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

OFFICE OF
PREVENTION, PESTICIDES AND TOXIC
SUBSTANCES

March 6, 2008

MEMORANDUM

SUBJECT: Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held February 5-8, 2008 on the Agency's Proposed Action under FIFRA 6(b) Notice of Intent to Cancel Carbofuran

TO: Debbie Edwards, Ph.D.
Director
Office of Pesticide Programs

FROM: Sharlene R. Matten, Ph.D.
Designated Federal Official
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

THRU: Steven Knott, Executive Secretary
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

Elizabeth Resek
Acting Director
Office of Science Coordination and Policy

Attached, please find the meeting minutes of the FIFRA Scientific Advisory Panel open meeting held in Arlington, Virginia on February 5-8, 2008. This report addresses a set of scientific issues being considered by the Environmental Protection Agency's proposed action under FIFRA 6(b) Notice of Intent to Cancel Carbofuran

Attachment

cc:

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Steven Bradbury
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OPP Docket

FQPA Science Review Board Members

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Audra Stinchcomb, Ph.D.

SAP Minutes No. 2008-02

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

The Agency's Proposed Action Under FIFRA 6(b) Notice of Intent to Cancel Carbofuran

February 5-8, 2008
FIFRA Scientific Advisory Panel Meeting
held at the
Environmental Protection Agency Conference Center
Arlington, Virginia

NOTICE

These meeting minutes have been written as part of the activities of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP). The meeting minutes represent the views and recommendations of the FIFRA SAP, not the United States Environmental Protection Agency (Agency). The content of the meeting minutes does not represent information approved or disseminated by the Agency. The meeting minutes have not been reviewed for approval by the Agency and, hence, the contents of these meeting minutes do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

The FIFRA SAP is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of FIFRA as amended by the Food Quality Protection Act (FQPA) of 1996. The FIFRA SAP provides advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the Environmental Protection Agency, Office of Pesticide Programs (OPP), and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. FQPA Science Review Board members serve the FIFRA SAP on an ad hoc basis to assist in reviews conducted by the FIFRA SAP. Further information about FIFRA SAP reports and activities can be obtained from its website at http://www.epa.gov/scipoly/sap/ or the OPP Docket at (703) 305-5805. Interested persons are invited to contact Sharlene R. Matten, Ph.D., SAP Designated Federal Official, via e-mail at matten.sharlene@epa.gov.

In preparing these meeting minutes, the Panel carefully considered all information provided and presented by EPA, as well as information presented in public comment. This document addresses the information provided and presented by EPA within the structure of the charge.

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The Agency's Proposed Action Under FIFRA 6(b) Notice of Intent to Cancel Carbofuran

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FIFRA Scientific Advisory Panel Meeting
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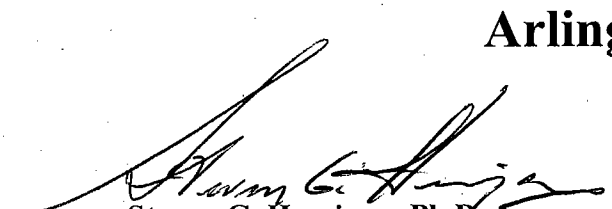
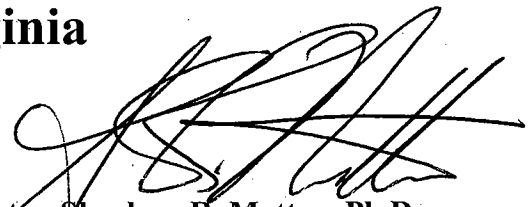


Steven G. Heeringa, Ph.D.
FIFRA SAP Chair
FIFRA Scientific Advisory Panel

Date: MAR 6 2008



Sharlene R. Matten, Ph.D.
Designated Federal Official
FIFRA Scientific Advisory Panel Staff
Date: MAR 6 2008

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
February 5-8, 2008

The Agency's Proposed Action Under FIFRA 6(b) Notice of Intent to Cancel Carbofuran

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INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed its review of **The Agency's Proposed Action Under FIFRA 6(b) Notice of Intent to Cancel Carbofuran.** Advance notice of the SAP meeting was published in the *Federal Register* on **November 20, 2007**. The review was conducted in an open panel meeting February 5-8, 2008 held in Arlington, Virginia. Dr. Steven G. Heeringa chaired the meeting. Dr. Sharlene R. Matten served as the Designated Federal Official. Dr. Debbie Edwards, Director, Office of Pesticide Programs (OPP), provided opening remarks at the meeting. Dr. Steven Bradbury, Director of the Special Review and Reregistration Division, OPP, provided an overview of the goals and objectives for the meeting. Jude Andreasen provided an introduction and background of the carbofuran regulatory history. Dr. Donald Brady, Director of the Environmental Fate and Effects Division provided an overview of the carbofuran ecological risk issues to be considered. Jack Housenger, Associate Director of the Health Effects Division provided an overview of the carbofuran human health risk issues to be considered. Presentations of technical background materials were provided by Dr. Edward Odenkirchen, Dr. Melissa Panger, and Dr. Christopher Salice of the Environmental Fate and Effects Division, OPP and by Dr. Anna Lowit and Dr. Elissa Reaves of the Health Effects Division, OPP. Additional technical clarifications by EPA were provided by Dr. Woodrow Setzer (EPA-Office of Research and Development (ORD)-National Center for Computational Toxicology (NCCT) and Dr. Viginia Moser, EPA-ORD-National Health and Environmental Effects Research Laboratory (NHEERL) and by John Liccione and Jeffrey Dawson of the Health Effects Division, OPP. William Jordan, Senior Policy Advisor, OPP, also provided clarifying remarks.

Carbofuran is an *N*-methyl carbamate (NMC) pesticide. Like other NMCs, carbofuran causes neurotoxicity through the inhibition of acetylcholinesterase (AChE). Inhibition of AChE is the critical toxic effect for evaluating human health risk to carbofuran. A key aspect of the toxicity profile of carbofuran is the rapid onset of toxicity followed by rapid recovery. In 2006, the Health Effects Division (HED) and the Environmental Fate and Effects Division (EFED) of the Office of Pesticide Programs (OPP) developed human health and environmental risk assessments for carbofuran. The human health assessment evaluated exposure to and risk from food and water in a variety of age groups and from occupational activities. At that time, the Agency identified risks that exceeded the level of concern from dietary exposure to food and water as well as from occupational exposures. The environmental risk assessment identified risks to wildlife, particularly birds. These identified risks led the Agency to determine that carbofuran was ineligible for reregistration in August, 2006.

As required by FIFRA, EPA asked the SAP to address whether the Agency has reasonably assessed carbofuran's impact on health and the environment based on the available data, as outlined in the draft Notice of Intent to Cancel Carbofuran (NOIC) and supporting documents. EPA interpreted this statutory directive to mean that the SAP review should focus on providing comments about whether EPA has reasonably assessed the nature and magnitude of potential risks to public health and the environment posed by the use of the pesticides that are the subject of a draft NOIC. Most of the methods and approaches used and policies followed in EPA's carbofuran risk assessments have already been through extensive peer review. At those SAP

meetings, EPA requested and received detailed recommendations regarding the types of information to be used in risk assessment, as well as how to analyze the data. Consequently, the Agency did not ask the Panel to comment on such previously peer reviewed aspects of the carbofuran risk assessment. In addition, unlike those previous SAP meetings, at this meeting the Agency did not ask for (and the statute does not require) the SAP to provide advice and recommendations on a new scientific methodology or whether the scientific basis for a regulatory decision could benefit from additional data. In addition, the Agency posed human health and environmental charge questions to the Panel regarding new data that became available since the Interim Reregistration Eligibility Document (August 2006) was signed or where new analyses had been performed that affected the carbofuran risk assessments.

PUBLIC COMMENTERS

Oral statements were presented by:

1) John Cummings, Ph.D., FMC Agricultural Products Group, on behalf of FMC Corporation
2) Keith Solomon, Ph.D., University of Guelph, on behalf of the FMC Corporation Avian Risk Assessment Expert Panel
3) Dwayne Moore, Ph.D., Intrinsik Environmental, Inc., on behalf of FMC Corporation's Carbofuran Avian Risk Assessment Expert Panel
4) James Lamb IV, Ph.D., D.A.B.T., F.A.T.S., The Weinberg Group, on behalf of FMC Corporation
5) Jeffrey Driver, Ph.D., D.A.B.T., M.T., C.L.S., risk sciences.net, LLC; on behalf of FMC Corporation
6) Robert Sielken, Jr., Ph.D. Sielken & Associates Consulting, Inc., on behalf of FMC Corporation
7) Robert Morris, Ph.D., FMC Corporation, on behalf of FMC Corporation
8) Bernie Engel, Ph.D., Engel Consulting on behalf of FMC Corporation
9) Richard Fawcett, Ph.D., Fawcett Consulting on behalf of FMC Corporation
10) W. Martin Williams, P.E., Waterborne Environmental Inc., on behalf of FMC Corporation
11) Ray Young on behalf of Young and Young Consultants
12) Larry Kleingartner, Executive Director, on behalf of the National Sunflower Association
13) Bruce Unruh, Farmer, Burlington, Colorado
14) Michael Fry, Ph.D., on behalf of the American Bird Conservancy
15) Jennifer Sass, Ph.D., on behalf of the National Resources Defense Council
16) Chance McLean, Farmer, Benedict, Nebraska
17) Donald Sklarczyk on behalf of the National Potato Council
18) Michael Horrall, Farmer, President, Melon Acres, Inc., Oaktown, Indiana
19) Brian Bresnahan, on behalf of Servi-Tech Consulting, Benedict, Nebraska
20) Scott Schertz on behalf of Schertz Aerial Service, Inc., Bloomington, Illinois
21) Gary Edwards on behalf of the Iowa Corn Growers Association
22) Douglas Hanks, Farmer, St. Anthony, Idaho

Written statements were provided by:

1) Larry Price, President, on behalf of the Oregon Alfalfa Seed Growers Association
2) Nsedu O. Witherspoon, MPH, Executive Director on behalf of the Children's Environmental Health Network
3) B. Sachau, Private Citizen
4) Caroline Kennedy on behalf of the Defenders of Wildlife
5) Mr. Basil Tangredi, DVM, Private Citizen
6) "Jeannie", Jane@flyingace.net, Private Citizen
7) Diana Post, President, on behalf of the Rachel Carson Council
8) Tim Recker, President, on behalf of the Iowa Corn Growers Association
9) Jennifer Sass, Ph.D., on behalf of the National Resources Defense Council

10) Kenneth Weinstein and Claudia O'Brien, Latham & Watkins LLP on behalf of FMC Corporation
11) Louis Best, Ph.D., Larry Brewer, Ph.D., Don Carlson, Ph.D., Jeffrey Driver, Ph.D., D.A.B.T., M.T., C.L.S., Bernie Engel, Ph.D., Richard Fawcett, Ph.D., John Giesy, Ph.D., James Lamb IV, Ph.D., D.A.B.T., F.A.T.S., Dwayne Moore, Ph.D., Robert Morris, Ph.D., John Ross, Ph.D., D.A.B.T., Robert Sielken, Jr., Ph.D., Keith Solomon, Ph.D., and W. Martin Williams, P.E. on behalf of FMC Corporation
12) Louis Best, Ph.D., Keith Solomon, Ph.D., John Giesy, Ph.D., Larry Brewer, Ph.D., and Dwayne Moore, Ph.D., on behalf of FMC Corporation's Carbofuran Avian Risk Assessment Expert Panel
13) John Cummings, Ph.D., FMC Agricultural Products Group, on behalf of FMC Corporation
14) Don Carlson, Ph.D., Registrations Manager, on behalf of FMC Corporation
15) Michael Fry, Ph.D., on behalf of the American Bird Conservancy
16) Jennifer Sass, Ph.D., on behalf of the National Resources Defense Council
17) Elizabeth Cole, Private Citizen
18) Bill Norman, D. Engr., Vice President Technical Services on behalf of the National Cotton Council of America
19) Keith Solomon, Ph.D., University of Guelph on behalf of FMC Corporation

SUMMARY OF PANEL DISCUSSION AND RECOMMENDATIONS

Ecological Risk Summary

The Panel was asked by the United States Environmental Protection Agency (EPA) whether it had reasonably assessed carbofuran's impact on the environment based on the available data, as outlined in the draft Notice of Intent to Cancel (NOIC) and supporting documents. The Agency asked the SAP five charge questions that paralleled the three lines of evidence used by EPA to assess the acute mortality risks of carbofuran to birds at the scale of a treated agricultural field and the immediate surrounding habitat. The lines of evidence were as follows:

Line 1: Deterministic Risk Assessment;
Line 2: Probabilistic Risk Assessment (Charge Questions 1 and 2);
Line 3: (Part 1) Wildlife Mortality Incidents (Charge Question 3) and (Part 2) Field Studies (Charge Question 4).

A summary of the Panel's responses to the charge questions, in conjunction with the lines of evidence presented, is provided below.

No Specific Charge Question – First Line of Evidence: The Panel agreed with the Agency that the deterministic risk assessment was a conservative screening evaluation and that it indicated risk to birds from carbofuran exposure.

Charge Questions 1 and 2 – Second Line of Evidence: The Panel, however, found that the probabilistic risk assessments (PRA) based on the TIM (TIM v.1.0, v.2.0, and v.2.1) modeling for the Agency and on the LiquidPARAM modeling for FMC ("the Registrant"), predicted different levels of risk associated with the use of carbofuran when the newly generated data were included. The Panel agreed that the Agency had implemented their probabilistic risk assessment models in a manner that was consistent with previous Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) recommendations and that sufficient "bridging" of older and newer PRA models, i.e., the TIM v.1.0 with older data and TIM v.2.0/2.1 models with new FMC data where available) had been completed, and that these bridging data showed sufficient equivalency. As a result, the Panel concurred with the Agency's risk conclusion, namely that the results of the PRA continue to support the conclusion that there is a risk of avian mortality in and around carbofuran-treated sites.

The Panel agreed that the new FMC data (i.e., avian avoidance of pesticide treated food, the role of dietary matrix in avian toxicity, and estimates of carbofuran acetylcholinesterase (AChE) recovery kinetics in birds), taken in aggregate, did provide a means to further assess avian risk, but that the utility of these data in the modeling was limited due to experimental uncertainty and would be most appropriately used as screening tools. More than one Panel member thought that the approach of changing all of the data variables simultaneously in the Agency's model was not advisable and added to the confusion of interpreting the models' predictions of risk. In spite of these reservations, the Panel agreed these new data did not significantly alter the overall PRA estimates, and therefore, would not alter the risk conclusions drawn by the Agency.

Charge Questions 3 and 4 – Third Line of Evidence: The Panel agreed that neither the wildlife incident mortality data nor wildlife monitoring studies alter the risk conclusions, though

interpretation of more recent incident reports/monitoring studies is confounded by multiple concurrent changes in reporting and registered uses. For example, changes in labeled uses, improved stewardship by the registrant, reduced state monitoring efforts, and changes in the regulatory reporting requirements all occurred simultaneously over the information collection time period. Observed changes in avian mortality may be due to any or all of these factors. Similarly, the Panel found the data from field studies was of limited utility due to difficulty in designing and executing these studies, as well as interpreting the resultant probabilities of avian mortality due to exposures in the field. Despite the limitations of the incident mortality and field study data, the Panel agreed that both the incident reports and field monitoring studies provide useful information, but that a more systematic approach to collecting and interpreting the data is needed before they can be used quantitatively in the probabilistic risk assessment.

Charge Question 5 – Integration of the Three Lines of Evidence: The Panel believed that definitive conclusions regarding the significance of the avian risk, as requested in Charge Question 5, were difficult to draw due to several factors. These factors centered on data quality issues and study design features that introduced uncertainty into the utilization of the most recent data submitted to the EPA in 2007. These were: 1) the lack of time to adequately compare the performance of the two most recent models, EPA's TIM v.2.1 and FMC's LiquidPARAM, 2) simultaneous but different decisions by EPA and FMC on model parameterization, performance, and resulting conclusions based on outputs, and 3) judgment of the quality and utility of new data. Both the Agency and FMC incorporated additions into their respective models that each considered improvements for risk assessment, but each had different levels of uncertainty. Some of these additions had significant and disparate effects on the resulting outputs and conclusions, depending upon how they were parameterized. The Panel could not assess the magnitude of the avian risk given uncertainties associated with the lines of evidence put forth by the Agency. On the other hand, the Panel does not believe that the new data supports changing the Agency's conclusion regarding avian risk.

Several recommendations were put forward by the Panel for the Agency to consider:

- Define "significant" risk including interpretation of the magnitude of effects;
- Provide better guidance as to the criteria that delineate high, moderate and *de minimus* risk;
- Provide standard approaches to the implementation of probabilistic risk assessments (e.g. fixed and variable input parameters, ranges of variation when applicable and clear delineation of other input parameters);
- Verify mathematical representations with real world data when possible;
- Develop input parameters to realistically quantify effects across species;
- Improve the development, integration and understanding of cumulative effects resulting from exposure to multiple AChE inhibiting compounds on a landscape scale;
- Run additional probabilistic risk assessment modeling with the consideration of a range of exposure scenarios should the Agency choose to retain or add uses of carbofuran;
- Develop an industry-wide task force to share data and to compile a comprehensive database of laboratory and field data for use in future probabilistic risk assessments. This could help alleviate the problem of differential interpretation of data by developing consensus on base data inputs to be used in risk assessment models; and
- Develop a system by which to categorize and group data on a scale that is consistent with probabilistic risk assessments.

Human Health Risk Summary

The Panel addressed four related charge questions (1a-d) regarding the point of departure (PoD) for assessing human health risk from carbofuran. Briefly these are: 1a) Is acetylcholinesterase (AChE) inhibition in PND11 rat brain the proper measure of toxic responses and age group for defining the point of departure for carbofuran risk assessment? 1b) Are FMC's red blood cell (RBC) AChE data unacceptable because of poor replication, limited inhibition, and lack of dose response? 1c) Although EPA-Office of Research and Development (ORD) data indicate that RBC AChE is more sensitive than brain, is the $BMDL_{10}$ (i.e., lower confidence limit of the bench mark dose at the 10% inhibition level) uncertain because the data do not extend to low doses? 1d) Does one get a reliable $BMDL_{10}$ for the most sensitive endpoint by adjusting for the difference between the linear, steep mid-portions of the dose-response curves in RBC and brain AChEs?

The Panel answered charge questions 1a and 1b with an unequivocal "yes". The final two charge questions, 1c and 1d, aroused controversy amongst the Panelists, and issues overlapped between these questions, further complicating the Panel's task. For question 1c, there was little argument with EPA's conclusion that lack of good data at the low end of the dose response curve for inhibition of RBC AChE in young rat pups leads to uncertainty in the $BMDL_{10}$ for that measure. In contrast, the Panel was split with regard to the tacit implication that RBC data are actually relevant in this case. This issue came to the fore in the discussion of question 1d regarding the Food Quality Protection Act (FQPA) safety factor for infants and children.

Five FQPA uncertainty factor scenarios were considered by the Panel in response to charge question 1d (see Table 1). No consensus was reached as to which scenario was favored. Several members proposed to start from the most sensitive measurements in a *bona fide* target organ of juvenile subjects (i.e., PND11 rat brain), and apply a 10X interspecies correction factor to extrapolate to humans without an additional FQPA uncertainty factor (Panel Scenario 1). There was also significant support for using the same data with the incorporation of a small (1.5 to 2 X) FQPA safety factor for the protection of infants and children (Panel Scenario 2). This approach accounts for both the possibility that inhibition of RBC AChE in pups might correlate with inhibition in true target tissues like heart and muscle (not measured) and the use of the intra-species and the inter-species factors of 10X as proposed by the Agency. A third suggestion was to use brain AChE data from adult rats corrected by the two default 10X safety factors for inter-species and intra-species uncertainty and a 10X FQPA safety protection factor for children and infants because of the uncertainty of the juvenile data (Panel Scenario 3); after discussion, this option was rejected by the Panel. A portion of the Panel agreed with EPA's proposed recommendation to use a 5X FQPA safety factor or that even a more conservative 10X FQPA safety factor is warranted (Panel Scenario 4). Another portion of the Panel argued that, even if brain data were the only consideration, an additional 10X FQPA safety factor should be applied to the $BMDL_{10}$ from pups to account for the possibility that area under the curve (larger in the very young) would correlate better with subtle developmental effects that might arise from prolonged AChE inhibition or from as yet unknown mechanisms (Panel Scenario 5)

In conclusion, the Panel was not in agreement regarding the magnitude of a FQPA safety factor. A summary of the various Panel recommendations for the uncertainty factor determination for carbofuran is provided in the table below.

Table 1. Various Recommendations for Uncertainty Factor Determination for Carbofuran (Note: $BMDL_{10}$ data from Table 3 and Table 4, page 21 found in EPA's document: Issue Paper for the FIFRA SAP Meeting on Carbofuran: Human Health Risk Assessment, January 3, 2008)

Scenario	$BMDL_{10}$[1]	Factors		
		Inter-species	Intra-species	FQPA
Panel 1	0.031	10	10	1
Panel 2	0.031	10	10	1.5-2
Panel 3[2]	0.048	10	10	10
Panel 4	0.031	10	10	5-10
Panel 5	0.031	10	10	10
EPA Recommendation	0.031	10	10	5
FMC Recommendation	0.031	10	3	1

[1] The $BMDL_{10}$ values were calculated from PND11 brain (mg/kg) data except for Scenario 3 in which $BMDL_{10}$ values were calculated from adult brain (mg/kg) data.
[2] This Scenario had little support from the Panel and was rejected after further discussion during the meeting.

Finally, several of the Panel members, in discussion following the introduction of an additional question by the Panel, argued that the brain AChE inhibition data, not the RBC AChE inhibition data, should be used as the endpoint for the risk assessment. Not only are the brain AChE data more robust than the RBC data and less dependent on extrapolation to determine low-dose effects, the main reason for this preference is that brain AChE inhibition results in toxicity in a target organ, whereas RBC AChE inhibition is a biomarker of exposure, not toxicity. However, other Panel members believed that inhibition of RBC AChE was the appropriate endpoint for risk assessment because of the greater sensitivity of RBC AChE compared to brain AChE in some studies and because RBC AChE is not merely an index of exposure but can be a surrogate for AChE in peripheral tissues for which data were not available.

A second charge question on the topic of human health risk assessment concerned the potential hazards from dermal exposure to be applied to worker risk assessments. The Panel was in agreement that dermal toxicity studies in rats (MRID 47143701-2) are not acceptable for use in extrapolating dermal risk to workers because of the lack of confidence associated with the study design and sample analysis. With the lack of other experimental data, optimally a properly designed dermal toxicity study, it is reasonable to cautiously consider an estimate of dermal toxicity based on oral toxicity measurements with a reliable maximal effect endpoint combined

with an estimate of dermal absorption. However, assuming 2-6% absorption likely underestimates absorption because the doses to the exposed skin are likely to be much smaller than the 63 $\mu g/cm^2$ (285 $nmol/cm^2$) used in Shah et al., but because elimination of the chemical is relatively rapid compared with skin absorption, it is also possible that the toxic effects from a dermal exposure will be reduced relative to the total amount that penetrates the skin during and after a 6 hour exposure. If the oral dosing extrapolation is used, then the oral bioavailability of carbofuran needs to be included in the MOE calculation, to adjust the oral Point of Departure (PoD) dose to a systemic (or internal) exposure.

Additional Comments

The charge questions posed to the Panel did not specifically address the dietary exposure modeling. However, the Panel noted its agreement with FMC's position that residue inputs to the DEEM dietary exposure model should reflect the most up-to-date data and measurement standards for residue levels on commodities. For potatoes, the Panel recommended that the limit of detection (LOD) for current technologies (i.e. 0.001-0.004 ppm) be used as the basis for the EPA's ½ LOD interpolation of a residue value for a "treated" potato food item.

ECOLOGICAL RISK SECTION DETAILED RESPONSES TO CHARGE QUESTIONS

Many of the methods, approaches and/or policies reflected in EPA's assessments have already been through extensive peer review. At previous SAP meetings, EPA has requested and received detailed recommendations regarding the types of information to be used in ecological risk assessments, as well as how to analyze the data, including the use of probabilistic risk models. Consequently, the Agency will not be asking for this Panel to comment on those aspects of the carbofuran risk assessment.

The Agency is focusing its ecological charge questions to the Panel in one key area, which concerns the data and methods to assess acute mortality risks of carbofuran to birds at the scale of a treated agricultural field and the immediate surrounding habitat. This area is the focus of the panel review as it represents the primary area of the risk assessment where new data have been provided by the registrant that could result in alternate input values or assumptions for estimating risks to birds using probabilistic models.

1. Terrestrial Model Version Effects on Risk Conclusions.

In 2001, the Scientific Advisory Panel (SAP) supported the modeling approach presented by EPA and provided recommendations for additions to the Agency's probabilistic risk assessment (PRA) model, TIM v.1.0 (Terrestrial Investigation Model). This model was developed to estimate risks of acute mortality to birds at the scale of an agricultural field treated with a pesticide. The recommendations included addressing dermal and inhalation exposure routes, more frequent feeding time steps, and avian diurnal behavioral patterns. These recommendations were addressed in TIM v.2.0, which was reviewed by the SAP in 2004, and who again supported the Agency's approach. In the period of time between these two versions of TIM, the probabilistic risk assessment (PRA) for carbofuran was initiated. At that time, TIM v.1.0 was the only fully functional avian PRA model available. Subsequent to the SAP review of TIM v.2.0 and the release of the carbofuran IRED in August, 2006 the Agency has conducted modeling for a subset of carbofuran scenarios using TIM v.2.1, a version that incorporated the 2004 SAP recommendations, to ascertain the extent to which the updated model version would alter carbofuran risk conclusions.

a. *Based on the document (D347916) provided for review containing model results using TIM v.1.0 and the newer version TIM v.2.1, which addresses 2004 SAP recommendations, EPA has determined that the results of the new modeling do not support altering the previous conclusion that carbofuran poses a risk of mortality to avian species in and around a carbofuran-treated use site. Do you concur with EPA's determination? Please provide a basis for your conclusions*

Also, in 2001 the SAP suggested that the Agency explore a separation of pesticide residue variation into two components: variance within a given treated field and variance across different fields. The Agency's probabilistic modeling approach for birds has assumed that variability estimates in the UTAB database represent within-field residue variability, and has described why this may result in somewhat conservative model estimates. An alternative assumption is that all

variance associated with avian exposure is a function of avian biology (body size and behavior) and that there is no residue variance within a field. The Agency has conducted a brief review of a number of pesticide residue datasets and carbofuran-specific field data and has determined that residues on food items do vary within a field.

b. *Based on support document (reference document D348020) provided for review, EPA has determined that assuming within-field pesticide residue variance to be zero is not supported. Do you concur with EPA's determination? Please provide a basis for your conclusions.*

Panel Response – Question 1a

The Panel noted that all models discussed (TIM v.1.0, TIM v.2.1, and LiquidPARAM) represent a large step forward in the ecological risk assessment of pesticides as compared to previous reliance solely on deterministic modeling. EPA has recognized the need to modernize their ecological risk assessment approach in order to keep pace with evolving knowledge and the increasing availability of technology and methods which allow better integration of uncertainty and variability. Although it is imperative that methods used for risk assessment be scientifically sound, it must be recognized that consistency, both across risk assessments for different chemicals and within chemicals over time, must be maintained. For these reasons, the Panel acknowledged that advances in risk assessment occur in a stepwise fashion.

The Panel interpreted this charge question as asking them to focus primarily on a comparison between the application of TIM v.1.0 and TIM v.2.0/2.1 models and their suitability for estimating risk to birds from exposure to pesticides. The Panel also recognized that the TIM models had been through extensive scientific peer review both within the Agency and via the Science Advisory Panel's public forum. Newer model versions reflected the advice and recommendations from previous SAPs and incorporated them into the most recent model version TIM v.2.1.

The Agency originally ran the FMC data through TIM v.1.0 and then when FMC had submitted new data, reprocessed the data through TIM v.2.1. This second set of computations formed a bridging set of data points to the first, more comprehensive data set and demonstrated equivalency between the models. The Panel agreed that when using the same or similar scenarios, the results of the model runs with each TIM version displayed consistency in the output distributions and resulted in similar conclusions with respect to the risks posed by carbofuran to avian fauna.

The Panel concurred with EPA in their conclusion that the results of the new modeling do not support altering the previous conclusion that carbofuran poses a risk of mortality to avian species in and around carbofuran-treated sites. Additional discussion of the TIM and LiquidPARAM models is found in the Panel's responses to Question 2.

Panel Response – Question 1b

The Panel concurred with EPA's determination that the within-field pesticide residue variance is not zero. However, to examine within field and between field variance, the Panel recommended a thorough analysis of the Uptake/accumulation, Translocation, Adhesion, and Biotransformation database (UTAB), which contains extensive data on organic chemicals and heavy metals in vascular plants. The null assumption is that variance exists unless data show otherwise. The analysis presented in reference document D348020 indicates, based upon field data, that there is variance in residue in food items within fields and includes data provided by FMC. There are a number of factors that contribute to this variance, including but limited to application equipment, meteorology, micro-topography of the field and application method (e.g. banded vs. foliar).

The same limited data have been either utilized or considered by both the Agency and FMC. What is in question is the rationale for the coefficients of variation selected by the Agency to use in TIM v.2.1 (i.e. the application of a "safety" factor of 2-4X). Additionally, the Panel stated that there should be clarity in describing what the variance reflects, namely, that variation in initial concentrations on food items at T0 across and in the field could result in an apparent increase in residues between time steps because of non-uniform deposition at applications time. The relative effect (significance) of this variation needs to be evaluated in the two models (TIM v.2.1 and LiquidPARAM).

The Panel stated that the Agency should be clear in how it distinguishes between in-field variation, that is a function of application and measurement error versus variation due to actual concentrations decreasing post-application as the compound degrades. Although environmental concentrations equal to or greater than initial concentrations may be encountered in the time frame shortly following field application, as time post-application increases, the likelihood that higher environment concentrations will be encountered will decrease at a rate consistent with the environmental degradation rate of the compound. The relative effect and significance of this variation should be evaluated in the two models (TIM v.2.1 and LiquidPARAM).

While the coefficient of variation reported within fields is less than values used in the original modeled results, the subsequent assessment using TIM v.2.1 using both original and lower variability did not alter the risk conclusions.

2. Analysis of New Data Impacts.

Between April and June 2007, the Agency received four studies from FMC. These studies were intended to provide data to address uncertainties in the avian risk assessment that were identified by the 2001 SAP. The Agency has reviewed these studies and evaluated the extent to which these data would alter the Agency's carbofuran risk conclusions (reference documents D347778 and D347916). The following questions relate to the results of EPA's review and analysis of each study and their overall impact on risk conclusions.

Panel Response - General Comments

The Panel agreed that both the TIM and LiquidPARAM models have strengths and weaknesses, but recognized that the state of probabilistic risk assessment modeling is an evolving science. Many issues were discussed and debated with respect to modeling over the course of the SAP meeting, including how to adequately represent and quantify *in situ* aspects of an animal's biology (e.g. habitat use, feeding behavior, etc) with mathematical constructs, sometimes with limited data and information. An additional challenge to the modeling was how to interpret and project effects from laboratory studies to field situations.

The Panel noted that one of the side-effects of moving from deterministic to probabilistic approaches is that the uncertainties become more apparent and can become important points of debate with respect to the interpretation of results.

The Panel was presented with two different probabilistic approaches and risk characterizations; one generated by the Agency (TIM models) and one by FMC (LiquidPARAM). Both started from a common point, the TIM v.1.0 model. The results differed in part because of differences in model structure, but also in part because of different interpretations of the currently available science. The Panel had been charged to comment on one of these approaches, but being scientists, it is our nature to be inquisitive and to consider alternative information from a scientific perspective – this is reflected in our response.

2a. Avoidance of Pesticide Treated Food.

Due to a lack of relevant test data, the terrestrial PRA presented in the 2006 Reregistration Eligibility Science Chapter for Carbofuran, Environmental Fate and Effects Science Chapter does not quantitatively address the potential that birds may avoid carbofuran-treated food items. In May 2007, FMC provided EPA with a study on one bird species purporting to demonstrate avian avoidance of carbofuran-treated feed (MRID 47128701). EPA reviewed this study and concluded that it was suitable as a screen for potential avoidance behavior, indicating that avoidance of carbofuran by birds may occur (reference document D347778). EPA believes, however, that robust avoidance studies should include pens instead of cages, non-concentrated food sources and some degree of hunger stress; the study submitted by FMC included none of these considerations. However, to evaluate the potential impact of avoidance on risk conclusions EPA conducted probabilistic model runs using a relationship between carbofuran concentration in feed and reduced avian feed consumption (reference document D347916). In conducting the evaluation of reduced food consumption as a function of dietary exposure EPA used the TIM v.1.0 model. EPA elected to use this model as opposed to the TIM v.2.1 model because of important limitations to the data in the food avoidance study; namely that the data were based on daily observations of food consumption.

To use these data in TIM v.2.1, which has an hourly time step, would require adjusting the derived relationships between carbofuran dose and reduced food consumption to an hourly basis, which is inconsistent with FMC-provided data. For example, one approach would be to multiply hourly estimates of exposure by 8 hours (or other duration representing study observation times).

EPA did not use this approach because of a likely bias towards low consumption rates and hence, lower exposures.

i. *In light of the limitations of the FMC study methodology, please comment on EPA's decision to use this study only as a screen for potential avoidance behavior? Please provide a basis for your conclusions.*

Panel Response

While the Panel believed that the food avoidance study design was less than optimal to achieve its goal, the concept of examining the impact of avoidance behavior was quite reasonable given the results of previously published studies (Bennett & Price, 1981; Bennett, 1989; Grue et al., 1997). As indicated in these studies, avoidance behavior could potentially have a large impact on birds' exposure to a pesticide. However, because of confounding factors in FMC's study, the Panel could not draw any definitive conclusions with respect to avoidance behavior with respect to carbofuran. As such, the Panel agrees with EPA's decision to use this study only as a screen for potential avoidance behavior. The Panel noted that the results of FMC's study should promote additional research.

The Panel stated that care must be taken in interpreting the avoidance study. First, the Panel believed that the terms of "avoidance" and "repellency" were used inappropriately. Second, the Panel concluded that the study was not designed to assess repellency, but rather that the results focused on impacts on food intake. Third, the current study confounds three things: neophobia (fear of new things), physiological response to a toxicant (i.e. toxic anorexia), and conditioned avoidance response. One Panel member noted that the study design confounded two possible effects – toxic anorexia (Burger et al., 2002) and selective avoidance of contaminated food in favor of clean food. Toxic anorexia might be expected to be dose dependent, while the ability to detect and avoid contaminated food might be expected to be concentration dependent. Because the study design confuses these two possible effects, it is impossible to determine which one is driving any changes in consumption.

The dose response relationship observed in FMC's study indicated that irrespective of the observed "pen effects", exposure to carbofuran resulted in a reduction in food consumption. This response was similar to that observed in other birds exposed to AChE inhibitors (Grue, 1981; Grue et al., 1997; Grue et al., 2002), and included the observation of a threshold effect (Grue, 1981). It is important to note that the observed effect may be due to physiological distress (malaise) and/or neurological effects on components within the central nervous system governing appetite (Grue et al., 1997).

Clarification of terms with respect to the effects observed in FMC's study is required. The Panel believed that the results observed could more accurately be referred to as "pesticide-induced anorexia" (Grue, 1981) vs. repellency or avoidance. This is important because of the relative hazards in the field (e.g. in the case of repellency) the effect would "prevent" exposure following learning, whereas "pesticide-induced anorexia" is the result of exposure but subsequently may result in reductions in exposure until the animal recovers its appetite, and again can be subject to exposure via the same food items. The Panel had concerns that included both the results of the

study and how representative the data for one species were for multiple species. If the results are representative of multiple species exposed to carbofuran, then this effect needs to be included in the risk assessment. Even if the data are considered as a screening study by the Agency, the results suggest that the effect may occur in the field, and that the potential effect on outcomes of the risk assessment are significant at the higher exposure levels based on the Agency's analyses.

The time step may also be important in representing anorexia in the model, as the effect likely would not be realized until a threshold dose was achieved. This issue is discussed in the Panel's response to Question 2aiii.

The Panel concluded that the FMC "avoidance" study demonstrated food intake suppression (toxic anorexia), and further noted that the dose response pattern observed in mallards from this study were similar to the patterns observed in a study with organophoshate pesticides using grackles (Grue, 1982) in which the degree of suppression varied as a function of concentration of applied to the food; there was clear evidence of general reduction of food consumption once the treated material was introduced into the diet. Based on Panel analysis of study results, they concluded that the reduced food intake was irrespective of pan type (carbofuran treated food or clean food) and that the magnitude of food intake reduction was greatest on the first two days whereupon the intake increased. This pattern was exhibited for all concentrations tested, with the magnitude of general food intake suppression varying as a function of concentration tested. There was no evidence of discrimination between carbofuran treated food and clean food. Thus, the implication from these data was that carbofuran suppressed food intake and that there were no flavor (e.g., odor, taste, tactile, irritation) characteristics that the subjects detected or attended to. There was no evidence of repellency or learned avoidance for carbofuran. The Panel believed that the results of the study should be characterized as toxic induced food suppression. Potential bias in individual bird's preferences to feed on one side or the other (right vs. left) did not seem to have any bearing on the interpretation of the study because the general suppressive effect transcended any side biases.

There is ample evidence in the literature that conditioned avoidance can occur for birds exposed to carbamate compounds (Gras et al., 1981; Sayre and Clark, 2001). However, the mechanism is as follows: 1) the unconditional stimulus (the toxicant) induces an unconditioned response (illness); 2) the bird is exposed to a visual stimulus (the conditional stimulus); and 3) the bird subsequently learns to avoid the conditional stimulus that is paired with the food (the conditional response). This paradigm has been used successfully to protect crops with carbamate pesticides. There is no reason to suspect that a similar paradigm could not be used for carbofuran, but the FMC experiment did not address or test this possibility. The Panel also noted that the results state that no signs of intoxication were observed yet failure to feed was listed as one of the symptoms of AChE inhibition (Burger et al. 2002). More than one Panel member stated that the presentation of the data analysis was incomplete. While tests were described, the full results were apparently not presented, nor were error bars or confidence limits on the results, which was problematic for interpretation. An analysis of confidence limits on the results led to the recommendation that the comparisons should be corrected for multiple comparisons in some cases, and that this might eliminate some of the significant results as well. The derived variables should be subject to an analysis that includes error propagation.

Additional analysis by Panel members revealed high variance in response, as represented by calculated repellency factor to treatment over days, indicating little difference between days during pre-exposed time periods and days during the exposure period (Figure 1). In addition the dose response relationship appeared to be discontinuous. Significant responses were only observed in the 3 mg/kg (ppm) diet for males and in the controls and the 135 mg/kg (ppm) dose for females.

Figure 1. Box Plots of Raw Repellency Factor Values for Male and Female Mallards Exposed to Carbofuran. Data from Stafford, J.M. 2007. Assessment of mallard duck (*Anas platyrhynchos*) avoidance to feed containing Furadan 4F. FMC Unpublished Study. MRID No. 47128701.

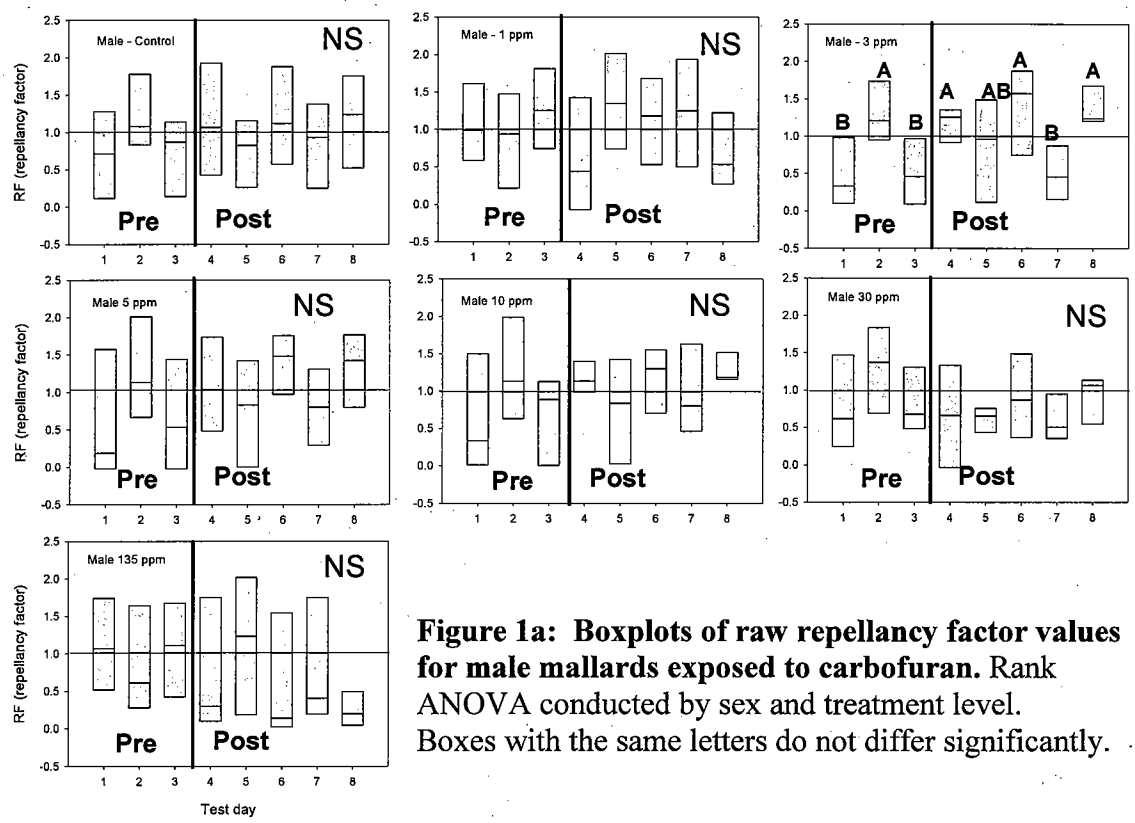

Figure 1a: Boxplots of raw repellancy factor values for male mallards exposed to carbofuran. Rank ANOVA conducted by sex and treatment level. Boxes with the same letters do not differ significantly.

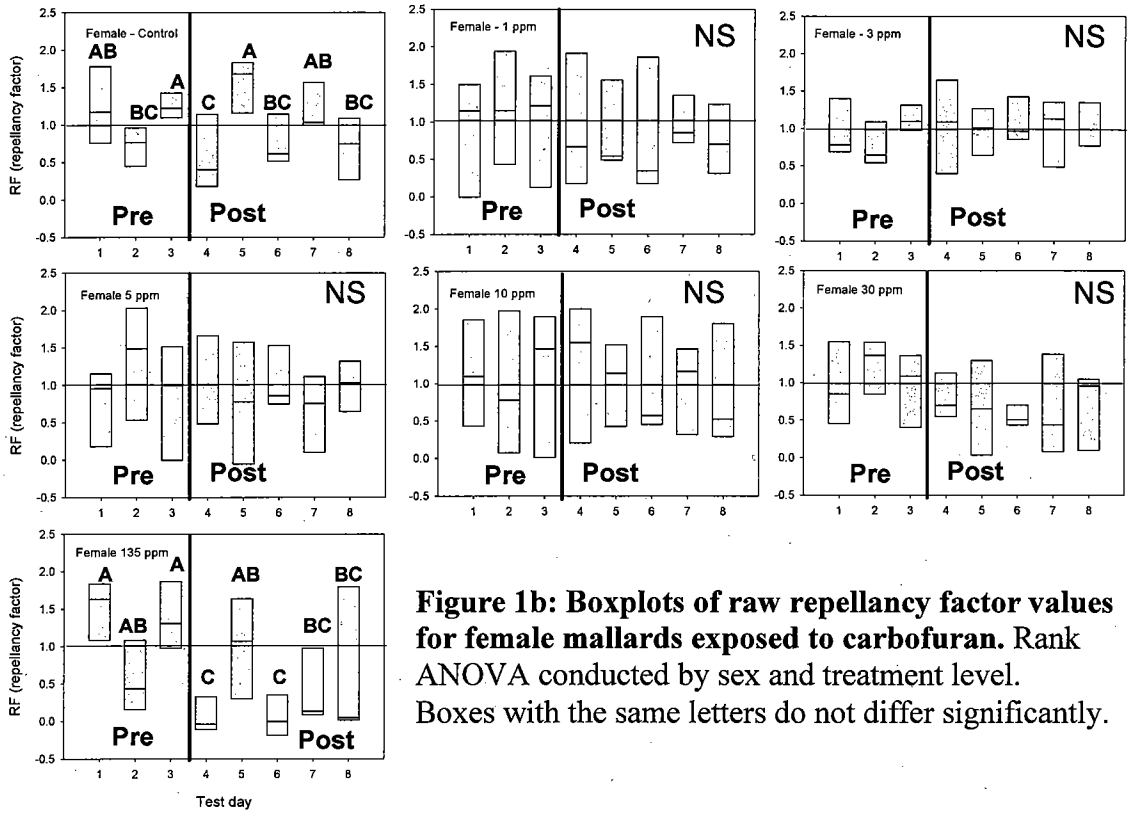

Figure 1b: Boxplots of raw repellancy factor values for female mallards exposed to carbofuran. Rank ANOVA conducted by sex and treatment level. Boxes with the same letters do not differ significantly.

There are other factors that need to be considered with respect to use of the avoidance study in the environmental risk assessments. From a scientific perspective, information on the avoidance/repellency factor for a wider range of avian species is desirable. This will allow for better interpretation of the potential impact on exposure for focal species. The Panel noted that based on information provided in FMC's presentations, the avian species chosen for the test (i.e., mallard) was the most discriminatory. Normally, the choice of the most sensitive test species is viewed as conservative. However, because of the potential impact on exposure, the use of a sensitive species might not be representative of species that do not avoid or discriminate to the same extent, where the potential reduction in food intake and hence exposure might be less. Lastly, the Panel believed that the results indicated an effect of the set-up of the holding facility used to conduct the experiment, which further confounded the results.

The Panel also concluded that EPA was justified in suggesting that the study design made it impossible to predict if any of these results were actually applicable to field situations. With respect to EPA's suggestions for a robust study, several Panel members believed that the design features suggested by the Agency might not be the best approach. One Panelist noted that the design features of such studies are being discussed by a scientific workgroup associated with the Organization for Economic Cooperation and Development (OECD) and that caution should be exercised in providing the Agency with any specific study design recommendations until this group has reached consensus. With this caveat in mind, some of the Panel offered the following observations regarding study design.

1. **Pens vs. Cages:** The caged environment could be more easily standardized for testing among laboratories and provides care and consistency in taking physiologic measurements (e.g. body mass, blood sampling) without imposing undue stress on subjects, and in measurement of food and water consumption. Pens (outdoor) provide none of these advantages but may introduce much uncertainty if the subjects to be treated are penned over a natural matrix such as turf or alfalfa. If the purpose of the pen is to provide space and distribution of additional feeding start times, then this purpose may be unattainable because these pens may increase the bird's stress during capture and thereby artificially increasing mortality. This increased mortality could then be interpreted as increased hazard. Earthen pens have inherent problems with sanitation and cleanup between studies. In this instance, practicality and control may prevail over idealistic study design. Earthen pens have inherent problems with sanitation and cleanup between studies.

2. **Test Species Selection:** Care should be taken to choose a relevant species and relevant would be defined by careful consideration of assessment and measurement endpoints; mallards may not be the best choice.

3. **Non-concentrated Food Sources:** Some aspects of this issue were addressed above. While increasing space, distribution, and random arrangement of feeding stations may at first seem desirable and representative, large pens for individualized birds may be difficult to manage, and for some flocking species may affect behavior. As avoidance may be learned by the test species in just a day or two, behavior-related stress may affect response and avoidance studies in cages may be improved by randomly switching feeders rather than simply reversing feeders on a daily basis.

4. **Additional Feeding Stations:** Carbofuran does not seem to be either an odor- or flavor-stimulated repellent, though emesis may be induced and death may result. If death does not result, recovered specimens often return to foraging on contaminated food without persistence of initiated toxicity, consequently, additional feeding stations would likely not change the outcome.

5. **Hunger Stress**: Some degree of hunger stress was suggested by the Agency as a future study design feature. This is a critical issue that has important policy implications in addition to scientific ones. It has long been recommended that under the standard 5 days feeding protocol (LC_{50}) that bobwhite quail be tested at 14 days of age and mallards at 5 days (Hill et al, 1977). These ages were selected to ensure that these species could not survive fasting for the test duration. Approximately 50 percent of 10-day old mallards can fast for 5 days indicating that for the life stage at which the study would be conducted, inducing hunger stress could significantly increase mortality and suffering.

6. **Nutritional Status of Birds in the Wild:** Wild birds are most likely to be exposed between late spring and late summer. During this time period changing light conditions and other environmental cues will cause birds to: 1) eat extra to fatten for migration, 2) migrate, a period with high energy demands and limited time for feeding, 3) establish territories and build up nutritional reserves for egg laying, 4) lay and incubate eggs which will include defending territories, 5) raise dependent young, an energetically demanding time, and 6)

molt, prepare for fall migration or in the case of young birds transition to independence, all times of nutritional stress,. All of these conditions will emphasize the stress on birds to find food and limit their ability to be "picky".

7. **Availability of Food Choice:** Applying this study result to a field situation assumes there is clean food available for birds to choose in the wild. This might be the case in some situations where groups of birds are highly mobile, but for many of the birds of concern, individuals will be confined to territories and may need to remain near nests during the relevant time periods. They may not have the luxury of moving to an unsprayed field.

   One Panel member noted that before the data can be considered representative and incorporated into the model, that field data showing that it is typical for birds to be exposed to a sub-lethal dose, recover, be exposed again and that at this time point of reexposure avoid the contaminated feed would be required

   The Panel did not advocate including the availability of food choice (i.e., data from FMC's study) in a risk assessment model without closer examination. To the extent that this scenario might occur in the field, it would be most likely to be important for larger species such as mallards rather than songbirds. For any species, the dose-response curves for carbofuran make it unlikely that a bird would receive a sub-lethal dose and survive the secondary effects of intoxication (e.g. predation).

ii. *Given the limitations in the food avoidance test study, did EPA employ a technically sound approach to use the data from the study as inputs to the TIM v.1 model to evaluate the potential for food avoidance to alter mortality risk estimates? Please provide a basis for your conclusions.*

Panel Response

The Panel agreed with the Agency to not include FMC's food avoidance study in the modeling because of the design flaws, the failure of FMC to adequately present the results in the study reports, and the apparent lack of repellency/avoidance behavior based on the Panel's analysis of the data. The Panel also concluded it was not unreasonable to include the results for feed suppression (avian anorexia) as effects in their analysis, or for compensatory feeding. Given the limited data available to parameterize the model, the Agency's approach to not include these data as inputs to the TIM v.1 model appeared to be appropriate. The Panel noted that protocols to evaluate avoidance/repellency that ensure quality data are available and that further investigation of the impacts of these attributes on outputs would be warranted, and if it they were to be included in any model structure, developed further. The Panel noted that avoidance/repellency/avian anorexia and how it is characterized, affects exposure, is important enough to be incorporated into models and is worthy of further study. In addition, the Panel noted that if avoidance behavior was removed as a parameter in the LiquidPARAM model, as presented at the SAP meeting, that the predicted probability of risk was similar to results obtained from the Agency's TIM models.

iii. Given that the data on food consumption is based on daily measurements, did EPA incorporate these data appropriately into TIM 1.0, which has a time step that is more consistent with the observation times in the data provided? Please provide a basis for your conclusion.

Panel Response

The Panel noted the following conclusion from the 2001 SAP (p. 33), to provide context for the response.

SAP 2001 - "A time-step model as presented by the Agency is reasonable as a Tier 2 approximation and should produce credible output provided: 1) pesticide intake does not affect the continued rate of intake (no avoidance - either conditioned aversion or post-ingestional feeding incapacity), or, 2) avoidance occurs too late relative to an intake commensurate with lethality. There is growing evidence that the rate of pesticide intake is key to an individual's probability of death in the case of highly toxic pesticides (Hart et al., 1999). Clearly, the effective feeding rate within a time step does matter in real life even if this is not currently captured by the model. The critical variable with respect to ChemX and other highly toxic pesticides may be the size of the meal rather than the maximal body burden attained over the course of a time step."

The time step may be important in representing anorexia in the model, as the effect would likely not be realized until a threshold dose was achieved. Therefore, the duration of effects (time not feeding) would depend on when in the day (daylight hours in most cases, depending on the species) the threshold was reached. For example, a bird reaching the threshold early in the day might not feed again until the next morning during which time the affected birds likely would regain their appetites and resume feeding. Irrespective of the time of day during daylight hours at which the threshold dose is achieved, affected birds might recover their appetites by the next morning because of a night-time hiatus in feeding. A shorter time step would allow for a more accurate incorporation of reductions in feeding and therefore exposure within the model, which would be more reflective of what might occur in the field. Lastly, it is important to note that the recommendations listed by the Agency as design criteria for future studies have not been peer reviewed or been open for public comment.

As noted above in the Panel's response to Question 2aii, if avoidance behavior was removed as a parameter in the LiquidPARAM model presented at the SAP meeting then the predicted probability of risk predicted by FMC's LiquidPARAM model is similar to results obtained from the Agency's TIM models. Differences in estimation of risk between the two models indicate the potential importance of the following factors: 1) the interaction of repellency/avoidance/feed suppression, 2) the time step, and 3) the dissipation of chemical and resulting diminishment of effects as they affect exposure and ultimately risk.

The Panel concluded that both the Agency's and FMC's modeling had merit, however, inclusion of an hourly time step with TIM v.2.1, as was done with LiquidPARAM, would be useful. The Panel recognized that food avoidance is intimately linked to foraging behavior making the driving factor in the choice of approach the feeding biology of the focal species in question

which would result in food avoidance being applied concurrent with food ingestion, no matter what the type of foraging behavior.

2b. The Role of Dietary Matrix in Acute Toxicity.

In 2001, the SAP indicated that the oral LD_{50} was more appropriate than the LC_{50} for use in avian probabilistic assessments for a chemical with an effects dataset similar to carbofuran. However, they did recognize that dietary matrix could play a role in modifying the acute toxicity of a compound. In May and June 2007, FMC provided the Agency with two studies on two bird species purporting to demonstrate that a dietary matrix can reduce acute toxicity of carbofuran (MRIDs 47152901; 47143706). EPA's conclusion regarding the studies (reference document D347778) is that there does appear to be an effect of the dietary matrix on acute toxicity of carbofuran. However, the study designs were limited by small sample sizes and sufficient experimental variability that adds uncertainty to the interpretation of results in at least one study. In addition, EPA does not believe that these two studies capture the range of likely responses for wild bird species associated with carbofuran use sites. However, to evaluate the possible impact of the food matrix on avian risk conclusions, the food matrix effects identified in these studies were used by EPA as inputs to the TIM v.1 andv.2.1 models to provide insight into the extent to which risk estimates could vary (reference document D347916).

i. Do you concur with the Agency's conclusions regarding the limitations of the data available in food matrix studies? Please provide a basis for your conclusions.

Panel Response

The Panel agreed with the Agency's concerns, but they also had concerns that food items in the field are qualitatively different and would effect how exposure is presented. Pesticide residues could be on the food surface as opposed to in the food matrix, and therefore could be more readily available with less matrix interference in one consumption scenario than the other. Additionally, the composition of the matrix itself must be representative of natural food items (e.g. insects vs. plant foliage vs. seeds). Once again the Panel agreed that from a scientific perspective, information from a variety of avian species, representing different focal species groups would be desirable for better interpretation.

The Panel considered it reasonable to expect that the matrix, in which or on which the pesticide enters the body via ingestion, will alter and undoubtedly reduce the toxic effect. This is the reason why animals are fasted in the standardized acute toxicity test (LD_{50}) and only a carrier or vehicle is used if necessary for accurately administering the pesticide. Data from FMC's tests with bobwhite and mallards indicated a 2-4X reduction in the toxicity of the pesticide. This was reflected as a shift of the dose response curve to the right and potentially a reduction in the slope of the dose response curve. Unfortunately, as in the case of the food avoidance study, measures of interspecies variation in response were not available, increasing uncertainty as to how to incorporate the results into the Agency's models. Simulations by the Agency suggested that matrix effects on model outputs can be significant and that this "effect" needs to be evaluated further.

From a "big picture" scientific perspective, the Panel believed that it would be interesting to explore this issue across pesticides to allow consideration of differences between chemistries and to examine relations with physical-chemical properties.

ii. Given the limitations in the food matrix studies, did EPA employ a technically sound approach to use the data from these studies as inputs to the TIM v.1 and v.2.1 model to evaluate the potential for food matrix effects to alter mortality risk estimates? Please provide a basis for your conclusions.

Panel Response

The Panel stated that the Agency's approach had technical merit given the available data, even though the data generated by FMC did not constitute a full dose-response study. Recognizing that feeding preferences could be linked to food preferences, ideally, a full dose response relationship should be used to account for differences in toxicity rather than multiplying the central tendency (i.e. the LD_{50}) by a simple factor. The approach used by EPA assumed that the slope of the dose-response relationship(s) remained the same throughout the study and that a simple shift along the x-axis of the overall dose-curve accounted for the effects of food matrix on toxicity. Given the link between food preference and food matrix, the driving factor in the choice of approach both for testing and for modeling should be the feeding biology of the focal species in question.

The Panel also concurred with the Agency's observation that species sensitivity is an important factor to be considered when considering potential for effects across the range of species that can be exposed. Given these considerations, the Panel supported both conclusions of the Agency to recognize both the potential importance of matrix effects on exposure and that these data were not suitable for use in risk assessment at this time.

2c. Estimates of Carbofuran Acetylcholinesterase Recovery Kinetics.

The PRA presented in the 2006 Reregistration Eligibility Science Chapter for Carbofuran, Environmental Fate and Effects Chapter, used whole bird elimination rates of carbofuran to estimate carry-over exposure, and its contribution to potential effects, between model time steps. The 2001 SAP suggested that compounds with well characterized modes of action might also be assessed on the basis of a target site clearance or using some biomarker indicating toxic activity. In April 2007, FMC submitted data on acetylcholinesterase (AChE) inhibition and recovery that purported to provide recovery estimates based on carbofuran's known mode of action (MRID 47107601). EPA has reviewed this study (reference document D347778) and found that results are consistent with carbofuran's known mode of action and recovery kinetics. However, at the highest dose, avian mortality was observed and, moreover, surviving birds did not reach full AChE recovery. For these reasons, EPA believes there is still uncertainty regarding recovery kinetics for birds receiving higher exposures to carbofuran. In order to account for the potential impact of these uncertainties on risk conclusions, the highest estimated AChE recovery half-life was used as an input in EPA's PRA model (reference document D347916).

i. *Do you concur with the Agency's conclusions regarding the AChE inhibition and recovery data provided? Please provide a basis for your conclusions.*

Panel Response

The Panel agreed that the study was technically sound and provided an excellent description of carbofuran inhibited brain AChE recovery for young, fully grown northern bobwhite with the exception that the study design did not allow for a full recovery of AChE at all dose levels. One Panel member noted that the data set was excessive for the purpose of the study, as the same result likely could have been achieved with as few as 40 or 80 birds (e.g. 10 sample periods x 4 dosages (including control) x 1 bird per sex at each sample period = 80 birds total).

Many studies have indicated that brain AChE was inseparable for male and female adult non-breeding northern bobwhite and it was further noted that these data might have been available in scientific literature during the time these data were being generated. In the future, better use should be made of previously generated data. The Panel also suggested that it would be useful to determine if there was a difference between the sexes in recovery of carbofuran inhibited brain AChE given the ample brain AChE data set that was generated for both sexes of adult non-breeding northern bobwhite, but that unless the photoperiod was lengthened to induce reproductive conditions, there would be little point in attempting to separate the sexes. One Panel member noted that the pattern of AChE recovery in this avian study was consistent with recovery of AChE found in fish studies (Zinkl et al., 1991; Grue, unpubl. data).

The Panel had concerns that during the recovery phase behavioral responses were not considered. It is well established that birds and mammals with AChE inhibited by 40 to 60% may suffer overt behavioral effects (Grue et al., 2002) and that these effects may occur during recovery while enzyme inhibition is at these levels. In the wild, the altered ability to react could increase secondary effects such as susceptibility to predation or weather conditions. Additionally, dependent young of the affected parents could be at risk.

The Panel also noted that the study design did not allow for the full recovery of AChE at all dose levels. In order to estimate the recovery kinetics with appropriate precision, it is necessary to establish approaches to develop appropriate time frames for study durations and sampling intervals through range finding studies or from existing data for birds and other animals.

ii. *Given the limitations in the AChE inhibition and recovery studies, did EPA employ a technically sound approach to use the data from these studies as carbofuran carry-over exposure estimates in the TIM v.1 andv.2.1 models to evaluate the potential for alternative mortality risk estimates? Please provide a basis for your conclusions.*

Panel Response

The Agency used a technically sound approach for inclusion of AChE inhibition and recovery in the TIM v.1 and v.2.1 models; however, several Panel members noted that the assumption of first order kinetics should be re-examined in light of the relationship between dose and half-life as determined by both FMC and Agency. The kinetic analyses of AChE recovery data indicated a zero-order process at the 3.0 mg/kg dose and first-order process at lower doses. Since elimination rates were not identical and varied with dose, no true first order half-life existed. It was stated by one Panel member that the inclusion of zero-order kinetics in the models should be relatively simple. Another Panel member suggested an alternate approach would be to consider the use of Physiologically Based Pharmacokinetic (PBPK) Modeling.

With respect to the recovery of AChE levels to control levels, the Panel pointed out that recovery might occur more quickly during a feeding hiatus. One Panel member noted that the ED_{50} for brain AChE activity was not indicative of mortality, but if a dead animal has its brain AChE inhibited by at least 50 percent, then the death could be attributed to exposure to AChE depressing agents.

2d. Quantitative Results of New Data

The Agency has presented individual and combined impacts of the new datasets on avian acute mortality predictions in and around a carbofuran-treated use site, using the TIM framework. EPA believes that the new data do provide a limited means to further quantify the range of possible risk estimates based on different model inputs or assumptions concerning avoidance of carbofuran-treated feed, toxicity of carbofuran in different feed matrices, and carbofuran carry-over exposure between feeding events. However, the results of additional probabilistic modeling, using the TIM framework, with incorporation of the newly submitted data produce mortality estimates to birds that are comparable to those reported in the Agency's 2006 Reregistration Eligibility Science Chapter for Carbofuran, Environmental Fate and Effects Chapter and do not alter EPA's avian risk conclusions.

Does the SAP agree that these new data when considered together do not significantly alter the Agency's overall probabilistic estimates of carbofuran's risk of mortality to avian species in and around a carbofuran-treated use site? Please provide a basis for your conclusions.

Panel Response

Although beneficial, the additional data developed by FMC provided limited resolution to previously identified SAP concerns. The data were limited for a number of reasons and from a scientific perspective, there were concerns expressed by the Panel that the data were not representative of the wide range of species that could be affected. Given the limitations of the data, integrating the results into the model was problematic. Furthermore, interactions among these metrics and those already in the model are currently undefined. Given the limitations of the data and the use of FMC's results as a point of departure to do a "what if" analysis, inclusion of this information by the Agency in the models provided useful insight into how risk may vary in relation to the specific issues addressed. With these caveats, the Panel's conclusion was that

the risk estimates based on these models and the scenarios used were not significantly altered by the addition of new data.

The Agency's analysis of each of the studies independently was appropriate. However, some Panel members did not think the aggregate approach where EPA changed all of the variables simultaneously was justified. The Panel believed that EPA was correct in considering the implications of the AChE inhibition recovery study and the food matrix studies. Whatever the limitations of each study individually were, additional questions were raised when their results were used together. Therefore, incorporation of these data in an aggregate into any model may not be warranted.

The Panel accepted the assumption of the importance of food matrix on toxicology; however, other variables based on aqueous bolus dose methods, including the recent AChE recovery study and "gorge" dosing should be reexamined. There were no data to evaluate the validity of applying both the correction from the food matrix study and the AChE recovery data to a single model and the results of the food matrix study suggested that this may not be a reasonable approach. Specifically, the fact that the time to onset of symptoms was longer with the food dose approach suggests that the time course of AChE inhibition might actually be longer than assumed. Likewise the study noted that the recovery of birds that did not die could take more than seven hours, which indicates that delayed AChE recovery with this dosing method is a plausible hypothesis. Similarly, the uncertain effect of the gorge-feeding scenario of the matrix study needs to be considered. According to FMC's LiquidPARAM model, up to 50% of the daily intake may, or may not, be replicated in a study where birds are provided small doses of food over a long period rather than a single "gorge" dose.

The Panel noted throughout the discussions that from an ecological perspective, dose response effects should be studied in multiple avian species to develop a better understanding of how laboratory results relate to possible responses under field conditions. The Panel also suggested that EPA consider the formation of one or more task forces to help pool existing data to overcome current data limitations, especially if the Agency wished to further examine the field use and foraging behavior of birds.

Additional comments related to modeling

Various members of the Panel had additional comments related to the models, their structure and their ecological relevance. These additional comments are summarized below.

The Panel stated that the LiquidPARAM model builds on the TIM1.0 model and includes many of the recommendations made by the 2001 and 2004 SAPs. FMC indicated that the LiquidPARAM model had been created and reviewed by their panel of technical experts; however, the model structure and parameterization had not, as yet, been made public and had not undergone a public peer review process, such as the SAP. Such peer review would greatly enhance understanding of the LiquidPARAM model and its results.

The Panel believed that their reviews of the most recent versions of both the TIM and LiquidPARAM models were limited in that they did not have the modeling code for either of the

models available for their evaluation. Consequently, the Panel's conclusions were based solely on the materials provided by the EPA and FMC, namely, the respective analyses and modeling results, descriptions of their model structure, as well as the Panel's own evaluation of the more recent data.

Avian feeding behavior remains one of the key uncertainties in both the TIM and LiquidPARAM models. The 2004 SAP noted, *"Adult altricial birds that are provisioning nestlings most likely would have a more uniform feeding distribution throughout the day."* This is a reasonable and testable hypothesis. Reviews of studies of the rate at which adult passerines deliver food to their dependent young is a reasonable basis for proposing an *initial* hypothesis that adults themselves feed at an even rate through the day, which is the assumption employed in the LiquidPARAM model. However, relying on feeding rates, derived from adult passerines using central place foraging to feed dependent non-mobile nestlings to conclude that the adults' intake of food is constant over the course of a day, assumes that adult eating follows the same pattern as that of their rapidly growing young. This assumption is critical for the TIM and LiquidPARAM models and needs to be reexamined using a broader range of published studies.

Feeding patterns can vary widely. While the smallest birds, such as hummingbirds, need to eat frequently, the birds most likely to be exposed on carbofuran-treated fields are at least an order of magnitude larger and can easily go several hours between feeding bouts. This has been demonstrated by the ability of birds to spend hours migrating without eating, or fasting during long winter nights when energy demands for thermoregulation can approach the demands on parents feeding dependent young.

Work on captive passerines shows that some birds do exhibit a diurnal pattern in feeding with peaks in the morning and evening (Polo and Bautista, 2006). In addition, at least some time budget studies of wild passerines show that birds do exhibit a temporal pattern of feeding over the course of the day, with feeding peaks in the morning and in the evening (Morton 1967, Verbeek, 1972; Hutto, 1981). These temporal variations in feeding patterns likely apply to non-passerines as well (e.g., doves and shorebirds) (Losito et al., 1990).

Based on these and other studies, it is plausible that the feeding patterns for wild birds show temporal variability during relevant times of the year when they might be exposed to pesticides such as carbofuran. The Panel noted that it was important to consider all phases of avian feeding cycles to assess exposure. This includes, at a minimum, feeding over the course of a day for the nestling phase, migration, premigratory fattening, and other periods when they are not feeding dependent young. For many small passerines such as dickcissels (known to use fields on which carbofuran may be applied), the nestling phase lasts around 10 days, leaving ample time for other behavior patterns. Based on the uncertain and variable behavior of avian foraging patterns, the Panel commends the EPA's model for paying attention to previous SAP recommendations that the feeding pattern assumed in models needs to be flexible.

In addition, the Panel recommended that the assumptions about movement patterns of feeding birds should be re-examined and should not assume central place foraging for all life history stages. Even if the assumption that adults are constantly feeding their young is accepted, this period can be short at both the species and individual level. During the rest of the spring and

summer season, their foraging patterns may vary greatly by either foraging in one place for long periods or ranging widely in search of food. The feeding pattern assumptions used in LiquidPARAM could be used to model risks to the nestlings that are being fed, but it should be noted that this would introduce additional uncertainty into the modeling regarding the sensitivity of developing altricial birds to pesticides. Data from precocial species, such as mallards and quail, would not be acceptable for this purpose. For adults, it is a reasonable assumption that consumption patterns of adult birds more closely mimic the pattern used in the TIM modeling.

The Panel had several recommendations with respect to presentation of the TIM models and results:

1) Modeling results should capture the numerical (percentage) changes between TIM1.0 and TIM2.1 run on the same scenarios. The percentage change in results should be related to the degree of change that would result in a change to the risk conclusions. Expanding this tabular comparison to include LiquidPARAM would be beneficial.
2) Modeling results should capture the numerical (percentage) changes in model runs attributable to modified inputs based on most recent FMC data. Expanding this tabular comparison to include LiquidPARAM would be beneficial.
3) Modeling results should increase the transparency of the model development process by listing the parameters used in both models side-by-side, identifying which are fixed, which vary (with distribution types), and what assumptions changed between model versions. Expanding this tabular comparison to include LiquidPARAM would be beneficial.
4) Modeling results should include error/uncertainty metrics as a standard component of all model output associated with risk estimates produced by TIM1.0 and TIM2.1 model runs. Expanding this to include LiquidPARAM would be beneficial.
5) Modeling results should consider modifying the TIM model or implementing it in a manner to evaluate both food-based and water-based pathways independently; total exposure/risk would then be the sum of both water-based and diet-based exposure. Such an approach would be consistent with the differences in bioavailability between the two media-based exposure pathways.
6) Multiple models should be developed and implemented to address different aspects of pesticide exposure and risk as part of a robust modeling framework. These models would address different aspects of exposure and risk and would include both spatially explicit models as well as population models. Spatially explicit models would assist in the integration of variability in spatial distribution of residues, habitat availability, and exploitation by potentially exposed receptors (e.g. Spatially Explicit Exposure Model (SEEM, U. S. Army Center for Health Promotion and Preventive Medicine (CHPPM) lab). Population models would allow investigation of the implications of differential mortality and reproductive strategies by species in response to pesticide exposure (e.g. Leslie matrix models). Application of population models would help address the percent effects that a given species would be able to support, while still maintaining viable populations. Using multiple models, with complimentary strengths and weaknesses, would be beneficial and could be used as a component of the weight of evidence evaluation.

3. Interpretation of Incident Reports.

Since 2000, the Agency has observed a decrease in the number of reported wildlife incidents for pesticides as a whole based on data in the Agency's Ecological Incident Information System (EIIS 2.0). This decline corresponds to a decline in State-sponsored wildlife incident monitoring programs (Avian Incident Monitoring System, Final Report). Incidents associated with carbofuran also have followed this trend, with a decrease in the number of wildlife incidents reported in the last several years.

Please comment on the Agency's conclusion that the decrease in recent reported wildlife mortality incidents associated with carbofuran is likely related to an associated reduction in monitoring and/or reporting and does not provide affirmative evidence that the use of carbofuran, as currently registered, does not continue to cause a risk to wildlife, specifically birds. Please provide a basis for your conclusions.

Panel Response

The question posed by the Agency incorporates two components: 1) whether the apparent decline in reported incidents is evidence for a decline in actual mortality events, and 2) whether the apparent decline is "likely related to an associated reduction in monitoring and/or reporting." The Panel generally agreed that monitoring systems are extremely valuable. The incidence databases, however, were not designed for nor were they appropriate for evaluating the absolute numbers of incidence or birds killed.

Only a small portion of bird mortality will be reflected as incidents in the databases because there is a long chain of events that must occur for bird mortality to be reported as an incident. There was no way for the Panel to quantify the probability or uncertainty of any of these events. These events appear to be biased towards larger birds and events that kill large numbers of birds in one event, and as such, the Panel concluded that the events were useful only in providing evidence that bird mortality associated with carbofuran use does occur. The Panel was in general agreement with the Agency that the incident data were insufficient to demonstrate that carbofuran no longer poses risk to birds. Given the unknowns about the chain of events leading up to incidences being reported, the databases presented are not capable of showing the lack of mortality, only the presence of mortality.

The Panel did not agree with the Agency on the second part of the question, i.e., whether the likely cause of the apparent decline was due to changes in reporting. The Agency's conclusion from interpreting incident reports is confounded by at least three factors that may account for the observed decline in incident reports of bird deaths: 1) a reduction in the use of carbofuran resulting from label changes and improved stewardship, (2) a reduction in state monitoring efforts due to funding limitations, and (3) a change in the regulatory requirements under FIFRA 6(a)(2) for the reporting of incidents by registrants. Each of these factors was discussed in the Agency's supporting documents and presented to the SAP. The Agency dismissed the possibility that the reduction in reported incidents may have resulted from changes in carbofuran label in 1998 and associated improvement in product stewardship. This rejection was based, in

part, on avian incident data associated for the use of carbofuran on grapes in California that suggested that incident reporting was associated with monitoring efforts (i.e., one incident pre-1992, 27 incidents from 1992 to 1993, and no incidents thereafter). However, this use was mitigated shortly after these incidents occurred, which likely resulted in the reduction in subsequent incidents reported.

Of equal importance are two temporally overlapping events that potentially contributed to a reduction in incident event reporting to the Agency. The first arose from changes in the carbofuran labels and use patterns enacted in 1998, which may have resulted in a significant reduction in the use of carbofuran, in turn resulting in a decline in the reports of avian incidents (FMC 2008). The second arose from improved stewardship within the industry that contributed to the abrupt decline in carbofuran-related incidents beginning in 1994 that could have been associated with restrictions in the use of the granular formulations in 1992.

A second and potentially related event that could have contributed to a reduction in reported incidents arises from the Agency changing their reporting requirements in 1998 under FIFRA 6(a)(2) for registrants, so that only "major" incidents must be reported. For birds, "major" was defined as ≥200 deaths per event of a flocking species, ≥50 deaths per event of a songbird species, or ≥5 deaths per event of a predatory species. These changes in reporting requirements occurred at the same time as the 1998 label changes when new mitigation measures were made for the use of carbofuran. The potential effects of these new reporting thresholds on the number of incidents reported and the quality of the reports, irrespective of the pesticide involved, are significant (American Bird Conservancy, 2008). As a result of these events overlapping temporally, it was difficult to determine the cause of the decline in carbofuran-related avian incidents.

In a visual comparison of the frequency histograms presented by the Agency for "carbofuran" and "non-carbofuran" related incidents, the Panel noted that there were declines for both groups of incidents. In addition, it appeared that the number of carbofuran incidents dropped off rapidly in the mid-1990s in association with the rapid drop of carbofuran use following changes in the labeled uses. Reductions in the number of reported incidents would support the argument of usage decline contributing to incident decline. The fact that the majority of the avian incidents associated with the use of carbofuran since 1998 depended on fate of the 16 "undetermined" incidents that were found to be associated with misuse of carbofuran also supports this conclusion (i.e., 90% according to FMC and 60-95% according to EPA).

Arguments were presented that the distinction between mortality resulting from labeled uses and misuse were not important because the efficacy of a pesticide in illegally killing birds is a reflection of its toxicity to birds, its availability and its capability to be used for illegal purposes (American Bird Conservancy 2007). At a minimum, the number of incident reports stating misuse as the cause indicates that the toxicity of carbofuran to birds is high and that safeguards such as labeling information and product stewardship need to be in place to reduce the potential for misuse incidents.

Given the need for "environmental surveillance" as the only means by which "false negatives" can be identified in the Agency's current regulatory paradigm, the Panel had difficulty in

understanding why reporting requirements would be relaxed and funding for the most comprehensive incident reporting database (i.e., AIMS, American Bird Conservancy) would not be renewed. The changes in reporting requirements and reduced funding have, at a minimum, virtually negated one of the three lines of evidence (i.e., incident identification and reporting) used by both the Agency and FMC in the current regulatory decision and will affect other regulatory decisions in the future.

In conclusion, the Panel believed that without targeted field studies and effective environmental surveillance, the utility of the modeling approaches currently being emphasized has been severely compromised. As such, the Panel agrees with the Agency's conclusion that carbofuran continues to pose a risk to avian fauna despite a reduction in monitoring and/or reporting of wildlife mortality incidents associated with carbofuran, but that they cannot pinpoint the specific reasons why the reporting of wildlife mortality incidents associated with carbofuran have declined, although they believe that product stewardship, implementation of new mitigation measures, changes in 6(a)2 reporting requirements, reductions in state funding for monitoring, and changes in the carbofuran label adopted in 1998 may have all contributed to reductions in reporting of incidents of bird deaths.

4. Interpretation of Field studies and Monitoring Efforts.

In the 2006 Reregistration Eligibility Science Chapter for Carbofuran, Environmental Fate and Effects Chapter (pp. 106 - 130), the Agency discussed certain State-conducted carbofuran monitoring studies and available field studies on the effects of carbofuran. The Agency concluded that the State-conducted monitoring studies were flawed and provided only limited insight into the effects of carbofuran, and that overall the available field studies support the conclusion that carbofuran use causes a risk to wildlife, specifically birds.

Does the SAP concur with the Agency's conclusions regarding the state-conducted monitoring studies and the available field studies on the effects of carbofuran? Please provide a basis for your conclusion.

Panel Response

The Panel acknowledged that conducting field studies that adhere to *a priori* conditions of study design are difficult; however, in spite of these challenges, the Panel emphasized that even field data must conform to a minimum number of quality standards to be used quantitatively in the assessment of mortality to birds. The Panel concurred with the Agency's conclusions that while there are uncertainties associated with the data from the State monitoring studies, overall the data supported the conclusion that carbofuran-treated fields posed a risk to wildlife, specifically birds.

In support of the utility of the data, the Panel stated that the Ecological Incident Information System (EIIS) database is a usable, reliable database; the records are not limited by number of animals per incident and are supported by residue analyses, allowing cause and effect relationships to be defined for specific pesticides. Additionally, most reports come from conservation agencies, which the Panel believed gave more credence to the reports than if the database had been open to the general public's unedited input.

The Panel noted that extending the findings of pesticide residues from a sub sample of birds to the total number of birds that are dying raised a few questions of over generalizing the data, but agreed that this was the only economical way of assessing cause and effect. Monitoring programs have reported numerous cases of avian mortality associated with application of carbofuran, however, only 21% of the 399 carbofuran related incidents in the EIIS database could be attributed to registered uses of this specific pesticide. The Panel agreed that the Agency was correct in suggesting that carbofuran would not be used in abuse cases if it was not effective in killing birds; however, it must also be noted that in most cases the incidents involving carbofuran were abuse or misuse cases.

Unfortunately, the Panel also noted that most, if not all, of these studies suffered from one or more deficiencies. In addition, there were some discrepancies between the Agency's and FMC's descriptions and interpretations of the studies that need to be clarified. The Panel suggested that the carbofuran records be more fully examined in order to avoid giving more weight to studies that might confirm a predisposition to a particular finding of bird deaths, e.g., more deaths attributable to carbofuran use. The Panel identified the following deficiencies in the studies.

1) **Lack of True Control Plots:**

a. Interference of Pesticide Treatment on Control Plots: Many of the state studies (e.g. Jorgensen et al., 1989) referred to plots not treated with carbofuran as control plots but because these plots had been treated with other pesticides (e.g. chlorpyrifos), the Panel stated that they were not true controls. As a consequence, the analysis would not, strictly speaking, be testing the carbofuran treatment against a null condition. Rather, the controls would be comparisons of known carbofuran treatments versus plots not treated with carbofuran.

This distinction is important because it is difficult to interpret any findings of no effects attributed to carbofuran, if the effects seen in these "control" plots are due to other treatments. For example, the "control" plots may have higher mortality because of other pesticide effects, which would mean that "control" plots are not representative of natural mortality rates. In this sense, the Agency was correct in their statements that a strict carbofuran effect relative to natural mortality is difficult to assess from these data. The Panel feels that inferences from these studies should be constrained.

b. Mortality Rates Prior to Treatment: The Jorgensen et al. (1989) and Booth et al. (1989) studies discovered dead birds prior to the pesticide events and in the controls. This finding suggested that well-conducted, thorough searches should find some birds regardless of pesticide-related mortality. The failure of studies in the mid-1990's to find any birds post-application raises questions about the ability of these studies to detect bird mortality if it occurs.

FMC claimed that if significant mortality were occurring due to pesticides than this would be obvious to field biologists, the public, etc. The Panel argued that this was a debatable point, particularly when consideration was given the uncertainty in the ability of the field procedures to detect bird mortality pretreatment. Dramatic die-offs of large numbers of birds,

in particular larger birds, may catch people's attention, but lower density die-offs of smaller or more secretive birds, or single bird deaths could easily go undetected and hence unreported.

Another confounding fact is the simple conclusion that significant mortality would be obvious was that deaths of small, territorial breeding birds were also unlikely to be discovered and reported. To illustrate this point, the United States Geological Survey (USGS) Bird Banding lab (U.S. Geological Survey, 2003) found that 689,019 non-game birds were banded in North America in 2001, but only 8,057 birds were recaptured, resighted, or recovered during this time. As typical rates, these results suggested that less than 1.2% of these non-game species were recovered and for the smallest birds, recovery was even less likely - 131,110 vireos and warblers were banded and 89 were recovered (~ 0.07%). Based on these data, large numbers of known bird populations cannot be tracked, meaning avian mortality could easily be under-reported. The Panel concluded that it was unreasonable to assume that additional mortality of these small birds, especially in agricultural areas with relatively few people, would be noticed as FMC had suggested.

c. **Pretreatment Search Controls:** The Panel agreed with the Agency's statement that the proportion of carcasses found could vary due to a number of factors. Most of the field studies included some estimate of locating efficiency, but different habitats at the edge and in the center of a field can affect percent location efficiencies. Using pre-treatment searches for carcasses is a useful tool for determining differences in mortality before and after treatment but these pre-treatment searches were open to undetermined durations, hampering the temporal correlations of search findings to treatment (e.g. feather piles may have been around for several days to weeks but carcasses would be found for a much shorter duration).

2) **Extrapolation of Data and Associated Uncertainties:**

a. **Extrapolation of Existing Data to Estimate Impact and Mortality on Local Populations:** The Panel was concerned that the Agency and FMC each extrapolated through several steps to estimate impact and mortality on local populations. Each party used search estimates and bird counts from the State studies to estimate detection efficiencies, which were used to both correct estimates of mortality and to estimate populations, which were then used to estimate impact and mortality on local populations. Such successive extrapolations increase the uncertainty of both the final conclusions and the representativeness of the final data. The Agency argued that because of uncertainties in the State studies, data from these studies should not be used for quantitative analysis, yet both the Agency and FMC used these studies to estimate field mortality effects and to compare these estimates against model predictions. The Panel asks for consistency in the application of arguments for use of the data.

b. **Derivation of Estimates for Absolute Number of Birds Killed:** The Panel was also concerned about attempts to use the data to derive estimates of the *absolute* numbers of birds killed, specifically from the Booth et al. (1989) and Jorgensen et al. (1989) studies cited by FMC (2008). The approach employed by FMC (2008) required one to know not only how many dead birds were recovered in the field, but also how many birds died and

were not recovered. The contradiction here is that a precise estimate of recovery efficiency would be needed for the FMC approach but that such a precise estimate does not exist.

Attempts to quantify efficiency of bird recovery in these studies primarily involved "seeding" study sites with dead birds. Such studies may be useful for comparing search efficiencies of different field workers and possibly to compare recovery efficiencies at different sites, but the Panel believed that these efficiencies are in all likelihood, insufficient both to demonstrate that searchers will find kills of wild birds and to be used as a quantitative measure of the percentage of natural kills recovered, even when corrected for scavenging.

A key unknown in estimating the number of birds killed is the propensity of impaired birds to leave the study site or hide. Burger et al. (2002) noted that one observed effect of AChE inhibition could be hiding. In one study, captive European starlings were exposed to another AChE inhibitor, chlorfenvinphos (Fryday et al., 1996). In this study, exposed birds moved away and hid after exposure to the pesticide and even in the simplified environment of an aviary, the researchers noted they had trouble locating dosed birds. While this study was not conducted with carbofuran, the results suggested that simple "seeding" of birds is insufficient to mimic the difficulty of locating dead birds in a field. Even studies that utilized radiotagging experienced difficulties in relocating tagged birds that had died, further supporting the argument that quantifying bird recovery efficiency is difficult.

c. **Realized vs. Observed Mortality:** Realized mortality may be very different than observed mortality. In addition to the scavenging and the decomposition of carcasses, an unknown proportion of intoxicated birds may leave the affected field to die elsewhere or conceal themselves from searchers. Many birds may also become moribund and as a result suffer indirect mortality through predation, disease, etc. These birds may not be counted as mortalities in searches, which would introduce a negative bias into the mortality assessment.

d. **Population Effects:** The Panel agreed that the State-sponsored field studies demonstrated avian mortality occurred and in some cases, indicated that the cause of the mortality could be associated with carbofuran treatment. What was not clearly demonstrated by the State-sponsored field studies was what impact carbofuran had on local, regional, or national populations of affected birds. To show a true population effect, a study would have to show that the mortality produced by carbofuran was additive, not compensatory. In other words, would the birds that die from carbofuran have died during the time period (e.g. year) of interest, or did carbofuran result in mortality that was in addition to that caused by other factors of mortality such as disease, weather or predation? The field studies and incident reports do not clearly show a population effect.

Summary:

The Panel agreed with the Agency that incident reports and field studies do not allow for quantification of the level of wildlife mortality associated with carbofuran but rather provide general estimates of the gross magnitude of risk to wildlife, specifically birds.

Other Comments:

Acceptance Criteria and Guideline Development: Some of the Panel commented that given the tremendous amount of effort devoted to the state-conducted monitoring studies and the field studies described in the documentation provided, that it was unfortunate that these studies did not meet acceptance criteria; criteria that have not yet been defined. The Agency consistently stated that the absence of mortality did not imply that mortality did not occur. On the other hand, these Panel members suggested that the absence of mortality could simply be taken at face value. These Panelists believed that it would be important to develop guidelines to promote consistency in interpretation of the data for future use in risk assessment.

Avian Mortality Study Design: Some of the Panel recommended that in the future, scientifically reliable studies on avian mortality should include all of the following: 1) pre-treatment surveys of fresh carcasses, feather piles should be examined for freshness - dried piles should be disregarded; 2) rapid (2-12 hours) post treatment surveys; 3) later (12-48 hr) surveys; 4) sampling points or transects that are randomly chosen; 5) surveys should be in areas sensitive and as inclusive as time allows - ideally the entire experimental area should be searched; 6) residue analyses of carcasses are needed to verify insecticide exposures; 7) spray cards and/or vegetation in all habitats and plots must be used; and 8) control sites should not be exposed to other pesticides within a period less than the half life of the pesticide in question or during the experiment. These Panel members indicated that undoubtedly, there would be other experimental design requirements but believed that studies that lack these basic criteria would suffer serious weaknesses and be of limited value. Using birds equipped with radio telemeters would help answer many problems about dispersion and whether floaters or breeders are being affected by carbofuran or other toxicants (see discussion on "Radio Telemetry" below).

Habitat Quality (Edge Habitat vs. Field Habitat): Some of the Panel discussed how examination of habitat associated with field borders vs. the field proper was another factor that has been used to evaluate the quality of these studies. The Avian Effects Dialogue Group (AEDG, 1994) expressed concerns with respect to monitoring and field studies associated with edge habitats because it was assumed that these habitats would support the greatest number and diversity of avian species. Field studies at the time were divided into two tier types, screening and definitive, with the former focused on documenting exposure and mortality, and the latter on refining exposure and determining effects on avian populations.

These Panelists noted that the Agency's paradigm for assessing the risks pesticides posed to wildlife changed so that field studies were, in most cases, no longer required to support

pesticide registration. This occurred at the same time as the AEDG's consideration of monitoring and field studies and the associated findings were developed. As a consequence, the motivation for the conduct of field studies and for refinements in the methodologies for conducting these studies was severely reduced. These Panelists commented that the Agency's third line of evidence, incident reports, monitoring, and field studies were of very little value other than to indicate that under some conditions birds can be exposed to lethal levels.

Indiscriminant vs. Selective Mortality: Some of the Panel addressed whether mortality from carbofuran is indiscriminate or selective towards breeding or non-breeding birds. During the breeding season there is some fraction that are non-breeding or 'floater' birds and some fraction that are actively breeding and reproducing for most avian populations. They argued that mortality among non-breeders would be less deleterious to a population than mortality to the breeding segment of the population. These Panelists commented that utilizing known case studies would shed light on mortality risks experienced by local populations of birds

Radio Telemetry and Statistical Sampling Approaches: Some of the Panel would like to encourage the Agency to examine the use of radio telemetry studies to resolve the issue of mortality estimates. In the absence of known fate data, estimates of mortality should be interpreted as indices and not as true estimates of mortality. This is important if the data are to be used to estimate impact on population structures. These Panelists noted that there are specific techniques that could help overcome this problem for future studies, such as the application of statistical sampling approaches that have become virtually mandatory for bird surveys in the past decade to estimate detectability (e.g. distance sampling, double observer sampling, etc. (Burnham et al., 1980; Buckland et al., 1993; Nichols et al., 2000; Rivera-Milan et al., 2004).

5. Risks of mortality to birds in and around a carbofuran-treated use site.

Consistent with the EPA's Ecological Risk Assessment Guidance, the ecological risk assessment that supports the 2006 IRED, as well as the draft NOIC, uses multiple lines of evidence to assess risks of mortality to birds in and around a field treated with carbofuran. These lines of evidence include results from deterministic risk estimates, probabilistic risk estimates, field studies and wildlife mortality incident reports. The Agency incorporated SAP-reviewed methods and models in developing and evaluating these lines of evidence. Since the IRED was published, new avian data (MRIDs: 47128701, 47152901; 47143706, 47107601) were provided by the registrant for consideration as alternate model inputs to estimate the probability of mortality risks to birds. As discussed in EPA's draft NOIC and supporting documents, EPA did not find that these new data alter EPA's previous probabilistic risk assessment conclusions.

Having heard the EPA presentations and the public comments on EPA's proposed action, has the information provided in this meeting, taken as a whole, caused the panel to reach a conclusion contrary to EPA's assessment that carbofuran poses a significant risk of mortality to numerous avian species in locations where carbofuran is used? If so, please provide the basis for that conclusion.

Panel Response

The SAP came to the meeting with a large compilation of reports and voluminous analyses of data that were summarized in U.S. EPA's IRED and draft NOIC, both of which used multiple lines of evidence to assess impacts to birds in and around carbofuran treated fields. The Agency's charge questions asked the SAP to review the risk assessment and to examine the quality of the new data as well as its impact on the probabilistic risk assessment (PRA) and its conclusions.

Specifically, the Panel was asked to examine the EPA's assessment and to decide if they concurred with the EPA's conclusion that carbofuran poses a significant risk of mortality to numerous avian species in locations where carbofuran is used based upon the information provided prior to and at the meeting.

The U.S. EPA's Ecological Risk Assessment Paradigm requires that receptors and complete or potentially complete exposure pathways coexist for there to be risks. Further, the risk associated with an exposure is a function of dose received and the toxicological properties of the chemical of concern. The Panel was asked to consider three lines of evidence:

Line 1: Deterministic Risk Assessment;
Line 2: Probabilistic Risk Assessment (Charge Questions 1 and 2);
Line 3: (Part 1) Wildlife Mortality Incidents (Charge Question 3) and (Part 2) Field Studies (Charge Question 4).

The Panel evaluated these lines of evidence and EPA's interpretation of available data in the context of the Charge Questions. The Panel's findings are summarized below.

Line 1: Deterministic Risk Assessment
All parties agreed this was a conservative screening assessment and agreed that it indicated risk to birds from carbofuran exposure.

Line 2: Probabilistic Risk Assessment

Terrestrial Model Versions, Models TIM v.1.0 and TIM v.2.0/2.1 (Charge Question 1):
The Panel believed that the Agency did implement the probabilistic models in a manner that was consistent with previous SAP's recommendations and that sufficient "bridging" of the TIM v.1.0 and TIM v.2.0/2.1 models, carried out with new FMC data when available, showed that the risk calculations were not significantly altered when the newer models were used.

As a result, the Panel concurred with the Agency's risk conclusion, namely that the results of modeling continue to support the conclusion that there is risk of avian mortality in and around carbofuran treated sites.

New Data Impacts (Charge Question 2):
The Panel commended FMC for their efforts in generating new data (avian avoidance of pesticide treated food, food matrix effects on toxicity, and AChE recovery kinetics) in an attempt

to advance the PRA of carbofuran but found the limitations in the data, primarily due to study design, introduced uncertainty and limited their utility in the risk assessment.

There were minor differences in opinion within the Panel regarding EPA's analysis of each of the studies, but overall, the Panel believed the Agency's application of the new data as screening data was appropriate, though uncertainties were associated with this. While the Panel understood the Agency's attempts to utilize the data in the PRAs, they believed that these uncertainties were significant and that the Agency would have been justified in not including the new data in the models. More than one Panel member thought that the approach of changing all the variables simultaneously was not advisable. For example, evaluating the implications of the AChE inhibition recovery study or food matrix effects might each be appropriate singly but because the interactions among these responses are unknown, jointly incorporating them into the model introduced additional uncertainties. Similarly, if one accepted the importance of food matrix on toxicology, then other variables based on aqueous bolus dose methods, including the recent AChE recovery study, should have been reexamined. In addition, the uncertain effect of the gorge feeding scenario from the food matrix study where birds are provided small doses of food over a long period rather than a single "gorge" dose should have been reexamined.

In spite of these reservations, the Panel agreed that the new data, taken in aggregate, did provide a means to further assess avian risk but that due to the limitations in data quality, these new data did not significantly alter the overall PRA estimates, and therefore, would not alter the risk conclusions drawn by the Agency.

Line 3: Wildlife Mortality Incidents and Field Studies

Part 1: Wildlife Mortality Incidents (Charge Question 3):
Given the information provided, the Panel did not believe definitive conclusions could be drawn from the wildlife incident mortality data. Variables such as the effects of label use changes, improved stewardship, reduction in state monitoring efforts and the change in the regulatory requirements for reporting were happening simultaneously over the collection period, confounded the interpretations.

Part 2: Field Studies (Charge Question 4):
The Panel acknowledged that field studies are difficult to structure, execute, and interpret; however, they can, and in this case did provide useful information regarding probabilities for avian mortality in the field. Some Panel members observed that data were sometimes used for both sides of the argument, adding to the confusion. For example, not finding dead birds did not mean they weren't present, but conversely, finding dead birds did not mean they died because of carbofuran use.

The Panel agreed that both the incident reports and field monitoring studies provided useful information, but that a more systematic approach to collecting and interpreting the data was needed before it could be used quantitatively in PRA.

Overall Conclusion of the Avian Risk Assessment (Charge Question 5):
The Panel concluded that the magnitude of the avian risk remains in question given uncertainties associated with the lines of evidence put forth by the Agency. On the other hand, the Panel does not believe that the new data supports changing the Agency's conclusion regarding avian risk.

The Panel's underlying concern is that both the Agency and FMC have sought to incorporate refinements to the models suggested by the 2004 SAP. These refinements had significant and disparate effects on the resulting outputs and conclusions from the modeling depending on how each model was parameterized. Issues associated with how data were incorporated in the revised Agency's TIM modeling and FMC's LiquidPARAM modeling were the subject of Charge Question 2d.

Much of the Panel's discussion centered on data quality issues and study design features that introduced uncertainty into the utilization of the data. There were also concerns expressed at various points in the discussions that the studies and models were developed by FMC and their panel of experts outside of a public peer review process and without stakeholder involvement (e.g., Agency involvement in the design of non-guideline laboratory studies, development of LiquidPARAM). Therefore, quantification of the avian risk was difficult given the uncertainties associated with the "best" ways to incorporate both the recommendations of the 2004 SAP and new data and approaches presented by FMC.

Clarifications and Additional Panel Comments:

Significant Risk: "Significant" as used in the risk conclusions was never defined by the Agency for the Panel, but given the toxicity profile of the active ingredient, the Panel was willing to concur with the general risk conclusions they were asked to review and comment upon. The Panel encouraged EPA to define how they will interpret magnitude of effects and risk and to set criteria that delineate high, moderate and *de minimus* risk criteria for future assessments. See also comments under **"Impacts on Abundant versus Rare Species"** below.

Standardized Approach to Implementation of PRA: Summaries of fixed and variable input parameters, ranges of variation when applicable, and clear delineation of other input parameters, would decrease misinterpretation of input parameters, increase the transparency of the PRA approach, and decrease widely divergent risk outcomes from the same set of data. For example, the model results are very sensitive to the feeding time step and avoidance scaling, two factors that the Agency and FMC interpreted differently. To avoid the generation of widely disparate modeling results, a standardized approach for input, conversion, and presentation of parameters is essential.

Model Evaluation: However sophisticated they might be, models are only mathematical representations of the real world; a more precise model is not necessarily a more accurate model. There is a need to evaluate operating parameters and assumptions with actual field data.

Differential Species Sensitivity: The Panel noted in its discussions that for any effect studied, that responses across species (i.e. species sensitivity) needs to be better understood and

represented before better correlations between laboratory and field observations can be made. This understanding is critical and needs to be integrated into the modeling parameters and the risk calculations, as well as being considered in the interpretation of risk conclusions.

Impacts on Abundant versus Rare Species: One Panel member offered the following comments on the possible differential impacts of carbofuran use on abundant versus rare species. Much of the Panel's discussions of risk were centered on carbofuran impacts on relatively abundant species such as red-winged blackbirds or mallards. These studies tended to focus on impacts to relatively abundant birds because these are birds that can be worked with in the lab and in the field, but not all birds are abundant. For these abundant species, determining the significance of risk using population size as an endpoint may be analogous to determining harvest rates for hunted species. This is a challenging undertaking even in the case of game birds where available data and other resources are greater than those available for most birds. With the data and resources available, trying to determine how many birds can be killed by pesticides with out threatening the population will be exceptionally difficult.

While the Panel recognized that consideration of acceptable losses to different species' populations was beyond the scope of this SAP, they believed that consideration should be given in the future to this issue, particularly for less abundant species (e.g. Henslow's sparrow, mountain plovers etc.) that show population reductions, are protected by the Endangered Species Act (ESA), or that occupy or stopover on agricultural lands, adjacent Conservation Reserve Program (CRP) land, windbreaks and other areas that are treated or proximate to treated land. A different criterion of "significant" mortality would need to be applied to these species.

For example, the populations of Henslow's Sparrows have dropped dramatically, approximately 90%, since the 1960s. The center of the Henslow's Sparrow's range is in the corn belt of the United States where they can be observed in CRP land adjacent to cropland. American Golden Plovers are also a conservation concern. These birds use these lands adjacent to corn and soybean fields in the Midwest and Great Plains during their migration. Further west in the Great Plains, Mountain Plovers are the subject of significant conservation concern and investment and they nest directly in crop fields. These are not species listed under ESA, but with their small and declining populations, we need to carefully consider the impact of excess mortality on these species. This is not to suggest that these example species are known to be at risk from carbofuran, but rather to emphasize that the status of rare but not endangered species should not be ignored.

Cumulative AChE Inhibiting Compounds: In many agroecosystems, a variety of organophosphate and carbamate pesticides are applied at varying rates and on different time schedules. Because avian and other ecological receptors exploit multiple fields and field edges as a function of the food availability and habitat attributes and are not restricted to individual fields, the Panel recommended that the use and management of AChE inhibiting compounds on an integrated landscape scale be considered. The EPA and state agencies currently manage water quality in watersheds using the total maximum daily load (TMDL) approach. Development and application of the terrestrial equivalent of the TMDL could be investigated as a tool to evaluate and manage exposure and risks to pesticides that exhibit common modes of action, such as carbamates and organophosphates. A terrestrial 'TMDL' that takes into account habitat

availability/quality, non-target species presence, diversity, and phenology, crop types, pest diversity and phenology, and availability/diversity of pest control options may provide a more robust approach that minimizes aggregate risks to non-target biota, while maximizing flexibility of pest control options available to the agricultural community.

Additional Probabilistic Risk Assessment Modeling:
The Panel was instructed to consider only registered uses of carbofuran as the basis for the Agency's ecological risk assessment for the draft NOIC. Some Panel members believed that additional probabilistic risk assessment modeling using a range of exposure scenarios should be done if the Agency chooses to retain or add uses of carbofuran.

Industry Wide Task Force for Data Sharing: Several Panel members noted that data might be available in the published literature which has not been fully utilized, specifically with respect to the use of habitat by avian species and on feeding behavior. The Panel noted at several points during discussions the uncertainty generated in modeling and subsequent interpretation of results with respect to these types of data. These Panelists recommended the formation of a stakeholder (e.g., EPA, industry, and academia) task force to share data and to compile a comprehensive database of laboratory and field data, as well as guidelines for how to utilize these data in future regulatory risk assessments for pesticides. This could help alleviate the problem of differential interpretation of data by developing consensus on base data inputs to be used in risk assessment models.

HUMAN HEALTH RISK SECTION DETAILED RESPONSES TO CHARGE QUESTIONS

For human health, EPA is seeking SAP comment on two specific areas: 1) the point of departure (PoD) and FQPA safety factor determination for dietary risk assessment for infants and children and 2) the PoD for dermal risk assessment for workers.

1. Point of Departure (PoD) and FQPA Safety Factor Determination for Dietary Risk Assessment for Infants and Children

In the 2006 human health risk assessment for carbofuran, the Agency used a benchmark dose (BMD) approach from one comparative AChE study (adult and juvenile rats) submitted by FMC, to derive the PoD for risk extrapolation. This study showed that PND11 pups were more sensitive to carbofuran when compared to adult rats based on brain AChE inhibition. Although RBC AChE data were also provided in this study, these data were determined to be unreliable. At that time, the Agency applied a FQPA safety factor based on the lack of RBC AChE data in pups. The value of the safety factor was based on a 5-fold sensitivity of RBC AChE for carbofuran in adult rats compared to brain AChE inhibition (i.e., RBC AChE was inhibited at lower dose than brain AChE). The Agency assumed that RBC AChE inhibition would also be more sensitive than brain AChE inhibition in pups.

In the last year, three more studies in juvenile rats became available. One study was sponsored by FMC; two were performed by EPA's Office of Research and Development (ORD). The two FMC comparative AChE studies and ORD's PND11 study provide remarkably similar brain AChE data and when evaluated in combination, provided data from low to high doses. However, the Agency identified problems with the RBC AChE data from the 2007 FMC study. Furthermore, the ORD studies fail to provide RBC AChE data in juvenile rats at the low end of the dose-response curve. The sensitivity of RBC AChE inhibition in juvenile rats at lower doses remains uncertain.

1a. New Comparative Acetylcholinesterase (AChE) Studies

The pesticide registrant sponsored two comparative AChE studies with carbofuran. EPA previously concluded that the RBC AChE data included in the first study (MRID 46688914) were unreliable. The Agency has similarly concluded that the RBC AChE inhibition data in the second comparative AChE study, conducted in 2007 (MRID 47143705), are not sufficiently reliable for extrapolating human health risk. The justification for this determination is summarized in the issue paper and discussed in detail in the data evaluation record (DER). In brief, the RBC AChE data from this study were highly variable in all animals, especially PND11 pups, with control values differing between component studies and even within a study. Moreover, re-analysis of samples due to failure of acceptance criterion likely led to less detected inhibition.

Please comment on whether, in light of the available scientific evidence, it is reasonable for EPA to conclude that the second comparative AChE study (MRID 47143705) contains reliable brain AChE data for use in human health risk assessment but not RBC AChE data.

Panel Response

The Panel unanimously agreed it was reasonable for EPA to conclude that the second comparative AChE study (MRID 47143705) contained reliable brain AChE data for use in human health risk assessment but did not contain reliable RBC AChE data.

Since the early 1990s, much effort has gone into defining standard operating procedures that would enable any competent laboratory to assess AChE inhibition in RBC after exposure to carbamate or organophosphorus pesticides. To date, however, this goal has not been fully attained. The difficulty in part reflects hemoglobin interference with spectrophotometric assays, which, in the classic Ellman method, generate a reaction product whose absorption spectrum (max at 412 nm) largely overlaps with hemoglobin. The difficulty is compounded in samples from rats and mice, whose RBC carry only 10% as much AChE as do human RBC. Studies involving carbamates must cope with the further complication of rapid recovery in vitro because rate constants for regeneration of *N*-methyl carbamylated enzyme allow 50% recovery in less than one hour.

All of these problems appeared to have been operating in FMC's studies on inhibition of RBC AChE by carbofuran. The data were highly variable, with coefficients of variation approaching 50% in some cases and, partly in consequence, no significant reductions were observed in treated rat pups at any time or dose despite mean value shifts up to 39%. Additional factors contributing to this unsatisfactory outcome, as documented in the Data Evaluation Record for MRID 47143705, appeared to have been slow sample preparation, use of diluted samples, failure to keep samples cool before assay and the necessity of resorting to multiple re-assays because of inconsistent results. On grounds of high variability, with many samples failing to replicate, and on grounds of inadequate procedures, the RBC data are of dubious value. The Panel agreed that EPA is well-justified in taking the position that the data on AChE inhibition in rat RBC, particularly with PND11 pups, are not acceptable for the purpose of predicting health risk from carbofuran.

The brain data from the same study are considerably more robust, with much less variability, and clearer dose-response relationships than RBC data. These data also agree with those from a similar study that the EPA ORD carried out. In the draft "NOIC," EPA finds the brain data informative, but chooses to rely mainly on internally generated RBC data because of a published study suggesting that this is the more sensitive endpoint.

This decision can be questioned for the following reason. Inhibition of RBC AChE is at best a surrogate for toxicity elsewhere including a variety of sites outside the brain where enzyme inhibition generates acute toxicity. Such sites include motor endplates of skeletal muscle, synapses in autonomic ganglia, the heart, the vasculature, and the gastrointestinal tract. It is recognized that, after uptake through dermal, oral, or inhalational exposure, any pesticide must reach its tissue targets via the blood stream. Such pharmacokinetic considerations explain why a

given dose of inhibitor might affect RBC AChE sooner or somewhat more extensively than brain, muscle, nerve or other tissues. In fact this may be true with carbofuran, although data on a variety of carbamates show that RBC AChE is rarely more affected than brain AChE. In any case, such effects do not mean that inhibition of RBC AChE is preferable to that of brain AChE as an index of toxicity. It was generally agreed by the Panel that good RBC data are of value when data from target tissues are unavailable. Most also emphasized, however, that data showing inhibition in this non-target tissue, even if measured accurately, were of questionable relevance when good data are available for brain.

Brain AChE was used as the appropriate endpoint for the previously conducted cumulative risk assessment of the *N*-methyl carbamates (NMCs), because it is a target of toxicity, and RBC AChE was not used as the endpoint. The following are quotes from the September 24, 2007 "Revised *N*-Methyl Carbamate Cumulative Risk Assessment."

"Toxic potencies for the NMCs were determined using brain AChE inhibition measures at peak inhibition following gavage exposures in rats. Brain AChE inhibition is a direct measure of the mechanism of toxicity and thus does not have the uncertainty associated with using blood measurements of cholinesterase inhibition, which serve as surrogates for cholinesterase inhibition in the peripheral nervous system. Furthermore, relative toxic potencies derived from brain data were shown in the preliminary assessment to be similar to those derived from red blood cell data but showed less variability, and thus less uncertainty, when comparing potency across the NMCs."

"Also, the agency has elected to use 10% inhibition in brain AChE as the response level for the RPFs and PoDs. The 10% response level is health protective in that no functional or behavioral effects have been noted at or below this level in adult or juvenile animals. Thus the 10% response level provides a point where functional or behavioral neurotoxicity is not expected."

From this perspective, with brain AChE chosen as the most suitable and reliable information for cumulative risk assessment, and with reliable brain AChE data for both adult and juvenile animals, many of the Panel believed it was reasonable to argue that brain AChE should be the primary endpoint for the carbofuran risk assessment as well.

In opposition, one Panelist pointed out that in choosing a common endpoint for cumulative risk assessment, the entire database for all cumulative assessment chemicals must be considered, but this does not preclude the use of a more sensitive endpoint for assessing the risk of a single chemical within the group. This Panelist argued that it is important to take into account all available data and that measures of overt toxicity are especially valuable for risk assessment. For example, a 1978 teratology study obtained clinical signs attributed to carbofuran (highlighted in a California toxicology data summary, http://cdpr.ca.gov/docs/risk/toxsums/toxsumlist.htm). In this study, pregnant rats showed a dose-related increase in chewing motions at the oral (gavage) LOEL of 0.1 mg/kg (lowest dose tested); mouth smacking or chewing is a valid index of neurotoxicity. There were no data to show whether brain or blood AChE would have been a better indicator for this endpoint. It is worth noting that the BMD_{10} and $BMDL_{10}$ in pregnant rats for this endpoint were 0.04 and 0.03 mg/kg, respectively, and approximated the present values for brain AChE in PND11 pups.

1b. Experimental Dose-Time-Response Model and the Derivation of BMD_{10}

The exponential dose-time-response model used by the Agency to derive BMD_{10}[1] and $BMDL_{10}$ estimates for carbofuran is similar to the model used in the NMC cumulative risk assessment and previously reviewed and supported by the SAP on two occasions (FIFRA SAP, 2005a, b). For the carbofuran risk assessment, the Agency's dose-response analysis for brain AChE in PND11 pups included data from three PND11 studies (two FMC-supported studies and one EPA-ORD study) and thus provides robust estimates for use in the PoD determination. Conversely, the Agency's RBC AChE dose-response analysis for PND11 rats only includes data from one EPA-ORD study where only high doses were used. The BMD and BMDL estimates for RBC AChE activity are not high confidence estimates as they are extrapolated over 50-fold lower than the lowest tested dose in the EPA-ORD PND11 study.

Please comment on whether the scientific evidence currently before the Agency supports the Agency's conclusion that brain AChE data provide a more robust PoD than the RBC AChE data.

Please also comment on whether the scientific evidence currently before the Agency supports the EPA's conclusion that the Agency's benchmark dose analysis of the brain AChE data from three studies provides a scientifically appropriate basis for assessing carbofuran risk to infants and children.

Panel Response

This question focuses on "EPA and FMC meta-analysis estimates" in the Agency's overview presentation of the carbofuran human health risk assessment during the SAP meeting. Unfortunately, information on the data used and the model and calculation applied to arrive at each BMD_{10} and $BMDL_{10}$ in the tables below was dispersed throughout the supporting documents the Panel were provided in advance and, in some cases, not provided to the Panel until after the meeting was underway. The most relevant documents were the FMC report "Meta-Analysis of Benchmark Doses for Acute Oral Exposure to Carbofuran" dated September 12, 2007 [MRID 47232801] and the EPA documents "Dose-Time Response Modeling of Rat Brain AChE Activity: Carbofuran Gavage Dosing" dated October 5, 2007 and "Dose-Time Response Modeling of Rat RBC AChE Activity: Carbofuran Gavage Dosing" dated October 23, 2007.

The following two tables show the BMDs that the Panel considered and indicate the data sources used.

[1] The BMD_{10} is the estimated dose where 10% inhibition of AChE is expected. The $BMDL_{10}$ is the lower confidence limit of the BMD_{10} and is the value used as the PoD in human health risk assessment.

Table 2. Rat Brain AChE Activity: Carbofuran Gavage Dosing

Age	Brain (mg/kg)		Data Source
	BMD_{10}	$BMDL_{10}$	
EPA PND11	0.041	0.031	1st FMC CCA study 2nd FMC CCA study EPA-ORD PND11 study
FMC PND11	0.035 M 0.028 F	0.026 M 0.021 F	1st FMC CCA study 2nd FMC CCA study
EPA Adult	0.073	0.048	Padilla et al. 2007 McDaniel et al. 2007 1st FMC CCA study 2nd FMC CCA study EPA-ORD PND11
FMC Adult	0.062 M 0.073 F	0.042 M 0.049 F	Padilla et al. 2007 McDaniel et al. 2007 1st FMC CCA study 2nd FMC CCA study

Sources: Brain AChE Activity: Carbofuran Gavage Dosing, October 23, 2007; FMC Meta-analysis of BMD for Acute Oral Exposure to Carbofuran, MRID 47232801.

Table 3. Rat RBC AChE Activity: Carbofuran Gavage Dosing

Age	RBC (mg/kg)		Data Source
	BMD_{10}	$BMDL_{10}$	
EPA PND11	0.0017	0.00054	EPA-ORD PND11 study
FMC PND11	0.070 M 0.36 F	0.029 M 0.022 F	2nd FMC CCA study
EPA Adult	0.063	0.024	Padilla et al. 2007 McDaniel et al. 2007 EPA-ORD PND11 Anderson S. 45675701
FMC Adult	0.069 M 0.10 F	0.045 M 0.061 F	Padilla et al. 2007 McDaniel et al. 2007 2nd FMC CCA study Anderson S. 45675701

Sources: EPA Dose-Time Response Modeling of Rat RBC AChE Activity: Carbofuran Gavage Dosing, October 23, 2007; FMC Meta-analysis of BMD for Acute Oral Exposure to Carbofuran, MRID 47232801.

There were two problems with the RBC data: (1) the small sample size ($n = 30$) given the large amount of variability in the data and lack of low-dose data in the EPA-ORD PND11 study, and (2) shortcomings in the FMC studies as identified by the Agency.

The Panel noted that the Agency was provided very limited data with which to calculate a $BMDL_{10}$. This deficiency led to a great deal of uncertainty regarding the $BMDL_{10}$ calculation. With such uncertainty in the calculation, the Panel could not be certain whether the apparently low $BMDL_{10}$ for RBC in juveniles was more a statement of our ignorance than it was an indication that juveniles are orders of magnitude more sensitive than adults. In any case, the Panel agreed that the data from the RBC assays presented were inadequate and inconsistent, and that they did not give reliable, consistent estimates of BMD_{10} and $BMDL_{10}$, especially for juveniles.

In contrast, the brain data showed remarkable consistency between EPA and FMC analyses. Furthermore, the $BMDL_{10}$ values are much closer to the BMD_{10} values than they were with RBC because the sample sizes were adequate. The Agency's data analysis and model fitting are well documented.

Relying on the BMD approach and determining from there a PoD, as practiced by the Agency for the carbofuran risk assessment, is state of the art science and the Panel strongly encouraged the Agency to follow this approach for all studies where possible. The BMD approach makes transparent use of all available dose response data in a traceable and reproducible manner and is the preferred approach.

Application of the BMD requires a careful selection of the Benchmark response (BMR) value which should be chosen such that precision of the BMD estimate is not unduly impaired by extrapolation, i.e. the BMR is usually chosen between 1% and 10% change, though a BMR equal to 20% has been used in Europe in some cases as PoD (Personal Communication, Wout Slob, RVIM, The Netherlands). Selection of a BMR represents a balance between the desire to choose a low and preferably non-adverse level of response and the need to be able to define BMD and BMDL values that are not critically dependent on the model(s) used. In practice, this means that the BMD should be estimated without substantial extrapolation below the dose range that would produce a measurable response. There are publications in the statistical literature that discuss usage of more than one BMR at the same time in a BMD analysis (e.g., Nitcheva et al., 2005, Wu et al., 2006).

It is common practice to use a limited number of default BMR values (either 5% or 10%). For continuous data, a 5% response level is often within the observed range in the BMD approach even though the effect sizes that can be detected by the NOAEL approach may exceed 5% (Health Council of the Netherlands, 2003). Cases may appear where the default BMR of 5% has to be increased to avoid estimating the BMD (and BMDL) with extrapolation. This seems to be the case for carbofuran where the effects at the low-end dose are large and not in all studies covered by dose groups, e.g., a BMR of 20% for inhibition of brain AChE could be necessary (JMPR, 1998).

The Panel discussed the BMD approach used by the Agency for continuous data; the exponential dose-time-response model is a new model class included into EPA BMDS software (BMDS 2.0) compared to the previous version (BMDS1.4.1c). Version 2.0 offers the exponential family, in addition to the linear polynomial, power, and Hill families. The Panel suggested that the Agency consider providing more information on model selection strategies and they should become part of the analysis and reporting. This comment applies in particular for the present BMD analysis where a meta-analysis over several studies and an analysis of dose-time response data has been performed. Overall, visual inspection of the dose-response curve will corroborate the BMD.

Close examination of the results led the Panel to some additional findings of interest. EPA's analysis (Setzer, EPA-ORD-NCCT) indicated that not only do the PND 11 animals have a lower "peak" AChE inhibition (by about 1.8 fold), but they also had a slower recovery (by a little more than 4-fold). Both of these factors influenced the "Area Under the Curve" (AUC) of brain cholinesterase inhibition. This AUC was likely to be a better dose metric for the influence of carbofuran presented in more continuous dosing patterns (e.g. repeated consumption of milk and milk-based formula by young infants, or consumption of carbofuran and other carbamate or organophosphate AChE inhibitors in different foods in the same day or before recovery is complete).

When the greater potency, as measured by the peak, was combined with the longer half life, the two combined appear to indicate a relative sensitivity in terms of AUC for inhibition of 4.379 * 1.825 = 8.1 fold with 5%-95% confidence limits of 5.5 – 14.3 based on EPA's standard errors for each estimate treated independently (Setzer, EPA-ORD-NCCT). On the other hand, it was not at all clear that the errors in these estimates are in fact independent. A more sophisticated analysis could be incorporated into the basic analysis to model the uncertainty distribution of AUC-based sensitivities directly based on the available data in both PND11 and adult experiments.

Some Panel members questioned the assumption that a 10% level of brain AChE inhibition (i.e., BMD_{10}) is sufficiently harmless to be used as a point of departure in risk assessment. It was noted that as more refined brain data become available, we are beginning to understand that not all regions of this organ show the same level of AChE inhibition. Thus a 10% inhibition for the whole brain may imply significantly greater inhibition in a more sensitive region. Another potential reason for concern about safety at BMD_{10} arose from one recent study on the organophosphate anticholinesterase, chlorpyrifos, published as yet only in electronic form (Yang et al., 2007). This study observed that chlorpyrifos suppressed neurite outgrowth by cultured mouse neurons. The effect was seen only in neurons expressing AChE that encoded an active site serine, but the mechanism of the effect remains uncertain because it occurred at doses that caused no measurable AChE inhibition. In contrast, other Panel members expressed concern about equating organophosphate effects to potential carbamate effects. The *N*-methyl carbamates and organophosphates are very different in their physicochemical properties, metabolism and disposition, and in their persistence as AChE inhibitors, so much so that findings with organophosphates should not be extrapolated to carbamates, particularly at levels below those causing AChE inhibition. Given that other organophosphate anticholinesterases, like echothiophate, and carbamate anticholinesterases have not been shown to exert similar toxicity, even at doses causing substantial inhibition (Brimijoin and Koenigsberger, 1999), some Panelists believed that it was premature to conclude that undetectable levels of AChE inhibition after carbofuran exposure pose significant risk to human infants. Nevertheless, the possibility that this might ultimately prove to be the case led some Panelists to conclude that current data were insufficient to overcome the statutory directive that a 10-fold FQPA factor should be imposed unless reliable data showed that a smaller factor would be safe.

In summary, AChE inhibition in PND11 rat brain was considered to be the best currently available point of departure for several reasons. First, brain AChE is a key target, closely related to the fundamental mechanism of toxicity. Second, robust data on brain AChE inhibition have been obtained both by FMC and by EPA-ORD, with good concordance. Third, these data allow estimation of BMD_{10} with fair precision. Fourth, the RBC AChE is at best a surrogate for the physiologically critical pool of AChE in real target tissues, where inhibition leads directly to toxicity. Some Panelists were concerned that the studies of PND11 rats did not tie inhibition to toxicity (behavior, motor, evidence of neurological damage). This limitation reflects the limited range of toxic signs detectable in very young pups. Nonetheless, it forces us to assume a constant relation between AChE inhibition and actual toxicity across subject age. With these qualifications, however, the Panel concluded that overall, the Agency's benchmark dose analysis of the brain AChE from three studies provided a scientifically appropriate basis for assessing carbofuran risk to infants and children as long as suitable safety/uncertainty factors were included.

1c. Red Blood Cell (RBC) and Brain Acetylcholinesterase (AChE) Inhibition

As noted above, in 2006 the Agency was concerned that RBC AChE inhibition was a more sensitive endpoint than brain AChE inhibition in both adult and juvenile rats. This concern was based on a more limited dataset of adult rat data available at that time (1 FMC study). With the availability of the new AChE studies from FMC and EPA-ORD, more data in both adult and juvenile animals have been evaluated. Based on the more extensive data, the Agency has concluded that for adult rats, RBC and brain AChE are similarly sensitive. In juvenile rats, the lowest dose tested in both EPA-ORD studies (PND11 and PND17) resulted in approximately 50% RBC AChE inhibition. At the BMD_{50}, RBC AChE activity was 3-5-fold more sensitive than brain AChE activity. OPP has concluded that there are remaining uncertainties surrounding the dose-response relationship of RBC AChE following carbofuran exposure in juvenile animals.

Please comment on whether you agree with the Agency's conclusion that, based on the available scientific evidence, there is remaining uncertainty regarding lack of dose response data at the low end of the dose response curve for RBC AChE inhibition with respect to extrapolating risk to infants and children. Please provide a basis for your conclusion.

Panel Response

Much of the response to Question 1b also applies to this question. The dose-response analysis done by the Agency for the EPA-ORD PND11 study data on RBC AChE was appropriate and led to a very uncertain BMD_{10}. The $BMDL_{10}$ was several orders of magnitude smaller than BMD_{10} indicating there was a high level of uncertainty. But the situation was even worse than that because the extrapolation to BMD_{10} and the calculation of the lower confidence bound $BMDL_{10}$ were based on an assumed dose-response curve. This curve fit well in the region where there were data, but there was no way to validate it at low doses. The Panel, therefore, could not be sure whether the extrapolation was valid, other than to note that the curve used fit well over a wide range of doses for adult data.

Data at low-end dose exposures would be helpful, as perhaps would the use of new methodologies like those of Lassiter and Brimijoin (2006) that improve precision and reduce the distance between BMD and BMDL. But, lacking such experiments and facing a decision that must be made with current information, the Panel could not be sure how much is gained by lower end data, which may well be more variable. What the Panel observed at the low end made it tempting to assume linearity at this part of the dose-response curve. However, the data could also be consistent with an exponential decay as a first approximation. In any event, even if low end data were available, it would have been important to examine the robustness of BMDLs.

Some of the discussion looked ahead to Question 1d and determination of a safety factor appropriate to allow for the uncertainty of extrapolation. EPA-ORD has provided excellent data regarding inhibition of RBC AChE by carbofuran. EPA-OPP elected not to use those data directly for the purpose of determining $BMDL_{10}$ because the tested doses were not low enough and extrapolation from the bottom of the data curve would introduce too much uncertainty.

Instead, EPA-OPP proposed to use the pooled data from FMC and EPA-ORD together, to calculate $BMDL_{10}$ for brain AChE, and then to apply a 5-fold factor to accommodate the probable extra sensitivity in RBC and obtain a final Point of Departure (PoD). This approach was reasonable if the dose response curves were parallel with a 5-fold horizontal displacement both at the midpoint BMD_{50} and at BMD_{10}. There were no data, however, to justify the assumption of parallelism at both levels, and the existing data suggested that the difference may be much less than 5-fold, as suggested by direct inspection of the dose-response curves (Figure 2 below).

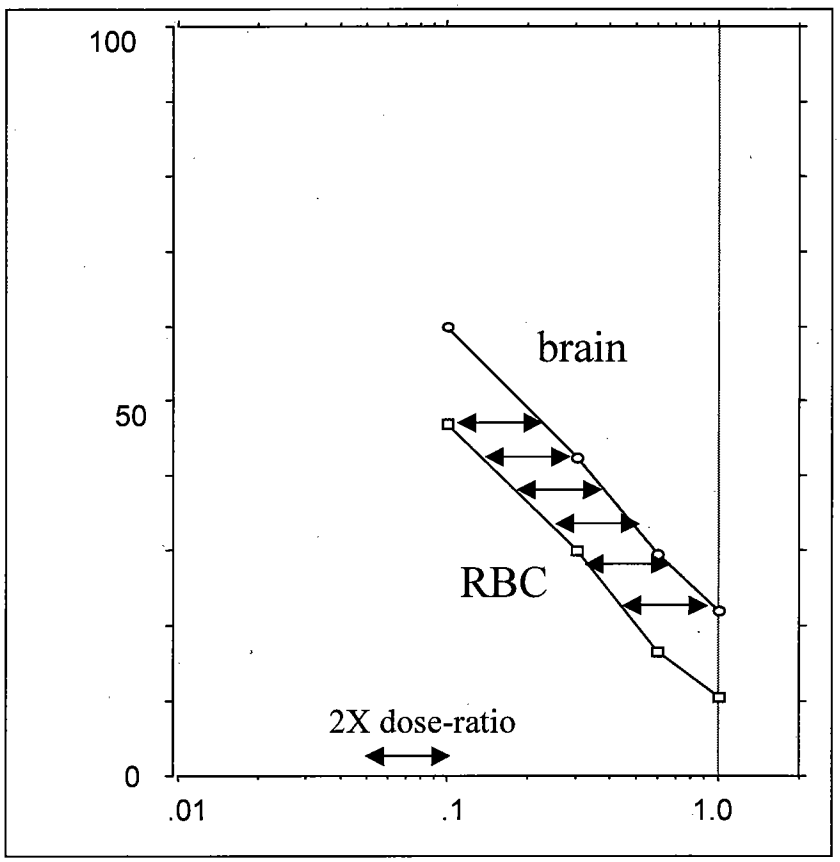

Figure 2. Carbofuran inhibition of brain and RBC AChE from PND11 rat pups

Data from Figure 2 of the draft NOIC plotted on a semi-log scale to reveal fold-shift in dose response curves. The replotted data show a 2X shift to the left, indicating that AChE inhibition in RBC is achieved at half the dose required to achieve that level of enzyme inhibition in brain.

Although the charge question stated that *"the value of the safety factor was based on a 5-fold [increased] sensitivity of RBC AChE in adult rats compared to brain AChE inhibition,"* it was not clear how this number was obtained or from which data set it was derived. The draft NOIC (pp 11-15) referred instead to EPA-ORD data on RBC and brain AChE in pups that appeared to be a more appropriate comparison, but reanalysis of those data indicated that a 2-fold factor accounted for the extra sensitivity in RBC AChE. Thus, according to some Panelists, the Agency's calculations appeared to be unnecessarily conservative and a deeper question was whether RBC AChE data should be used in the present case at all.

1d. Safety Factors in the FQPA Analysis

The FQPA requires EPA to apply a 10X safety factor for infants and children but the Agency "*may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.*" The Agency applied a 5X factor based on ratio of BMD_{50} estimates in brain AChE and RBC AChE in juvenile animals.

Based on the currently available data, does the panel agree that basing its safety factor on the ratio of BMD_{50} estimates in brain AChE and RBC AChE in juvenile animals is a reasonable approach? Please provide a basis for your conclusion.

Panel Response

Five FQPA uncertainty factor scenarios were considered by the Panel in response to charge question 1d (see Table 1). No consensus was reached as to whether EPA should derive FQPA factors from a blend of data on AChE inhibition in PND11 RBC and brain. At the present state of knowledge (or ignorance), the Panel did not wish to be dogmatic about such matters and disagreed on how to determine the FQPA safety factor.

There were Panel members who disagreed outright with EPA's recommendation of a 5-fold FQPA safety factor and answered "no" to Question 1d (Panel Scenarios 1 and 2). They argued that RBC AChE data should not be used to correct the BMD_{10} estimates derived from brain AChE. The brain AChE is a true target whose inhibition is a cause of toxicity, while RBC AChE is merely an index that may correlate with pesticide effects at various targets, both central and peripheral. These Panelists agreed that the most reasonable approach was to make decisions in light of the best available information regarding the possibility that younger individuals are more susceptible than adults to AChE inhibition by carbofuran. There is more than one way to attain that goal. If good data were available from target tissues and adult humans and from both adult and juvenile rats, for example, one could use the age-dependence of sensitivity in rats to adjust a PoD obtained with humans.

Alternatively, one could start with a PoD obtained from juvenile rats if they proved more sensitive than adults, and adjust that value by an interspecies protection factor, which would be 10X by default, or less, if well justified. As stated earlier in the response to Question 1a, the more reasonable approach from biological and toxicological perspectives is to rely upon the inherently more reliable and consistent brain AChE data. True, EPA (Viginia Moser, EPA-ORD-NHEERL) and others have shown that inhibition of RBC AChE correlates with inhibition of the enzyme in other tissues, and with neurobehavioral signs of cholinergic toxicity, however, RBC inhibition is not better than brain inhibition as a predictor of toxicity, nor has it been shown to correlate more closely with inhibition in peripheral target tissues such as muscle, nerve, heart, ganglia, or gut. Since there was no information about AChE in such target tissues, it would be better to stay with brain AChE. There was a robust agreement between ORD and FMC data from AChE in PND11 rat brain, a real target tissue that appeared moderately more sensitive than adult rat brain. By applying both inter-species and intra-species correction factors of 10X to the $BMDL_{10}$ from this juvenile tissue one can immediately reach a defensible PoD for humans that incorporates the FQPA protection factor. Admittedly this statement needs qualification. First,

one must be willing to assume that enhanced sensitivity in very young rats mirrors enhanced sensitivity in very young humans. Second, one must assume that measures of AChE inhibition capture the risks of developmental toxicity that could be subtle and based on alternate mechanisms.

Two options unfolded from the initial discussions on the FQPA safety factor. In the first option, the RBC data would be accepted for risk assessment, but the 5-fold FQPA safety factor was considered excessive and not justified by the evidence. Instead, this group believed it more appropriate to use a 2-fold FQPA safety factor based on the consistent horizontal difference between the steep parts of the dose response curves for RBC and brain. There was some support for a still smaller FQPA safety factor (i.e., no additional safety factor) as proposed by FMC based on differences in percent inhibition of RBC and brain AChE within a single treated individual. At least one Panel member, however, argued that RBC AChE might have predictive value and was reluctant to assume that $BMDL_{10}$ for inhibition in RBC is only 2-fold lower than for inhibition in brain. These Panelists stressed the uncertainties involved in extrapolating to low dose levels and argued that even a 5- or 7-fold difference might not be adequately conservative.

One Panelist offered a suggestion to use brain AChE data from adult rats corrected by the two default 10X safety factors, one for inter-species uncertainty and one for intra-species uncertainty and, in addition, a 10X FQPA safety factor for protection of children and infants (Panel Scenario 3) because of the uncertainty of the juvenile data. This Panel member posited that if the juvenile data are so uncertain and the brain AChE is the target, then it would be better to start with the adult brain-based estimate. Although this option was introduced at the meeting, the Panel rejected it and gave it no further consideration.

Other Panel members agreed with the EPA's recommendation of a 5X FQPA safety factor (Panel Scenario 4). They concluded that given the lack of data on comparable tissues across ages and species, and that AChE inhibition was the most sensitive endpoint for carbofuran acute toxicity, the ratio of brain to RBC AChE BMD_{50} should be used to correct the $BMDL_{10}$ for brain AChE inhibition to reach a reliable endpoint for inhibition of RBC AChE. According to the results of an analysis by USEPA-ORD provided to the SAP, this ratio ranged roughly from 2.5 to 7 (February 4, 2008 memo from Woodrow Setzer, USEPA-ORD-NCCT, to Elissa Reeves, Anna Lowit, and Jack Housenger, USEPA-OPP-HED), with a central tendency near 4. Also it was noted that the data under deliberation came from young rats, but no data were presented for pre-natal sensitivity as would have been desirable for addressing the need to protect developing individuals. Hence, these Panel members accepted EPA's proposal to use a 5X FQPA safety factor, which is close to the central tendency of 4, or a factor of 7X, which represents the upper range.

Additionally, some Panel members considered it reasonable to retain the full 10X FQPA safety factor (Panel Scenario 5). The FQPA does require that the Agency use a different factor "*only if, on the basis of reliable data, such margin will be safe for infants and children.*" Given the uncertainty in the data and in its interpretation for risk assessment by the entire Panel, these Panel members believed that this standard for change had not been met

An additional rationale for retaining the full 10X FQPA factor was offered. This Panel member argued that EPA might do well to focus on brain data but retain the full 10x FQPA factor because of uncertainty about both: (1) the relevant dosimeter for subtle developmental effects (peak inhibition vs. AUC for inhibition as discussed below), and (2) the implications of 10% cholinesterase inhibition in the light of the evidence cited earlier, in response to Question 1c, that a pesticide from a different class of anticholinesterases affects nerve outgrowth in vitro at still lower levels of inhibition. The point was made that, even if peak inhibition of 10% is adequately protective against acute symptoms, an AUC dosimeter (integrated area under the curve of % inhibition X time) may well prove more relevant for subtle developmental changes resulting from longer term adaptive responses. That would be especially true if exposures from such sources as milk are better characterized as repeated or continuous where doses cause a buildup of inhibition from one exposure episode to the next. If one does use an AUC dosimeter, then the key findings from the Setzer analysis include both lowering of the dose that gives rise to peak inhibition in PND11 pups (central estimate about 1.8 fold), and also a relative slowing of the recovery of brain cholinesterase activity after the peak inhibition (a bit more than 4-fold in PND11 pups as a central estimate). Both the lower dose required for a given peak inhibition level and the slowed recovery contribute approximately multiplicatively to greater PND11 pup sensitivity, resulting in an overall central estimate of about 8-fold for an AUC dosimeter with approximate confidence limits spanning about 4-fold to 14-fold; a span that, as it happens, includes the FQPA 10-fold factor. Thus, at the end, this Panel member, with support from some others, recommended using the $BMDL_{10}$ from AChE inhibition in PND11 pup brains, but corrected by three full factors of 10, one for interspecies differences, one for intraspecies differences, and the last for FQPA protection (Scenario 5).

In conclusion, the Panel was not in agreement regarding the magnitude of a FQPA safety factor. A summary of the various Panel recommendations for the uncertainty factor determination for carbofuran is provided in the table below.

Table 4. Various Recommendations for Uncertainty Factor Determination for Carbofuran (Note: $BMDL_{10}$ data from Table 3 and Table 4, page 21 found in EPA's document: Issue Paper for the FIFRA SAP Meeting on Carbofuran: Human Health Risk Assessment, January 3, 2008)

Scenario	$BMDL_{10}$[1]	Factors		
		Inter-species	Intra-species	FQPA
Panel 1	0.031	10	10	1
Panel 2	0.031	10	10	1.5-2
Panel 3[2]	0.048	10	10	10
Panel 4	0.031	10	10	5-10
Panel 5	0.031	10	10	10
EPA Recommendation	0.031	10	10	5
FMC Recommendation	0.031	10	3	1

[1] The $BMDL_{10}$ values were calculated from PND11 brain (mg/kg) data except for Scenario 3 in which the $BMDL_{10}$ values were calculated from adult brain (mg/kg) data.
[2] This Scenario had little support from the Panel and was rejected after further discussion during the meeting.

Additional Question Addressed by the Panel.

Because a number of Panelists believed strongly that the issue of the use of brain or RBC AChE as the endpoint in the risk assessment deserved a discrete discussion independent of the formal charge questions, the Panel requested discussion of an additional question be placed into the record: **On the basis of science, is RBC acetylcholinesterase preferable to brain acetylcholinesterase as the endpoint upon which to base the risk assessment?**

In general, it is understood that risk assessment must be conservative to be protective of human health, but risk assessment must be based upon scientific principles. The RBC AChE may display greater sensitivity to carbofuran than brain AChE *in vivo* and it is not surprising that this might happen because of toxicokinetic considerations. However, RBC AChE inhibition is only a biomarker of exposure, not of effects, and therefore does not reflect toxicity quantitatively.

Several Panel members believed that it did not seem reasonable from a scientific standpoint to base the carbofuran risk assessment calculations on a biomarker of exposure and not on a biomarker that reflects toxicity. The rat experiments provided reliable and robust brain AChE data from both adult and juvenile animals. The rationale of greater sensitivity for the choice of RBC AChE inhibition as the endpoint did not seem reasonable from a toxicological standpoint. There may be numerous parameters in the organism that are highly sensitive to inhibition or changes resulting from carbofuran exposure but that do not reflect toxicity endpoints. It should be borne in mind that brain AChE inhibition is itself a biomarker and is not a measure of toxicity

and it is only when excessive acetylcholine accumulates following AChE inhibition that cholinergic pathways will be affected.

From the standpoint of the data presented in the McDaniel et al. (2007) paper (provided by the Agency in its support materials), it is more likely that brain AChE is more sensitive than RBC. The motor activity changes appeared to be more consistent with cholinesterase inhibition in the brain than in RBC's. In adult rats, brain AChE inhibition correlated better with motor impairment (0.701-0.750) compared to RBC AChE (*r*-values of 0.580-0.683) after carbofuran treatment. In the EPA and FMC studies using PND17 rats, a general trend showing impaired motor activity corresponded with inhibition of both brain and RBC AChE. However, a Pearson correlation coefficient was not calculated in this age group. Moreover, no measurement of cholinergic toxicity (i.e., reflecting peripheral nervous system effects) was determined in PND11 rats. To assume PND17 and PND11 rats respond in the same manner as adults was thought to be both speculative and fraught with uncertainty. While brain measurements are preferable, RBCs could be considered as a separate compartment in addition to the brain, but the RBC data should not be put at the center of key calculations used in the risk assessment when the available data have problems, particularly at the low end of the dose range. In addition, the choice of RBC AChE inhibition is not consistent with the approach used and justified in EPA's NMC cumulative risk assessment based on their common mechanism of toxicity. Because of these factors, several Panel members urged EPA to seriously reconsider the use of RBC AChE as the endpoint for the carbofuran risk assessment, and rather to use the brain data that are considered robust from both adults and juveniles.

The Panel also noted that any measures of cholinesterase activity in humans will be from RBCs, and that information on RBCs from animals will be useful in these inter-species extrapolations. However, it should be remembered that human and animal RBC's display different basal levels of AChE activity and this would impact such extrapolations. RBC AChE inhibition should be utilized only when it has been calibrated against a measure of cholinergic toxicity (i.e., peripheral nervous system endpoints) in the life stage of interest (i.e., PND11). Ideally that measure of cholinergic toxicity should also be further extrapolated to human data allowing one to infer that RBC AChE inhibition by carbofuran correlates specifically with cholinergic toxicity in children exposed to that pesticide.

There was also support from some Panel members for use of both RBC and brain AChE in the risk assessment, depending on which is shown to be more sensitive. These Panel members believed that it is important that risk assessment takes into account all available information in the entire database. Neurobehavioral effects such as chewing motion or mouth smacking seen in adult rats indicated effects of peripheral origin (per oral comments from Dr. Moser (EPA-ORD-NHEERL)). Thus, when peripheral AChE data are not available, RBC data should be used especially when evidence showed that RBC AChE is more sensitive in the young. In this application, the support of the EPA's choice to use RBC instead of brain AChE is not because RBC AChE is merely a biomarker of exposure, but because it is a surrogate toxicity endpoint for the lack of peripheral AChE data to protect infants and children as required by the FQPA.

Different regulatory agencies arrive at science policies regarding this issue through extensive discussions and review. It was noted by one Panelist that the California Environmental

Protection Agency, for example, came to the same conclusion as EPA on the use of RBC AChE. This issue had gone through several iterations of large scale discussions in the past, and can continue to be revisited periodically as new data become available.

2. Point of Departure (PoD) Determination for Dermal Risk Assessment for Workers

In the 2006 and 2007 human health risk assessment for carbofuran, the Agency has relied on oral studies in adult rats for deriving the PoD for dermal risk assessment for workers. The Agency applied a dermal absorption factor of 6% to extrapolate from the oral route to the dermal route. The Agency acknowledges the uncertainties associated with route-to-route extrapolation.

In 2007, FMC submitted a 21-day dermal rat toxicity study (MRID 47143702) that also included a 7-day range-finding study (MRID 47143701). In these studies, carbofuran at various doses was applied to shaved skin for 6 hours/day, 5 days/week with the skin occluded after application. These studies failed to provide measurements to address time of onset, time of peak, or time to recovery information necessary for the dermal risk assessment. Furthermore, the RBC AChE measurements from both studies were unreliable. The Agency has therefore relied on oral studies for assessing dermal risk of carbofuran to workers.

Do you agree with the Agency's conclusion that the dermal toxicity studies in rats (MRID 47143701-2) are not acceptable for use in extrapolating dermal risk to workers? Please provide a basis for your conclusions.

Panel Response

Carbofuran is a skin permeable molecule, because of its physicochemical properties. Without review of any previous dermal absorption or toxicity studies, it can be predicted from the Potts and Guy equation that with a molecular weight of 221.25 and the experimental log octanol/water partition coefficient of 2.32 (Hansch et al., 1995) carbofuran is very skin permeable. The estimated maximum flux (i.e., from a saturated solution with no depletion during the period of absorption) using the calculated permeability coefficient from water (0.0038 cm/h) from the Potts and Guy equation (from Potts and Guy, 1992); which is also described in U.S. EPA (2001) and the experimental water solubility of 0.32 mg/mL (from the Syracuse Research database http://esc.syrres.com/interkow/webprop.exe?CAS=1563-66-2) is 1.2 $\mu g/cm^2/h$.

Use of the Dermal Toxicity Studies in Rats

The Panel was in general agreement that the dermal toxicity studies in rats (MRID 47143701-2) are not acceptable for use in extrapolating dermal risk to workers for the following reasons.

The first major area of concern was the lack of certainty that the study endpoint of 6 h was an appropriate time for assessing toxicity. There was no information about the effect of exposure time on onset, peak effect, or about the time of effect recovery for the study design presented. Therefore, it was not possible to ascertain that the acetylcholinesterase (AChE) levels measured in the brain actually were the worst effect that could occur. It was possible that the dermal absorption rate slowed substantially after evaporation of the water vehicle early in the 6-hour

exposure and that the AChE had substantial time for recovery during the exposure period before sacrifice and brain analysis occurred. It was determined that the RBC data could not be used because of the assay methods of the contract lab. It was clear that the AChE measurement data obtained from the two dermal studies (MRID 47143701 and 47143702) did not reflect the true enzyme activity, or inhibition at the point of time when the blood samples were collected, and therefore handicapped the use of the RBC data in the risk assessment.

The second major area of concern was in the chemical application method used in the dermal toxicity studies, regardless of whether or not general guidelines were followed. In these studies, the technical material was applied to the skin of the rats in an aqueous slurry that was then covered with a semi-occlusive dressing that allowed evaporation of the treatment vehicle. It was possible that after the water evaporated from the skin that the absorption rate of the chemical decreased significantly. It was also possible that the small amount of liquid in the slurry was removed from the skin by absorption into the gauze, thereby reducing chemical contact with the skin surface. The particle size of the technical material would also influence the absorption rate of the chemical. The carbofuran product contained multiple components, including surfactants, which would cause skin permeation enhancement, better surface contact, and also potentially a longer duration of significant absorption as compared to the technical material exposure in a slurry with water. Without further information about the effects of an application method using the technical material in a powder slurry for a 6-hour exposure, there was a significant potential that the NOAEL recommended by FMC of 50 mg/kg/day for adult rats was too high to ensure protection of human health from dermal exposure to the carbofuran product in actual use.

Confusion was created by the EPA charge questions, presentations, and supporting documents which described the FMC dermal toxicity studies incorrectly. This included statements that the 21-day study involved pesticide application of 5 days per week versus the actual protocol of 7 days per week exposure, and 1 hour versus the actual 15 minute post-exposure brain tissue sampling.

Use of the Oral Toxicity Studies

With the lack of other experimental data (optimally a properly designed dermal toxicity study), it was reasonable to cautiously consider an estimate of dermal toxicity based on oral toxicity measurements with a reliable maximal effect endpoint combined with an estimate of dermal absorption. Although dermal absorption results from a previously published study are available (Shah et al., 1987), the conditions in that study do not correspond directly to the 6-hour exposure or anticipated exposed doses on the basis of per skin surface area that are relevant to the worker exposure risk assessment. The 6% absorption value used by the Agency was based on 5.7% absorption reported from a 24-hour exposure to an applied dose of 63 $\mu g/cm^2$/day (285 $nmol/cm^2$/day). Shah et al. (1987) also present a dermal absorption measurement of 2% for the same exposed dose after 6 hours of exposure.

The Agency recommended using the 24-hour number on the basis that carbofuran in the skin, but not yet absorbed systemically at the end of 6-hour, would continue to absorb even if the chemical had been removed from the skin surface. While this is true, the absorption rate from chemical residue in the skin at the end of the exposure would be smaller than the rate while chemical was

still on the skin. Almost certainly then, most of the significant absorption will have probably taken place within the 6-hour period.

Dermal Absorbed Amount

Two percent (2%) absorption likely underestimates absorption because the exposed doses to the skin are likely to be much smaller than 63 $\mu g/cm^2$ (285 $nmol/cm^2$). Often the percent absorption increases with decreasing amount applied, especially when small amounts are applied. This was observed in the Shah et al. study of carbofuran, though unfortunately, the study authors only reported the effect of dose at 72 hours (i.e., the percent of the recovered dose that absorbed in adult rats was 83.4%, 13.0%, 8.3% and 6.0%, respectively for doses of 23, 285, 535 and 2680 $nmol/cm^2$, which correspond to 6.2, 63, 120, 590 $\mu g/cm^2$). For this reason, dermal risk assessments need to consider the amount of chemical per skin surface area in addition to the amount of chemical per body mass. If the exposure rate based on the mixing/loading of liquids for aerial application scenario is approximately 2000 µg/day (calculated using a unit exposure from the Agricultural Handlers Exposure Task Force (AHETF) database of 1.6 µg /lb active ingredient x 1200 lb active ingredient applied per day), then the dermal applied dose can range from 0.2-2 $\mu g/cm^2$/day using surface areas of 1000 cm^2 for hands (approximately) and 17,000 cm^2 for total body surface area of a 70 kg person. If the unit exposure is as high as the Pesticide Handlers Exposure Database (PHED) value of 8.6 µg /lb, then the dermal exposure could be as high as 10 $\mu g /cm^2$/day. The 6-hour data using the 2% absorbed dose had an applied exposure of 63 $\mu g /cm^2$/day (285 $nmol/cm^2$/day). This means, the percent absorbed dose could be more than 2% in the field exposure scenario, but it is not known how much more. Furthermore, the other worker exposure scenarios would have smaller exposed doses than the mixer/loader with an increased likelihood that the appropriate percent absorption number would be larger than 2%.

Dermal Absorption Rate

The time course of the dermal absorption relative to the toxicity response was unknown. In a calculation of internal dose for a given exposure (e.g., 100 cm^2 of exposure to a dose of 63 $\mu g/cm^2$) multiplied by a percent absorption number (e.g., 2% for a 6 h exposure), it was assumed that absorption (e.g., 126 µg = 100 cm^2 * 63 $\mu g/cm^2$ * 0.02) had occurred as a single bolus dose.

In fact, absorption occurred over the entire 6 hours, although not necessarily at a constant rate. As a result, at any given time during the exposure, the actual internal dose would be smaller than estimated using the percent absorption for the exposed period. This is particularly the case for a chemical like carbofuran that is eliminated quickly; for example, in the Shah et al. study of carbofuran, 75% of the absorbed dose had already been eliminated in the urine at the end of 6 hours.

Oral Bioavailability Concern

The percent absorption factor relates the internal dose that arises (i.e., the absorbed dose) from a given dermal exposed dose. If the oral dosing extrapolation is used, then the oral bioavailability of carbofuran needs to be included in the MOE calculation, to adjust the oral PoD dose to a

systemic (or internal) exposure. Additionally, the possibility of active metabolite formation needs to be considered.

Acetone Statement

Although acetone was used in the Shah et al. (1987) skin absorption studies, the amount applied to the skin was 200 µl on an area of 5.6 cm^2 (2.3% of the total body surface area). This amount of acetone evaporates very quickly and serves only to deposit the chemical into intimate surface contact with the skin. Acetone has little if any effect on the amounts that absorbed, except perhaps in the first few minutes. Acetone effects on skin are more problematic when the skin is exposed to acetone for a more extended period.

Additional comments:

It is the opinion of some of the Panel that the EPA Acute Dermal Toxicity and the 21/28-Day Dermal Toxicity Guidelines should be revisited for improvement of clarity. The "vehicle section" in particular needs to explain that the product be applied to the skin in a method that is similar to how it would make contact with the skin in the field. This should include using the actual product and not just the technical material alone, unless the technical material alone can be shown to have equivalent or greater toxicity than from the same amount of active ingredient applied to the skin in the as-used formulation. Additionally, the procedure for the application of the test substance and the covering with porous gauze should be reviewed. Application duration and time course of peak effects should also be reviewed in the Guideline. It may also be helpful for the Agency to review the Dermal Absorption Guidelines simultaneously, as these documents contain similar types of recommendations in scientific methodology.

In addition, one Panel member provided detailed comments on the quality of the Agency's analysis of the dermal toxicity studies submitted by FMC. A brief summary is provided below:

1) There were errors in the EPA oral presentations and in the support documents of what was done in the dermal toxicity testing for carbofuran that caused this Panelist to go back to the actual study submitted by FMC to "fact-check" statements from EPA before any comments could be made during the SAP discussion of Charge Question 2. This Panelist found several errors between the Agency's scientific reviews of the 7-day and 21-day dermal toxicity studies and the FMC study reports. Such errors encourage distrust of other information provided by the Agency.
2) There was a lack of clarity regarding EPA's concerns about the 21-day dermal toxicity with respect to the time-course of toxic response.
3) Key references and results of prior dermal toxicity studies were not provided to the Panel until the final EPA presentation clarifying the Human Health Risk Assessment Charge Questions (February 8, 2008). Lack of this information undermined the Panel's ability to assess whether the FMC data were inconsistent with results of prior dermal toxicity studies as EPA described in its documents.

Other Comments on Dietary Exposure Modeling

The charge questions posed to the Panel did not specifically address the dietary exposure modeling. The Panel, however, noted its agreement with FMC's position that residue inputs to

the DEEM dietary exposure model should reflect the most up-to-date data and measurement standards for residue levels on commodities. In the case of potatoes, where according to FMC there have been no detectable residues on 3000 samples assayed since 1995, the Panel recommended that the LOD for current technologies (i.e. 0.001-0.004 ppm) be used as the basis for the EPA's ½ LOD interpolation of a residue value for a "treated" potato food item.

REFERENCES

American Bird Conservancy. 2007. Final Technical Report: Avian Incident Monitoring System. American Bird Conservancy, Pesticides and Birds Program, EPA Agreement Number: X-82908201-0. 17 pp.

American Bird Conservancy. 2008. Comments to the FIFRA Scientific Advisory panel on the EPA Notice of Intent to Cancel Carbofuran, 5-8 February 2008. Memo dated 4 Feb 2008, Docket EPA-HQ-OPP-2007-1088. 8 pp.

Avian Effects Dialogue Group. 1994. Assessing Pesticide Impacts on Birds - Final Report of the Avian Effects Dialogue Group, 1988-1993. RESOLVE, Center for Environmental Dispute Resolution, Washington, DC. 156 pp.

Brimijoin S. and C. Koenigsberger. 1999. Cholinesterases in neural development, and toxicological implications. Env. Health Persp. 107: 59-64.

Buckland, S.T., D.R. Anderson, K.P. Burnham, and J.F. Laake. 1993. Distance Sampling: Estimating abundance of biological populations. Chapman and Hall, New York.

Burger, J., K. Kannan, J. P. Giesy, C. Grue, and M. Gochfeld. 2002. Effects of Environmental Pollutants on Avian Behaviour. Chapter 9, pp. 337-375. In Behavioural Ecotoxicology, G. Dell'Omo, ed. Wiley & Sons LTD, New York.

Burnham, K.P., D. R. Anderson, and J. F. Laake. 1980. Estimation of density from line transect sampling of biological populations. Wildlife Monographs, no. 72

FMC. 2008. Presentations of FMC Corporation in Support of the Continued Use of Carbofuran. 5-8 February 2008, Docket EPA-HQ-OPP-2007-1088. Var. pp.

Fryday, S. L., A.D.M. Hart, and S. D. Langton. 1996. Effects of exposure to an organophosphorus pesticide on the behavior and use of cover by captive starlings. Environmental Toxicology and Chemistry 15:1590-1596.

Gras, G., C. Hasselman, C. Pellissier, and R. Bruggers. 1981. Residue analysis of methiocarb applied to ripening sorghum as a bird repellent in Senegal. Bull. Environ. Contam. Toxicol. 26: 393-400.

Grue, C.E. 1982. Response of common grackles (*Quiscalus quiscula*) to dietary concentrations of four organophosphate pesticides. Archives of Environmental Contamination and Toxicology 11:617-626.

Grue, C.E., P.L. Gibert, and M.E. Seeley. 1997. Neurophysiological and behavioral changes in non-target wildlife exposed to organophosphate and carbamate pesticides: thermoregulation, food consumption, and reproduction. Zoologist 37:369-388.

Grue, C.E., S.C. Gardner and P.L. Gibert. 2002. On the significance of pollutant-induced alterations in the behavior of fish and wildlife. Chapter 1 (pages 1-90) in G. Dell'Omo (ed.) Behavioural Ecotoxicology, John Wiley & Sons, Ltd., West Sussex, UK.

Hansch, C, A. Leo, and D. Hoekman. 1995. Exploring QSAR: Hydrophobic, Electronic, and Steric Constants, American Chemical Society, Washington, DC

Health Council of the Netherlands. 2003. Benchmark dose method: Derivation of health-based recommended exposure limits in new perspective. The Hague: Health Council of the Netherlands, 2003; Publication no. 2003/06E.

Hill, E. F., J.W. Spann, and J.D. Williams. 1977. Responsiveness of 6 to 14 generations of birds to dietary dieldrin toxicity. Toxicol.Appl.Pharmacol. 42(2): 425-431.

Hutto, R.L. 1981. Temporal patterns of foraging activity in some wood warblers in relation to the availability of prey. Behavioral Ecology and Sociobiology 9:195-198

Joint FAO/WHO Meeting on Pesticide Residues (Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues) (JMPR). 1998. Report of a consultation on interpretation of inhibition of acetylcholinesterase activity. Geneva 8-9 January 1998.

Lassiter T.L. and S. Brimijoin. 2006. Determining precise benchmark doses for carbamate anticholinesterases. Toxicol. Sci. 96: 154-161.

Losito, M. P., R.E. Mirarchi, and G.A. Baldassarre. 1990. Summertime activity budgets of hatching-year Mourning Doves. Auk 107:18-24.

McDaniel, K.L., S. Padilla, S., R.S. Marshall, P.M. Phillips, L. Podhorniak, Y. Qian, and V. Moser. 2007. Comparison of acute neurobehavioral and cholinesterase inhibitory effects of N-methylcarbamates in rats. Toxicol. Sci. 98: 552-560.

Morton, M.L. 1967. Diurnal feeding patterns in White-crowned Sparrows, *Zonotrichia leucophrys Gambelii*. Condor 69:491

Nichols, J.D., J.E. Hines, J.R. Sauer, F.W. Fallon, J.E. Fallon, and P.J. Heglund. 2000. A double-observer approach for estimating detection probability and abundance from point counts. Auk 117:393-408.

Nitcheva, D.K., W.W. Piegorsch, R.W. West, and R.L. Kodell. 2005. Multiplicity-adjusted inferences in risk assessment: benchmark analysis with quantal response data. Biometrics 61: 277-286.

Polo, V. and L. M. Bautista. 2006. Daily routines of body mass gain in birds: 2. An experiment with reduced food availability. Animal Behaviour 72:517-522.

Potts, R.O. and R.H. Guy. 1992. Predicting skin permeability. Pharm Res, 9:663-669.

Rivera-Milan, F.F, M.E. Zaccagnini, and S. B. Canavelli. 2004. Field trials of line-transect surveys of bird carcasses in agro-ecosystems of Argentina's Pampas Region. Wildlife Society Bulletin 32:1219-1228.

Sayre, R.W. and L. Clark. 2001. Comparison of primary and secondary repellents for aversive conditioning of European starlings. Pp. 324-344. In: Pesticides and Wildlife. Ed., J.J. Johnston. American Chemical Society Symposium Series 771. American Chemical Society, Washington, D.C., USA.

Shah, P.V., M.L. Fisher, N.J. Month, M.R. Sunler, and L.L. Hall. 1987. Dermal penetration of carbofuran in young and adult Fischer. 344 rats. J of Toxicol. and Environ. Health 22:207- 223.

Stafford, J.M. 2007. Assessment of mallard duck (*Anas platyrhynchos*) avoidance to feed containing Furadan 4F. FMC Unpublished Study. MRID No. 47128701.

Thompson, W. L. 2002. Towards reliable bird surveys: accounting for individuals present but not detected. Auk 119:18-25.

U.S. Geological Survey. 2003. Bird Banding Laboratory. How many birds are banded? U.S. Department of the Interior, U.S. Geological Survey, Patuxent Wildlife Research Center. Online: http://www.pwrc.usgs.gov/bbl/homepage/howmany.htm. Last modification: 10/23/2003.

United States Environmental Protection Agency (EPA). 2001. Risk Assessment Guidance for Superfund, Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment), Interim Guidance, EPA/540/R/99/005, Office of Emergency and Remedial Response, Washington, DC.

Verbeek, N.A.M. 1972. Daily and annual time budget of the Yellow-billed Magpie. Auk 89:567-582.

Wu, Y., W.W. Piegorsch, R. W. West, D. Tang, M.O. Petkewich, and W. Pan. 2006. Multiplicity-adjusted inferences in risk assessment: benchmark analysis with continuous response data. Environ. and Ecol. Stats. 13: 125-141

Yang D, A. Howard, D. Bruun, M. Ajua-Aleman, C. Pickart, and P.J. Lein. 2007. Chlorpyrifos and chlorpyrifos-oxon inhibit axonal growth by interfering with the morphogenic activity of acetylcholinesterase, Toxicology and Applied Pharmacology (2007), doi: 10.1016/j.taap.2007.11.005 (In Press)

Zinkl, J.G., W. Lockhart, S.A. Kenny, and F.J. Ward. 1991. Biological consequences of depressed brain cholinesterase activity in wildlife. Pp 233-254. In: Cholinesterase-inhibiting Insecticides – Impacts on Wildlife and the Environment. Ed., P. Mineau. Elsevier Science Publishers B.Y., Amsterdam, The Netherlands.