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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: November 5, 2004

SUBJECT: Transmission of Background Materials and Charge to the Panel for the Session of the December 2, 2004 FIFRA Scientific Advisory Panel Entitled "Use of Pharmacokinetic Data to Refine Carbaryl Risk Estimates from Oral and Dermal Exposure".

TO: Joe Bailey, Designated Federal Official,
Office of Science Coordination and Policy
Scientific Advisory Panel (7201M)

FROM: Kit Farwell, D.V.M., Toxicologist; Jeff Dawson, Risk Assessor
Health Effects Division (7509C)
Office of Pesticide Programs

THRU: Jeff Herndon
Acting Director, Health Effects Division (7509C)
Office of Pesticide Programs

Attached are the document entitled, "Use of Pharmacokinetic Data to Refine Carbaryl Risk Estimates from Oral and Dermal Exposure", charge to the FIFRA Scientific Advisory Panel (SAP), and supporting appendices.

The Food Quality Protection Act of 1996 requires EPA to reassess all previously approved pesticide tolerances by August 2006. As part of the reassessment process, EPA's Office of Pesticide Programs (OPP) has completed the Phase 5 risk assessment for carbaryl which incorporates public comments and error corrections from the registrant, Bayer CropScience.

The carbaryl registrant, Bayer CropScience, has proposed an approach using pharmacokinetic data to refine carbaryl exposure estimates from oral and dermal exposure.

Appendices:

Appendix 1

E-file name: **Bayer proposal.pdf**

Application of carbaryl pharmacokinetic data in the estimation of potential post-application health risks associated with broadcast lawn care products. Ross, J; Driver, J; Lunchik, C. Bayer CropScience. September 8, 2004. 40 pages.

Appendix 2

E-file name: **Bayer metabolism study.pdf**

Metabolism of [^{14}C] Carbaryl in Rats. Krolski, et al. Bayer CropScience. May 7, 2004. 230 pages.

Appendix 3

E-file name: **Bayer mixed-dose study.pdf**

Metabolism and Pharmacokinetics of [^{14}C] Carbaryl in Rats Following Mixed Oral and Dermal Exposure. Krolski, et al. Bayer CropScience. May 7, 2004. 53 pages.

Appendix 4

E-file name: **MOE_Derivation_HtM_EPAScenario_10Jun04.xls**

Spreadsheet for calculation of plateau brain concentrations, Bayer CropScience.

Appendix 5

E-file name: **Proposed Path in Rats.pdf**

Charge to the Panel:

This section has the questions the Agency wishes the Panel to consider pertaining to the use of pharmacokinetic data to refine carbaryl exposure estimates from oral and dermal exposure.

Charge Question 1 - Design of Pharmacokinetic Studies:

A series of pharmacokinetic and metabolism studies were completed that serve as the basis for the proposed approach associated with childrens' exposure to carbaryl after lawn treatments. These studies included dosing rats via several routes (i.e., oral, dermal, and intravenous). In a subsequent study, carbaryl was administered to rats via the oral and dermal routes simultaneously at exposure levels similar to those calculated in the Agency's deterministic exposure assessment for toddlers playing on treated lawns.

(A) Please comment on the design of these experiments with respect to the usefulness of results to estimate peak tissue levels for risk assessement purposes.

(B) The design of the multi-route study was intended to mimic the concurrent oral and dermal exposures of toddlers playing on treated lawns. Please comment on this approach.

Charge Question 2 - Pharmacokinetic Approach:

Historically, risk assessments completed by the Agency have been based on comparison of endpoints associated with total administered dose levels from toxicology studies with daily human exposure. The proposed pharmacokinetic approach presented in this paper instead relies on the use of peak internal dose at the target tissue. Because of the rapid pharmacokinetics and pharmacodynamics of carbaryl, a more appropriate dose metric may be the use of peak target tissue levels for calculating exposure estimates instead of total daily absorbed dose values.

(A) Please comment on the appropriateness of using peak levels for estimating exposure.

(B) This pharmacokinetic approach assumes that toddlers put their hands in their mouths at a rate of 20 times an hour for 2 hours. A laboratory dosing regimen that exactly mimics this toddler behavior is impractical. As such, oral doses were administered in the multi-route rat study once per hour for 2 hours. The proposed approach uses an algorithm to adjust the results for 2 hourly bolus doses to that of a toddler which occurs 20 times per hour. Given the rapid metabolism of carbaryl, please comment on whether this algorithm can be reasonably used to predict the expected pharmacokinetic behavior of carbaryl.

(C) To convert the four 24-hour time periods in the biomonitoring study to a shorter time period and to account for plateau tissue concentrations, Bayer proposed extrapolating results from the rat mixed-dose study to the biomonitoring study in this manner. Because the margin-of-exposure calculated using estimated plateau brain concentrations was approximately 20-fold greater than the margin-of-exposure calculated using EPA's SOPs For Residential Exposure Assessment, Bayer proposed multiplying results from the biomonitoring study by an adjustment factor of 20. Please comment on whether this approach is appropriate for extrapolating from results in the rat pharmacokinetic study to the biomonitoring study.