Background Document for FIFRA Scientific Advisory Panel

"The N-methyl Carbamate Cumulative Risk Assessment: Strategies and Methodologies for Exposure Assessment"

December 3, 2004
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Arlington , VA

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I. Purpose

This document provides the members of the FIFRA Scientific Advisory Panel (SAP) and the public with background material and a brief historical summary of cumulative risk assessment for the December 3, 2004 FIFRA Scientific Advisory Panel (SAP) meeting. The document discusses the general framework for the development of the cumulative risk assessment for the N-methyl carbamate group of pesticides, summarizes the procedures used to identify the N-methyl carbamate cumulative assessment group, and describes anticipated "next steps" for the carbamate cumulative risk assessment. The document is designed to provide the regulatory context for the white paper entitled "Designing Exposure Models that Support PBPK/PBPD Models of Cumulative Risk" developed by the LifeLife Group Inc (LLG).; EPA is committed to the continual improvement of tools and methodologies available for developing risk assessments; the concepts discussed in this background document and the accompanying white paper are an important component in promoting further progress in the development of methods to evaluate cumulative risk.

The December 3, 2004 meeting of the FIFRA SAP is the first of what will be several meetings concerning the development of a cumulative risk assessment for the N-methyl carbamate class of pesticides. A second meeting of the SAP is anticipated to occur in February 2005 and will include a "case-study" example for which advice is sought by the Agency on several issues concerning the N-methyl carbamate cumulative risk assessment. The anticipated content of this February SAP is discussed and detailed in Attachment 1 of this document.

II. Brief History: Cumulative Risk Under the FQPA

In assessing the potential health risks associated with exposure to pesticides, EPA's attention has historically focused on single pathways of exposure (e.g., pesticide residues in food, water, or residential/ nonoccupational uses) for individual chemicals, and not on the potential for individuals to be exposed to multiple pesticides by all pathways (and routes) concurrently. In 1993, a report by the National Research Council (NRC) made several recommendations on how to improve the assessment of health risks posed by pesticides in the diets of infants and children (NRC, 1993). One recommendation included consideration of all sources of dietary and non-dietary exposures to pesticides and assessment of risks from exposure to multiple pesticides that cause a common toxic effect. The NRC publication provided an example for five organophosphorus pesticides.

Several years after the publication of the NRC report, Congress passed FQPA in 1996 which instructed EPA to base its assessment of the risk posed by the pesticide chemical on aggregate (i.e., total food, drinking water, residential, and other non-occupational) exposure to the pesticide; FQPA also required EPA

to consider available information concerning the combined toxic effects to human health that may result from dietary, residential, or other non-occupational exposure to chemicals that have a common mechanism of toxicity (i.e., cumulative risk). OPP has developed a guidance document for developing cumulative risks assessments under FQPA (USEPA, 2002a). This guidance document states that cumulative risk assessments differ from the single-chemical aggregate risk assessments both in focus and intent and that the objectives of a CRA are to:

- ❑ Define the characteristics of the exposure to a group of chemicals that act by a common mechanism of toxicity
- ❑ Estimate multichemical, multipathway risks reflecting real-world exposure to pesticides, including the changing patterns of residue levels as they relate to differences in location, time, and co-occurrence
- ❑ Identify significant contributors to risk
- ❑ Characterize the confidence in the conclusions and the uncertainties encountered in the assessment
- ❑ Facilitate a greater understanding of the potential results of changes in pesticide uses and possible mitigation activities.

Based on the above guidance and principles, OPP released the revised cumulative risk assessment for the organophosphorus pesticides (OP) in June 2002 (USEPA 2002b). In this assessment, OPP developed and demonstrated in detail the methods and parameters that should be considered in estimating cumulative risk associated with common mechanism pesticides by multiple pathways of exposure. Various aspects of the hazard and dose-response assessment and the exposure analyses were presented to both the SAP and the public for comment numerous times over the course of several years. Both the SAP and the public provided helpful and insightful comments and ideas which were incorporated into the revised documents. OPP is currently developing a cumulative risk assessment for the N-methyl carbamate class of pesticides. The SAP meeting scheduled for December 3, 2004 is the first in a series of scientific peer reviews expected for the cumulative risk assessment of the N-methyl carbamate pesticides.

III. Cumulative Risk Assessment of the N-Methyl Carbamates

A. Overview of Activities to Date

1. Determining the Common Mechanism Group

The first step of producing a cumulative risk assessment is to identify a group of chemicals that produce a common toxic effect(s) by a common mechanism of toxicity. OPP has developed a general framework for identifying the chemicals that belong to that group (USEPA, 1999). The cumulative guidance states that, in determining this common mechanism group (CMG), careful attention should be given to a variety of factors including the mechanism of toxicity, the time dimensions of the toxic effects and exposure, and the pesticide exposure patterns and treatment scenarios. Thus, assessing the potential for two or more carbamate pesticides to act by the same mechanism involves the consideration of three principles: 1) they cause the same critical effect(s); 2) they act on the same molecular target at the same target tissue; and 3) they act by the same biochemical mechanism of action perhaps because they share a common toxic intermediate (Mileson, 1998). OPP found that the three principles were met for the ChE-inhibiting carbamates and judged that cholinesterase (ChE) inhibition was a scientifically accepted mechanism of action for the carbamates which provides a sufficient basis for determining a common mechanism of toxicity for grouping carbamate pesticides (USEPA, 1999b).

Thus, OPP concluded that the pesticides that comprise the subgroup of N-methyl carbamates, based on their structural characteristics and similarity and their shared ability to inhibit acetylcholinesterase by carbamylation of the serine hydroxyl group located in the active site of the enzyme, should be designated as a CMG (USEPA, 2001).

2. Determining the Cumulative Assessment Group

Once the chemical members of a CMG are identified, a necessary follow-on step in assessing the cumulative risk of a common mechanism group (here, the N-methyl carbamates) involves selecting a subset of these CMG chemicals as a Cumulative Assessment Group (CAG). As the risk assessor proceeds with the cumulative assessment, it is important to determine candidate chemicals and uses, routes, and pathways from the CMG that may cause cumulative effects. As described in the Cumulative Guidance (USEPA 2002a), this subset of CMG

chemicals is selected because not all chemicals grouped by common mechanism of toxicity should necessarily be included in a quantitative cumulative risk assessment. For example, initial cumulative assessments should not attempt to quantify risk resulting from chemicals with low hazard potential or from minor exposure scenarios, but should instead focus on those chemicals that are likely to be risk contributors. Specifically, the CAG–and consequently the cumulative risk assessment–should exclude those chemicals, those chemical uses, and those exposure scenarios/routes/pathways for which risk and exposure does not contribute in any meaningful or substantive ways to the total cumulative risk picture[1]. Although a chemical(s) may be removed from the quantification of risk, the rationale for such decisions should be transparently explained. Thus, all chemicals that were grouped by a common mechanism of toxicity should be accounted for (qualitatively or quantitatively) in the final assessment

OPP began the process of determining the members of the CAG by identifying those carbamates which contained the N-methyl structural moiety[2]. OPP then further narrowed the list of the potential CAG-candidates by reviewing OPP databases to determine those CMG members that have active food or residential registrations. Those carbamates which have neither food nor residential (non-food) current registrations were eliminated from further consideration for inclusion in the CAG.

Next, OPP investigated the presence, pattern, and magnitudes of residues in the USDA's Pesticide Data Program (PDP) database through 2002. Those chemicals for which PDP did collect residue data but did not detect any residues were eliminated from consideration from the CAG if there were no residential uses. No chemicals were excluded from the CAG as a result of this analysis. Finally, those chemicals that are currently undergoing phase-out or cancellation were removed from the CAG. As was done with the OP assessment, chemicals currently undergoing phase-out or cancellation are not included in the CAG since exposures are expected to be zero at some point in the near future.

[1] As stated in the Cumulative Guidance , "This focus on likely risk contributors is important ... since a large number of chemicals may increase the complexity and uncertainty with no substantial change in total exposure. (USEPA, 2002b).

[2] Some exceptions were made as described in additional detail in the Federal Register Notice. For example, formetanate hydrochloride was included in this group due to its mode of action rather than its structural similarity to the N-methyl carbamates.

Based on the above information, OPP's final corrected and updated proposed list of N-methyl carbamates which OPP expects to include in the cumulative risk assessment for the carbamate pesticides is as follows:

Aldicarb/Aldoxycarb
Carbaryl
Carbofuran
Formetanate HCl
Methiocarb
Methomyl
Oxamyl
Pirimicarb
Propoxur
Thiodicarb

These carbamates all display ChE-inhibiting activity, have current active registrations, and are expected to contribute to the carbamate cumulative risk assessment through quantitatively meaningful exposure scenarios.

B. On-Going Activities

OPP is currently working with EPA's Office Research and Development to develop the cumulative hazard assessment using different approaches.

1. Empirical dose-response modeling

Work is on-going at the National Health and Environmental Effects Research Laboratory (NHEERL) to develop use empirical approaches to develop Relative Potency Factors (RPFs) using blood and brain ChE-inhibition data from rat toxicology studies. As the mechanism of action for this group is AChE inhibition followed by rapid recovery, this work also entails quantitative modeling of the available data for recovery of ChE-inhibition. In the RPF approach, the toxic potency of each chemical is first determined. The determination of toxic potency should, to the extent feasible with available data, be conducted on a uniform basis (i.e., same measure of potency, for the same effect, from the same test species/sex using studies of comparable methodology). To determine relative potency, a chemical from the CAG is selected to serve as the index chemical. The index chemical is used as the point of reference for standardizing the common toxicity of the other chemical members of the CAG.

2. Physiologically-Based Pharmacokinetic Model Based Approach

In addition to the empirical dose-response modeling described above, the cumulative guidance (USEPA, 2002a) describes other methods including the use of physiologically-based pharmacokinetic/dynamic modeling (PBPK/PD). As discussed in the cumulative guidance, the level of refinement for each cumulative risk assessment will depend on several factors; specifically included among these is the availability of adequate and appropriate data for the particular common mechanism group of interest.

The FIFRA SAP has previously encouraged OPP to consider using PBPK/PD models (FIFRA SAP 2001, 2002) in developing cumulative risk assessments. In December 2003, EPA discussed with the FIFRA SAP aspects of a draft strategy for including PBPK/PD modeling into its cumulative risk assessment. Key issues included in the December 2003 review included the key data needed to support parameterization of a PBPK/PD model and the basic structure for a multi-chemical model appropriate for the N-methyl carbamate pesticides. This common mechanism group has been identified as good case study for the application of PBPK/PD modeling into cumulative risk assessment.

PBPK/PD models are data and resource intensive. Very few PBPK models have been used by EPA's IRIS program (Integrated Risk Information System), and OPP has not used such models to support pesticide registration (or for developing cumulative risk assessments). Scientists from OPP and ORD's National Exposure Research Laboratory (NERL) are collaborating on the multi-chemical-PBPK/PD case study in order to gain experience for developing a PBPK/PD model that is sufficiently robust for regulatory purposes. OPP is developing this case study in a stepwise manner and soliciting scientific peer review at each stage. In this way, the learning and development process is transparent and open to public evaluation and participation. With this case study, EPA can identify critical needs and begin the process of filling these so that in the future the necessary tools may be both available and operational. Tolerance reassessment, including the cumulative risk assessment for the N-methyl carbamates, must be completed by August 2006. *Given the early stage of development of these models, it is not known to what extent the PBPK model can be used for cumulative risk assessment of the N-methyl carbamates.*

Two of the immediate critical needs that OPP has identified for development and use of these models are the generation of pharmacokinetic data for the pesticides or pesticide classes of interest and the development a “link” or interface between the models currently in use in OPP designed to provide exposure estimates and the PBPK/PD models currently being developed by ORD and others. These two data needs are discussed in more detail below.

Pharmacokinetic Data

Pharmacokinetic (PK) and pharmacodynamic (PD) data provide the basis for the development and evaluation of any PBPK/PD model. OPP has systematically evaluated the availability of PK and PD data for the N-methyl carbamates and has determined that for the majority of N-methyl carbamates the databases are not sufficiently complete for developing compound specific PBPK/PD models. PK studies typically submitted to OPP for purposes of pesticide registration were designed to evaluate absorption, distribution in tissues and organs, metabolism and elimination in fluids and excreta. The study protocols, however, were not specifically designed to obtain parameter values needed for developing robust PBPK/PD models. For example, sample collection is typically not targeted or specified to obtain blood/tissue partition coefficients or kinetic rates of metabolism or AChE inhibition for particular chemicals that may be identified with the critical metabolic pathways, or mechanisms of action. Instead, the guidelines are designed to account for fractional absorption, distribution of mass equivalents in tissue, and specific identity of major metabolites in fluids and excreta. In addition, the guidelines require absorption, distribution, metabolism, and elimination (ADME) studies be initially performed only for the oral (gavage) route of administration. Dermal absorption studies are only conditionally required. Ideally, oral, dermal and intravenous pharmacokinetic studies are needed to quantitatively distinguish between the kinetics of distribution, metabolism, and excretion from the kinetics of each absorption route. Lastly, radiometric measurements of tissue concentrations are not sufficient to identify the specific metabolites that would constrain the parameter values associated with chemical ADME. Therefore, mass balance of parent chemical and metabolites in tissues must be inferred from excretion data as mass equivalents remaining.

Although relevant PK data are not available for most of the N-methyl carbamates at this time, key data are available for carbaryl. As discussed in Use of Pharmacokinetic data to Refine

Carbaryl Risk Estimates from Oral and Dermal Exposure (USEPA, 2004), metabolism studies specifically designed for purposes of evaluating pharmacokinetics and for developing a PBPK/PD model have been recently performed for the single chemical (aggregate) assessment of carbaryl. These metabolism and pharmacokinetic studies were proposed by Bayer CropScience in the December 2003 and completed by September 2004 following consultation with OPP. The studies included evaluation of internal dose of carbaryl following oral, intravenous, and dermal exposures in rats using low and high doses. These studies are not discussed in detail here but instead are the subject of a separate FIFRA SAP review scheduled to occur on December 2, 2004. The carbaryl pharmacokinetic studies provided valuable information regarding internal dose(s) and temporal aspects of metabolism and excretion not available from the typical toxicology studies or typical guideline metabolism studies. As shown by the completion of four separate studies within nine months, pharmacokinetic data can developed quickly compared to other typical toxicology studies such as sub-chronic and chronic studies

Exposure Assessment Models

Another critical need identified by OPP regarding the use of PBPK/PD models in a regulatory setting is the linkage or interface between exposure assessment and PBPK/PD model(s). Typical probabilistic exposure models such as LifeLine, CARES, and DEEM/Calendex estimate distributions of exposure for exposure scenarios identified by the model user. For a variety of reasons including computational speed, memory and storage limitations, and perceived utility, the output of these models are typically expressed as distributions of exposure estimates for specified populations instead of specific, exhaustive, or detailed exposure information about each individual in the exposure simulation. In addition, the models are populated by data that is often grouped or summarized in some way or presented in such that necessary details are less readily extracted. For example, the three exposure models in current use by OPP (Lifeline, CARES, and DEEM/Calendex) use consumption data derived from the Food Commodity Intake Database (FCID) which summarizes exposures through food on a daily time-step basis, not on a smaller time step which is more relevant for PBPK modeling of the (short-lived) N-methyl carbamates. In addition, some models only save a fraction of the output records since storage, speed, memory, and other considerations prohibit saving all records from every day of every individuals life. An important advantage of using PBPK and PBPK/PD models is the capability of estimating internal

exposure(s) (or internal dose) and/or potential toxic effects following environmental exposures. PBPK/PD models, as indicated above, can account for dynamic biological processes such as absorption, distribution, metabolism, and excretion which may be occurring simultaneously depending upon the exposure history of the individual being considered and the toxicological and other characteristics of the chemical being considered. These models can estimate temporal aspects of internal dose(s) at the target site(s). In order to take advantage of the capabilities of PBPK/PD models, the format and content of output from exposure assessment models must be amenable to inputting information directly into PBPK/PD models. In other words, the output from the exposure assessment models needs to include specific, detailed information about individuals (e.g., sex, age, body weight) in addition to their exposure and behavior patterns (e.g., timing of eating events, timing of outdoor and indoor activities). By including this detailed information, the PBPK/PD model can appropriately estimate the temporal aspects of internal exposures or internal doses and the potential toxic outcome for different population groups.

This issue—the linkage between exposure assessment and PBPK/PD models---is the topic of the current SAP review and the topic of the conceptual paper developed by the LifeLine Group entitled "Designing Exposure Models that Support PBPK/PBPD Models of Cumulative Risk."

3. Developing Exposure Scenarios

Finally, detailed exposure scenarios for all of the uses remaining for each pesticide in the CAG are developed. This includes determination of potential human exposures by all relevant pathways, durations, and routes that may allow simultaneous exposures, or any sequential exposures among the CAG members that could contribute to the same joint risk of the common toxic effect (i.e., either by overlapping internal doses or by overlapping toxic effects). The framework for estimating combined exposures is based on exposure to individuals, representing differing attributes of the population (e.g., human activity patterns, place of residence, age) that link pathways/route of exposure through scenario building. Cumulative risk values for a given common toxic effect are calculated separately for each exposure route and duration and then combined. To the extent data permit, the temporal and spatial linkages should be maintained for the many factors defining a possible individual exposure. A decision must be made on the relative importance of scenarios and the need for their inclusion in a

quantitative assessment, as well as on the populations of interest and locations for evaluation in the assessment. The potential for co-occurrence of possible exposure scenarios is evaluated. Spatial, temporal, and demographic considerations are major factors in determining whether a concurrent exposure is likely to occur. In other words, all exposure events need to occur over a specific interval of time; events need to agree in time, place, and demographic characteristics; and an individual's dose needs to be matched with relevant toxicological values in terms of route and duration.

4. Next Steps

As described in detail in Attachment 1 (Overview of Topics for February 2005 FIFRA SAP meeting), EPA is planning to solicit additional comment from the SAP regarding specific topics related to the cumulative risk assessment for the N-methyl carbamates such as hazard assessment, PBPK/PD modeling for carbaryl, groundwater modeling, and the integration of hazard and exposure. The preliminary cumulative risk assessment for this group of pesticides is expected to be available to public in the summer of 2005.

IV. Summary

In 1996, passage of the Food Quality Protection Act (FQPA) imposed OPP the requirement to consider potential human health risks from all pathways of dietary and non-dietary exposures to more than one pesticide acting through a common mechanism of toxicity. At each step in the development of its cumulative risk assessment guidance and methodology, OPP has solicited scientific peer review. In 2001, EPA established the N-methyl carbamate pesticides as a common mechanism group based on their structural characteristics and also similarity and shared ability to inhibit acetylcholinesterase (AChE) by carbamylation of the serine hydroxyl group located in the active site of the enzyme. In early 2004, EPA announced the members of the CAG for the N-methyl carbamate pesticides. At this time, work is on-going to develop the cumulative risk assessment for this group of pesticides. EPA is committed to advancing the methodologies and approaches used in its cumulative risk assessments. The December 3, 2004 SAP meeting is the first in a series of meetings to solicit scientific peer review on different aspects of the cumulative risk assessment for the N-methyl carbamates. EPA believes that incorporation and use of pharmacokinetic and mechanistic-based modeling approaches will help refine and improve cumulative risk assessments. The current review of the issues discussed in the white paper developed by the LifeLine Group is a key step in the development of such approaches.

V. References

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