamate Risk Assessment.

2. Estimation of Cumulative Exposure from *N*-Methyl Carbamate Pesticides: A Case Study of 10 *N*-Methyl Carbamates.

The background document is common to all sessions and is designed to provide the members of the FIFRA Scientific Advisory Panel and the public with a brief historical summary of cumulative risk assessment as mandated by the Food Quality Protection Act of 1996 (FQPA); summarize the identification of the *N*-methyl carbamate cumulative assessment group; and provide a general framework and context for the development of the cumulative risk assessment for this group of pesticides. The Case Study document provides an example analysis which focuses on the science associated with conducting a cumulative exposure assessment for the *N*-methyl carbamate class of pesticides. As such, pesticide names are coded and identities are disguised.

Charge and Questions to the Panel:

1 There are several key principles for conducting a cumulative risk assessment. One such principle concerns the time frame of both the exposure (e.g., When does exposure occur? What is the exposure duration?) and of the toxic effect (e.g., What are the time to peak effects and the time to recovery? How quickly is the effect reversed?). Both should be adequately considered when performing a cumulative risk assessment so that an individual's exposure is matched with relevant and appropriate toxicological values in terms of duration and timing. There are several important considerations with respect to the temporal characteristics of the exposures and of the cholinesterase inhibitory effects of N-methyl carbamate pesticides in estimating their cumulative risk.

OPP used a Relative Potency Factor (RPF) approach in this case study which is based on cholinesterase inhibition data from acute dosing studies performed in the rat. A similar approach was used in the organophosphorus pesticide cumulative risk assessment several years ago. This RPF approach expresses toxicity of each chemical in terms of “index chemical equivalents”. In this approach, all exposure events within a day are adjusted by their RPFs and summed. The three exposure models (DEEM/Calendex, LifeLine, and CARES) used in the case study express exposure as a distribution of 1 day (24 hour totals) exposures within a population.

Since AChE inhibition caused by the NMCs recovers rapidly (minutes to hours), it might be important to consider the intra-day timing of exposure events. Specifically, if the exposure events within a day are distributed sufficiently far apart in time so that significant recovery of AChE inhibition occurs between any two exposure events, then summing exposures over 24 hours might overestimate the risk associated with AChE inhibition. For example, if an individual consumed 200 mL of apple juice in the early morning, an additional 200 mL during the afternoon, and another 200 mL late at night, this could present a very different risk picture than if the total 600 mL were presumed to be consumed at one time.

The current FCID database and the DEEM/Calendex, LifeLine, and CARES models are set up to consider food consumption on a per day (rather than per eating occasion) manner. Thus, the exposures reported in this case study reflect daily (24 hour) exposures. To the extent that a day’s eating occasion events leading to high (total) daily exposure are close together in time, the RPF approach described in the case study provides reasonable estimates of risk. To the extent that eating exposure events leading to high total daily exposures are widely separated in time such that recovery of AChE inhibition occurs, the risks under the RPF approach in

this case study may be overstated and a more sophisticated approach which accounts for intra-day eating patterns might be more appropriate.

OPP has investigated the degree to which high-end exposures can be attributed to specific eating occasions (within a day) that occur either closely spaced in time or widely separated by time by looking at the actual individual consumption events as reported in the CSFII. Specifically, OPP has looked at the CSFII –based dietary records for individuals at several locations in the upper end of the exposure distribution to determine the extent to which these daily high-end exposures can be attributed to a single eating event, several eating events spaced closely in time (over several hours), or eating events widely separated by time (more than several hours). As described in Section IV.H of the case study document, OPP found that that a sizable fraction of daily records contributing to the upper tail of the food exposure distribution represent single eating occasions. Assuming that subsequent, more detailed and extensive analyses provide confirmation of these preliminary observations and analyses, OPP believes and that it is unlikely that any more sophisticated, temporal-based approach which better accounts for temporal separation of eating/exposure events will result in substantial or significant changes in OPP's risk estimates.

QUESTION:

Part A. EPA requests the SAP provide comments on this exploratory analysis with respect to its adequacy and appropriateness. Please also provide suggestions for future, more detailed analyses.

Part B. Given the results of the initial exploratory analysis, EPA believes that a more sophisticated time-based intra-day model (e.g., PBPK in which the timing of intra-day eating events is explicitly incorporated) for exposures through the food pathway would not substantially change the assessment of potential risks through this pathway compared to the results produced using the RPF methodology used in the case study in which 24 hour food consumption data is used. Please explain why you agree or disagree.

2. A key concept that is unique to cumulative risk assessments is the concept of co- occurrence of residues (and thus co- or simultaneous exposure) to members of the Common Assessment Group (CAG). Specifically, a cumulative assessment must appropriately consider residues which co-occur in time and space since these exposures must by combined and considered jointly. This is true for exposures through the food pathway, the drinking water pathway, and the residential pathway.

The USDA's PDP data program uses multi-analyte methods and thus simultaneously measures co-occurrent residues in samples. The generated drinking water concentrations from the PRZM-EXAMS model considered regional NMC use and usage practices and thus implicitly considered co-occuring residues.

Exposures through the residential pathways can also co-occur. One of the unique aspects of the NMC cumulative exposure assessment is the use of the Residential Exposure Joint Venture (REJV) data provides current information on co-occurrent use patterns for residential exposure. The US EPA National Home and Garden Pesticide Use Survey (NHGPUS) can also be used to develop residential use profiles. The PDP, PRZM-EXAMS, and REJV/NHGPUS data were used, to varying degrees, in this case study.

QUESTION:

Please comment on the use of the pesticide use/usage data (e.g., REJV and NHGPUS) to account for co-occurring use patterns in assessing residential exposures.

The data sources and methodologies used in the N-methyl carbamate case study are similar in many respects to the data sources and methodologies used in the Cumulative Risk Assessment for the OP pesticides. For example, in both assessments the evaluation of exposure of the food pathway relied to a great extent on the USDA's PDP data, the evaluation of exposure through the water pathway used PRZM-EXAMS modeling data, and the evaluation of exposure through the residential pathway used standard SOP algorithms along with label information, professional judgments, literature values, and survey data (REJV, NHGPUS).

QUESTION:

Please comment on the data sources used in the cumulative exposure assessment and on how EPA has considered and incorporated the data. Does the SAP have any suggestions or recommendations regarding additional available data sources that EPA may wish to investigate?