Charge Questions: Scientific Issues Associated with the Agency's Proposed Action under FIFRA 6(b) Notice of Intent to Cancel Carbofuran

Introduction and Overview
1-7-08

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 which 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 is asking 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 NOIC and supporting documents. EPA interprets 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 will not be asking the Panel to comment on such previously peer reviewed aspects of the carbofuran risk assessment. In addition, unlike those previous SAP meetings, in this meeting the Agency is not asking 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 is posing further human health and environmental charge questions to the Panel regarding areas where new data have become available since the IRED was signed or new analyses have been performed which affect the carbofuran risk assessments.

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Ecological Risk Section

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 assessment, 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 v1.0 (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 v2.0, 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 v1.0 was the only fully functional avian PRA model available. Subsequent to the SAP review of TIM v2.0 and the release of the carbofuran IRED in August, 2006 the Agency has conducted modeling for a subset of carbofuran scenarios using TIM v2.1, a version that incorporated the 2004 SAP recommendations, to ascertain the extent to which the updated model version would alter carbofuran risk conclusions.

i. Based on the document (D347916) provided for review containing model results using TIM v1.0 and the newer version TIM v2.1, 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.

ii. 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.

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 which 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.

a. 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 1.0 model. EPA elected to use this model as opposed to the TIM 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 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 the registrant-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.

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 v1 model to evaluate the potential for food avoidance to alter mortality risk estimates? Please provide a basis for your conclusions.

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.

b. 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 v1 and v 2.1 model 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.

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 v1 and v2.1 model to evaluate the potential for food matrix effects to alter mortality risk estimates? Please provide a basis for your conclusions.

c. 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.

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 v1 and v 2.1 models to evaluate the potential for alternative mortality risk estimates? Please provide a basis for your conclusions.

d. 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.

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.

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.

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.

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Human Health Risk Section

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 [PND11] rats) submitted by the pesticide registrant, FMC, to derive the PoD for risk extrapolation. This study showed that PND11 pups were more sensitive to carbofuran 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 have become available. One study was sponsored by FMC. Two were performed by EPA's Office of Research and Development (ORD). The two FMC comparative ChE studies and ORD's PND11 study provide remarkedly similar brain AChE data and when evaluated in combination provide 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.

Q1a.
FMC, the pesticide registrant, has 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 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.

Q1b.

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.

Q1c.

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.

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

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.

Q1d.
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.

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.