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OFFICE OF
PREVENTION, PESTICIDES, AND
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MEMORANDUM January 4, 2008

SUBJECT: Impact of 2007 avian data on EPA's Probabilistic Risk Assessment for Carbofuran.

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Background:

Evaluation of Four Avian Studies Submitted by FMC

The registrant for the active ingredient, carbofuran, FMC, submitted four additional studies on the response of avian species to carbofuran exposure between May and July 2007 for OPP consideration. FMC's intent is to provide the Agency with additional information for use in probabilistic models used to reduce some uncertainties regarding the estimates of the magnitude carbofuran-induced effects on birds in agro-ecosystems. There are no available OPP guidelines for the submitted studies. One study was submitted to determine the inhibition and recovery of brain cholinesterase activity

following dosing with carbofuran. Another study was intended to provide insight into the avoidance behavior of birds when exposed to carbofuran in feed. The last two studies were submitted to provide information on the effect of a food matrix on the acute toxicity of carbofuran. EFED has completed scientific review of the submitted studies and has classified all four studies as SUPPLEMENTAL. This document provides a brief summary of the submitted studies and examples of how the new data impact EPA's risk estimates.

Modeling and Evaluation Approach

The Terrestrial Investigation Model version 1.0 (TIM 1.0) and 2.1 (TIM 2.1) were used to evaluate the impact of the recently reviewed data on avian risk projections. TIM 1.0 was reviewed by the Science Advisory Panel in 2001. In response to SAP comments, TIM version 2.0 was created and subsequently reviewed by the SAP in 2004 and further modified to TIM 2.1.

TIM 1.0 was used in the original ecological risk assessment chapter for carbofuran because it was the only fully functional probabilistic model available at the time the carbofuran assessment was initiated. In the original RED chapter, many scenarios involving several species and crop combinations were evaluated to provide a comprehensive understanding of the potential risks of carbofuran. For the purpose of evaluating the potential impact of the data submitted by FMC, three scenarios are used here to represent the range of likely impacts on risk conclusions. An edge insectivore (killdeer), edge granivore (mourning dove), and the red-winged black bird were chosen as representative species. As in the original chapter, the killdeer and mourning dove scenarios are evaluated at the 5^{th}, 50^{th} and 95^{th} percentile species sensitivity because toxicity data are not available for these species; the percentiles are obtained from body-weight adjusted LD50s and the established dose response relationship. For the red-winged black bird, toxicity data are available and the species-specific LD50s were used in model projections. In all cases, bird body weights and time on field are the same as was used in the previous, comprehensive assessment presented in the IRED. Also, because the submitted studies relate primarily to the dietary route of exposure, that was the primary route considered in this analysis, particularly for results from TIM 1.0. This also facilitates comparison between EPA's conclusions in the IRED and results using the FMC studies. Because TIM 2.1 includes multiple exposure routes, the potential risks associated with these routes of exposure were also explored and are presented here.

To evaluate the implications of the recently submitted data required modification of TIM 1.0 and TIM 2.1. In some cases, only the inputs changed while in others, new equations or relationships were added to address interpretations of the data. These are explained in detail below. Importantly, while data can often reduce uncertainty, it is not the case that it necessarily does so. In an effort to evaluate the implications of the uncertainty, a number of approaches were incorporated and the results should be interpreted as representing a range of possible outcomes.

Brain Cholinesterase Inhibition and Recovery in Bobwhite Quail

Study 1: Brewer, L.W., Stafford, J.M., and Moore, D. 2007. Determination of the Time Course of Brain Cholinesterase (ChE) Activity Depression and Recovery in Northern Bobwhite (*Colinus virginianus*) Following Scheduled Oral Dosing with Furadan 4F. Springborn Smithers Laboratories, 2900 Quakenbush Rd., Snow Camp, North Carolina 27349. Springborn Smithers Study Number 282.4110 and FMC Study Number A2007-6201. FMC Corporation, P.O. Box 8, Route 1 and Plainsboro Rd. Princeton, NJ 08543. June 7, 2007. Unpublished report. MRID 47107601

The objective of this study was to determine the time course of brain acetylcholinesterase (AChE) activity depression and recovery in northern bobwhite quail (*Colinus virginianus*) following exposure to carbofuran via scheduled oral dosing with Furadan 4F. The experimental protocol was not based on any procedures or guidelines specified by the EPA or the OECD; guidelines for this type of study do not currently exist. The following are key aspects of the protocol:

- Ten replicate groups, containing 10 birds each (5 males and 5 females), were established for dosing at each of the three dose level (0.75, 1.50 and 3.0 mg a.i./kg body weight; 300 birds total).
- A single control group of 10 birds received no dosing with the test substance, but was administered an equal dose of distilled water.
- The treatment replicates were assigned to respective time steps, which indicate the amount of time allowed to pass after dosing before a given bird was sampled for brain AChE analysis. The time steps for sampling were 5 min., 15 min., 30 min., 60 min., 90 min., 120 min., 150 min., 180 min., 240 min., and 360 min.
- Within a given time-step group and dose level, birds were dosed at 5-minute intervals to allow time between birds for euthanization and head removal (and freezing) after dosing.
- Once all dosing was complete, frozen brains were shipped and analyses for total AChE conducted.

The percent survival of bobwhite quail following dosing until euthanization of the control, 0.75, 1.5 and 3.0 mg a.i./kg treatment groups was 100, 100, 99 and 63%, respectively. Thirty-seven of the 100 bobwhite dosed with 3.0 mg a.i./kg body weight died while the remaining birds at this dose level died. All the deaths occurred between the 30- and 360-minute time-step.

The study authors successfully fit a negative exponential growth model to the recovery phase for each of the three dosing treatments ($p >> 0.05$ in the G test). Rearrangement of the fitted negative exponential growth models for time to 50% recovery indicated half-lives of 1.1, 2.9, and 4.4 hours for the 0.75, 1.5 and 3.0 mg a.i./kg bw treatments, respectively. They conclude from this study that the rate of AChE recovery is inversely related to carbofuran dose. These estimates of half life are based on recovery to brain AChE activity levels that actually exceed activity levels seen in control birds; therefore, study results may overestimate half life. Estimates of recovery half-life were

independently calculated by EPA using Excel and a logarithmic curve fit; half-life estimates were similar to those reported by the study-author (see below). The time to peak AChE inhibition is approximately 30 minutes and is consistent across all tested doses. The mean AChE level at which dosed bobwhite quail died was 1.24 (SD 2.2) µmoles/min/g brain tissue. Birds at the 0.75 and 1.5 mg ai/kg dose levels showed recovery of AChE activity that exceeded the control activity levels (> 12 µmoles/min/g brain tissue); birds dosed with 3.0 mg ai/kg, however, did not on average recover to control levels during the course of the study. Using the study author's regression equation, the estimated time to complete recovery for birds in the high dose is 10.9 hours.

Based on our review we conclude that the study is scientifically sound and provides useful insight into the mechanism of carbofuran AChE inhibition and subsequent recovery. However, because there are no guidelines for avian cholinesterase studies, this study is classified SUPPLEMENTAL.

Results Synopsis:

Bobwhite Quail endpoints

Mortality

37% mortality in high dose group (3.0 mg/kg)
1% mortality in medium dose group (1.5 mg/kg)
All deaths occurred between the 30 and 360 minute time steps

Brain cholinesterase inhibition and recovery

Time to 50% recovery (1/2 life) (7.4 µmoles/min/g brain) -study-author determined

High dose (3.0 mg/kg):	4.4 hours
Medium dose (1.5 mg/kg):	2.9 hours
Low dose (0.75 mg/kg):	1.1 hours

Time to 50% recovery (1/2 life) (7.4 µmoles/min/g brain) -EPA determined

High dose (3.0 mg/kg):	4.9 hours
Medium dose (1.5 mg/kg):	2.2 hours
Low dose (0.75 mg/kg):	1.1 hours

Time to 100% recovery (12 µmoles/min/g brain) - based on study-author analysis results

High dose (3.0 mg/kg):	10.9 hours
Medium dose (1.5 mg/kg):	5.0 hours
Low dose (0.75 mg/kg):	2.9 hours

Time to 100% recovery (12 µmoles/min/g brain) - EPA determined

High dose (3.0 mg/kg):	19.8 hours

Medium dose (1.5 mg/kg): 5.8 hours
Low dose (0.75 mg/kg): 3.1 hours

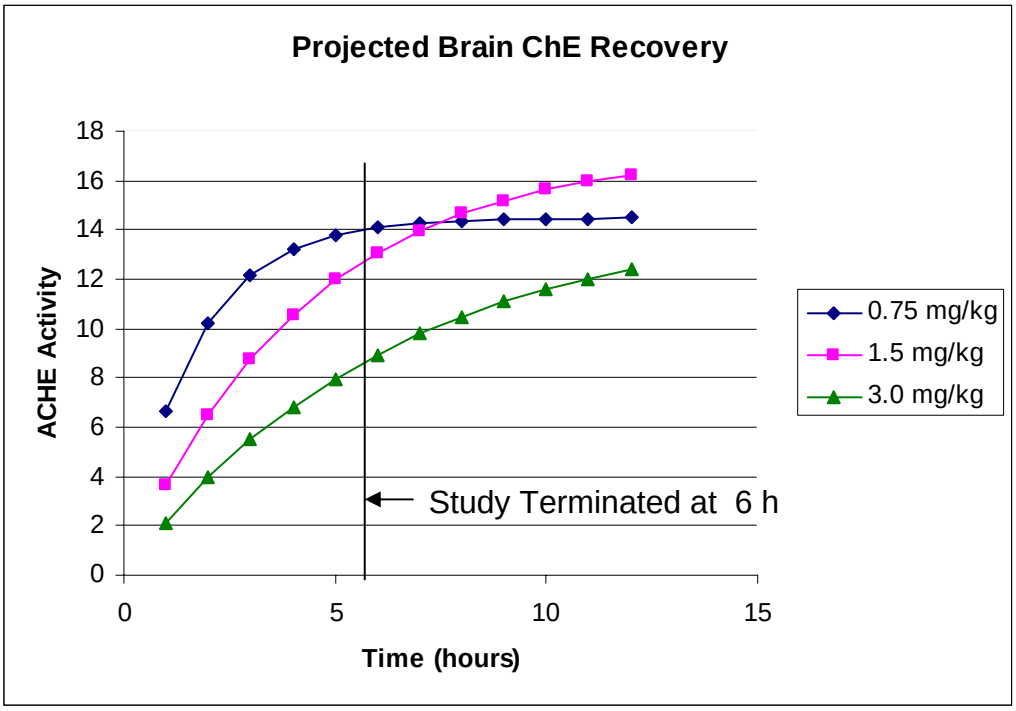

Figure 1. Projected brain AChE recovery for birds from three different carbofuran treatments. Curves based on estimated recovery half-lives.

Implications of Brain AChE Recovery for Avian PRA:

TIM version 1.0, which was used for probabilistic analyses in the carbofuran RED chapter, uses a carbofuran elimination rate based on a ^{14}C laying hen study (Hoffman and Robinson, 1994), which showed that most of the dose in a given day is excreted in urine and/or feces within 24 hours after administration. The average elimination was 82.8% based on three groups; this is equivalent to 17% retention of carbofuran at the end of a 24 hour period after dosing. TIM version 1.0 uses a 12-hour time-step to track the feeding and behavior of birds. Adjusting the retention rate to a 12-hour period yields a 12-hour retention rate of 41%.

An alternative to the physical elimination of carbofuran is a cessation of the effect at the site of action. Carbofuran acts as an inhibitor of cholinesterase, thereby allowing the buildup of acetylcholine and causing neurotoxicity. The effect, however, is reversible via hydrolysis of the carbofuran-cholinesterase bond. If the extent of cholinesterase inhibition by carbofuran exceeds a certain threshold, mortality or severe effects are likely. If inhibition is less, recovery of cholinesterase activity can occur. The study submitted by FMC indicates that the half life of recovery is on the order of 4-5 hours in surviving birds but complete recovery may vary from about 10-20 hours. However, it is important to note two important facts: the study was only carried out for 6 hours, and birds at the high

dose did not reach 100% recovery (in fact, 37% of bobwhite quail tested at the high dose died).

To use the AChE recovery half-life parameter in TIM 1.0 requires an adjustment to the time-step of TIM 1.0, which is 12 hours. The model includes an input for 24-hour elimination rate which is automatically adjusted to the time-step used in TIM 1.0 (two feeding events per day). Hence, to use the AChE recovery half-life requires estimating how much inhibition is present at 24 hours. (the 24-hour inhibition level is only used to calculate the per time step carry-over effect).

The following equation was used:

$$N_t = (0.5)^{\wedge \text{number of half-lives}}$$

Where Nt is the amount of AChE inhibition at 24 hours. The number of half lives is estimated by dividing 24 hours by the half life estimate (4.4 hours) provided from the FMC study.

Hence:

$$Nt = (0.5)^{\wedge(24/4.4)} = 0.0227$$

This value is then converted to a per-time step value of 0.15. For comparison, the original value was 0.17 carbofuran retention in 24 hours which corresponds to a retention rate of 0.41 per time step.

The probability of mortality for edge insectivore (killdeer) and edge granivore (mourning dove) are presented in Figure 2. Note that estimates of the probability of mortality were generated for the 5^{th}, 50^{th} and 95^{th} percentile sensitivities based on the dose-response relationship for a number of avian species; the points were connected by a curve to facilitate interpretation and to more clearly see trends. The baseline model scenarios were adjusted for AChE recovery as discussed above. **Results including the data provided by FMC in this study indicate that there is little impact of using the AChE recovery half-life to represent effects that carry-over between time-steps. Note, however, that as the probability of mortality decreases for the baseline, the relative impact of using the AChE recovery half life increases.**

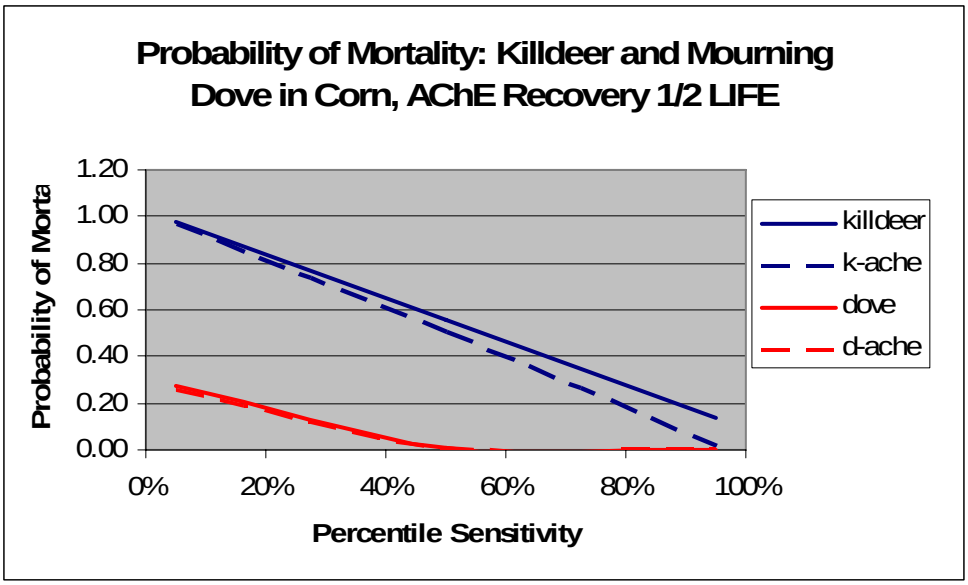

Figure 2. Probability of mortality was estimated for the 5th, 50th and 95th percentile sensitivity for edge insectivore (killdeer) and edge granivore (mourning dove). Baseline killdeer was adjusted for AChE recovery (k-ache, blue solid) as was the baseline for mourning dove (d-ache, red solid).

The SAP (2001) indicated that for chemicals with a well-defined mode of action, such as AChE inhibition, use of recovery at the site of action may be an appropriate way to model or capture carry-over effects. Although EPA used the AChE recovery half-life to address carry-over effects of carbofuran, it likely only represents one aspect of the potential for carbofuran effects to linger beyond the time of exposure. The C^{14} laying hen study, for example, indicates that approximately 17% of carbofuran remains in birds after 24 hours. It is likely that the true estimate of carry-over effects involve both the physical retention/elimination (as represented by the hen study) and the cessation of effects at the site of action (AChE recovery). That said, the comparison using each estimate independently provides a sense of the boundaries surrounding where carry-over effects lie. In addition, there is also the impact of regular food consumption on the dynamics of carbofuran body exposure, retention, and elimination. Both studies that form the basis for analysis of carry-over effects in the analysis presented here for carbofuran (AChE recovery and C^{14} laying hen) involve a single exposure although in reality exposure is likely to occur over the course of an entire feeding event. No studies are available to address this directly.

Avoidance of Carbofuran Treated Feed by Mallard Ducks

Study 2: Stafford, J.M. 2007. Assessment of Mallard Duck (*Anas platyrhynchos*) avoidance to feed containing Furadan 4F. Springborn Smithers Laboratories, 2900 Quakenbush Rd., Snow Camp, North Carolina 27349. Springborn Smithers Study Number 282.4111 and FMC Study Number A2007-6202. FMC Corporation, P.O. Box 8, Route 1 and Plainsboro Rd. Princeton, NJ 08543. May 15, 2007. Unpublished report. MRID 47128701

The objective of this study was to evaluate mallard duck avoidance to feed treated with Furadan 4F (active ingredient, carbofuran). The study employed a two-feed choice

(treated and non-treated diet) test design conducted with six concentrations of active ingredient (a.i.) mixed into the diet of six respective treatment groups.

The experimental protocol was not based on any procedures or guidelines specified by the EPA or the OECD; guidelines for this type of study do not currently exist. The following are key aspects of the protocol:

- Six treatment groups, each containing 10 birds (5 males and 5 females), were individually caged and offered feed in two feed pans per cage; one pan contained feed mixed with carbofuran and the other pan was feed only (no carbofuran).

- A control group with 10 birds (5 males and 5 females) was also maintained throughout the study; no carbofuran was offered to these birds at any time.

- The levels of carbofuran in feed for the six treatments were 1, 3, 5, 10, 30, and 135 mg ai/kg feed which corresponded to mean measured concentrations in feed of 0.67, 2.2, 3.9, 9.6, 30 and 145.4 mg ai/kg feed.

- Carbofuran was mixed in feed from a stock solution in distilled water. At each treatment level, ducks received treated feed in one feed tray and untreated feed in a second feed tray to provide a choice of diet; the location (left or right side) were alternated daily.

- Control birds received a single feed choice, provided in two separate feeders to mimic conditions in the treatment cages.

- Exposure occurred for 5 days (five 24-hour intervals).

- Non-treated feed was then provided to each cage in a single feeder for three additional days.

- Observations of birds were taken during acclimation and throughout the study, including the post-treatment recovery period. Body weights were measured for each animal to the nearest 0.1 g on the morning of day –18, -12,, -11 (begin acclimation), -5, -4, -3, -2, -1, time 0 (morning of study initiation, prior to feeding), at the end of day +1, +5 and +8. Body weights on days –11, -1, 0, 1, 5, and 8 were used to calculate proportional change in body weight over time in each group. Daily feed consumption was measured in all groups from day –14 to day +8. Feed consumption measurements for days –3 through +8 were used in statistical analyses and calculations.

No mortality or clinical signs of toxicity were observed in mallards exposed for 5 days to 0.67, 2.2, 3.9, 9.6, 30 and 145.4 mg ai/kg feed. However, birds in the 3.9, 9.6, 30 and 145.4 mg ai/kg feed treatments had significant reductions in total (treated and untreated) feed consumption (Fig 3). The 50% food avoidance concentration (FAC50), defined as the concentration at which test animal consume equal amounts of treated and untreated

feed was 10 mg ai/kg feed in this study. Food intake rates (FIR) and body weight measurements were used to calculate food repellency factors (RF) for all test groups. However, data suggest that from day –1 the test birds developed habits during the acclimation period that led to favouritism toward one feeder (side) or another (mean group RF ranging from 0.17 to 1.23).

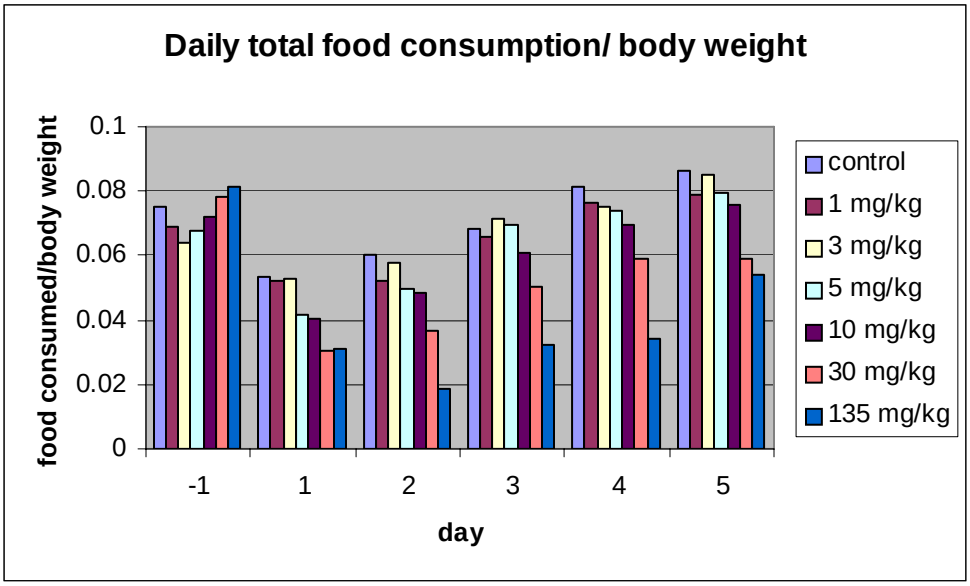

Figure 3. Day 5 feed total feed consumption .

Based on our review we conclude that the study provides useful insight into avoidance behaviour of mallard ducks to carbofuran-treated feed, but is limited to screening purposes only. .The results indicate that avoidance of carbofuran-contaminated feed cannot be entirely precluded; a more refined test is needed to better estimate avoidance behaviours. A refined study would include those study attributes characterized by an OECD workgroup on avian avoidance studies (OECD, 2003). Some important considerations include, creating a hunger-stressed condition in birds, using pens instead of cages (to more closely resemble reality) and providing food in a non-concentrated source (distributing feed throughout the pen). However, because there are no EPA guidelines for this study, it is classified SUPPLEMENTAL.

Although the study is of limited utility for avoidance, per se, it provides some insight into the effect of carbofuran on feed consumption. It is apparent from Fig. 3 that there is an effect of carbofuran on total feed consumption. Fig. 4 shows individual data points and a rough attempt at fitting a line to the data. We recognize that a linear regression is perhaps inappropriate for these data, given the wide scatter; it may be difficult to find a regression curve that explains more than 17% of the variation (note the r-squared). Statistical analysis of these data does indicate that the slope is significantly different than zero; however, the fit statistics suggest that factors other than carbofuran dose may explain the relationship. Indeed, even in the absence of toxicant exposure, birds appear to show strong feed consumption behaviors such as a tendency to consume feed from the same side of the cage.

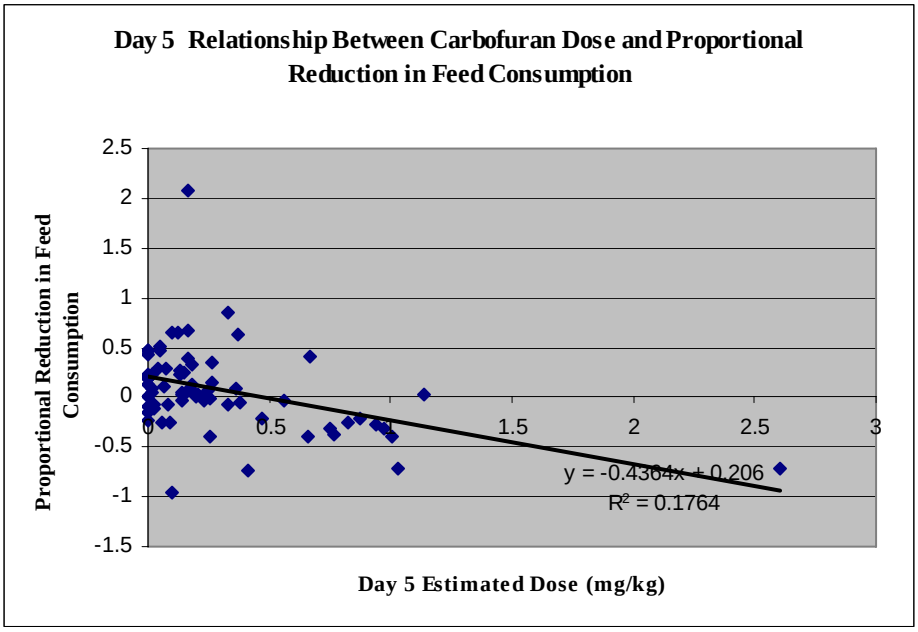

Figure 4. Day 5 feed reduction vs. Estimated carbofuran dose.

Despite the fact that these data are questionable for use in providing insight into the effect of carbofuran on total feed consumption, we have used the data to explore the potential effects on avian risk projections. In this case, the concept is that as birds consume carbofuran-treated feed items in time step x, they reduce their total feed consumption in time step x+1.

Implications of Mallard Avoidance Study for Avian PRA:

One interpretation of the data from this FMC study may provide insight into the effects of carbofuran on avian food consumption. The data on total food consumption shows an apparent effect of carbofuran exposure (Fig. 4), although there is within-day and day-to-day variation that precludes a strong relationship. Nevertheless, an analysis of alterations in food consumption may provide further insight into the potential effects of carbofuran and the response of birds to carbofuran exposure. A regression line was derived from the relationship between dose and reduction in food consumption. The equation was incorporated into TIM 1.0 to assess the impact of reduced food consumption on the probability of mortality.

The data indicate that, for the most part, if the carbofuran dose is below 0.1193 mg/kg there is no impact on total food consumption. Above this dose, the extent of feed reduction is dose dependent following:

$$Y = 0.543 * X + 0.0248$$

Where *Y* is proportion feed reduction and *X* is dose. This relationship indicates that above a dose of 1.79 mg/kg, feed consumption is basically 0. These relationships were programmed into TIM 1.0. Essentially, if exposure occurs at time x, exposure at time x+1 would be the product of whether the bird was on the field at that time step, the total exposure based on food ingestion rates, and a food consumption adjustment factor (calculated based on exposure at time x).

Effectively, this approach reduces exposure because birds are not consuming as much food. While this assumed avoidance does indeed limit exposure to carbofuran, it also generates a considerable amount of stress for birds due to an inability to meet daily energy requirements. TIM 1.0 was programmed to track the number of days that energy obtained (food consumed) was below daily energy requirements for the entire duration of the simulation. Also, the model was programmed to estimate the proportion reduction in meeting total energy needs based on the energy content of preferred food items and the estimated energy requirements of modelled birds. EPA elected to use TIM 1.0 as opposed to TIM 2.1 because of important limitations to the data in the food avoidance study. Food consumption regressions were constructed using the entire daily dietary exposure for subject birds. Using these regressions in the TIM 1.0 model would likely introduce less model uncertainty because TIM 1.0 employs two daily time steps for exposure. Alternatively, TIM 2.1 incorporates hourly time steps and a biphasic feeding pattern and while these features are likely more representative of feeding behavior in the field, they may not be appropriate for utilization of feeding behavior data derived from laboratory studies.

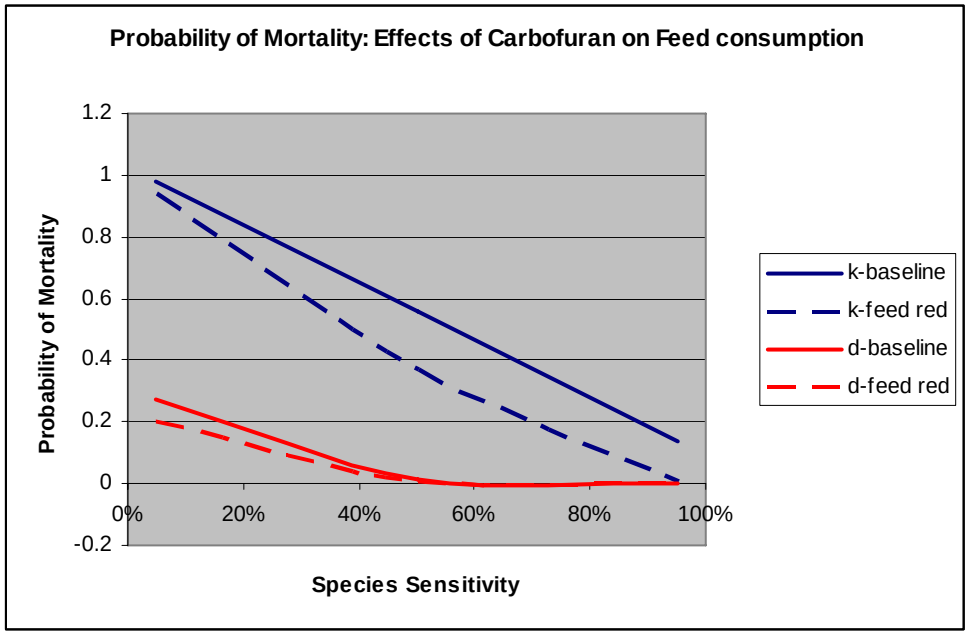

Figure 6. Effect of reduced feed consumption on probability of mortality for killdeer (edge insectivore; k-baseline and k-feed red) and mourning dove (edge granivore; d-baseline and d-fee red).

Simulation results (Figure 6) show that if total feed consumption is reduced as a function of carbofuran dose in the preceeding timestep, the probability of mortality decreases. This is not surprising as essentially total exposure is reduced in conjunction with feed consumption. The impacts on probability of mortality are greatest for less sensitive species and least for more sensitive species. For example, for 5^{th} percentile sensitive insectivorous species (killdeer), the risks of mortality go from a baseline of 0.96 to 0.88 when total feed consumption is adjusted following carbofuran dose. However, these conclusions should not be considered definitive, given the shortcommings in the study and the uncertainties associated with feed reduction/avoidance as a result of carbofuran exposure.

The effect of avoidance on reduced daily food consumption and resulting energy deficits demonstrated that for insectivorous species (killdeer), there were 13.6 timesteps that were below an individual's daily energy needs; this corresponded to a 36% deficit in obtained energy over the course of the simulation. For granivorous species (mourning dove), the effects were less severe, with about 6 timesteps where energy obtained was below energy required; this corresponded to about a 13% deficit in energy needs. Importantly, sustained energy deficits in birds may result in adverse effects on fitness (survival, growth, and reproduction). Given the high energy demands of birds, reductions in energy intake over relatively short time periods may cause mortality or force birds to adjust or modify behaviors thereby increasing risk of predation or decreasing successful reproduction. These effects associated with energy deficits were not explicitly considered here and hence, risk results should be interpreted cautiously.

In addition to above mentioned effects, the energy and feed consumption deficit in birds that is created by reducing feed intake as a result of carbofuran exposure likely introduces a hunger stressed condition in birds. In this case, birds that enter a hunger stressed condition may be willing to endure a higher carbofuran exposure. Figure 3 shows that birds in the highest exposure group, 135 mg/kg feed, showed a marked decrease in food consumption on day 1 and 2 of exposure but then began eating more, perhaps as a result of hunger stress. It is difficult, however, to accurately characterize a resumption in food consumption due to hunger induced stress or other factors.

In an effort to capture the potential that birds may compensate for a previous reduction in food intake due to carbofuran exposure, TIM 1.0 was adjusted in the following manner. The food reduction relationship as described above was left unchanged. Total food consumption for two continuous timesteps was added and compared to food requirements for the same two days. Two continuous days was chosen based on daily food consumption rates (Fig. 3) and in an effort to avoid unusually large hunger stress and compensatory feeding. The difference between what was required and what was consumed was used to estimate the proportional deficit (1 – (actual consumption / required)). This was factored into the estimate of food consumption. For each timestep, following time step one and two, the preceding two days were used to estimate a *food ingestion compensation rate*. Note that the food reduction rate is still included for each day. As an example, suppose a bird is exposed to carbofuran on day 3 to an extent that it's food consumption is reduced on day 4 by 0.7; carry-over effects indicate that food

consumption is reduced on day 5 by 0.3. For day 6, then there is an overall reduction in food consumption in the two preceding days (4 and 5) of 0.5. Hence there is a food ingestion compensation rate of 1.5. However, residual carbofuran (carry-over) indicates that overall food consumption is still reduced by 0.2 hence total exposure for day 6 would be:

Exposure = Food ingestion rate * food compensation rate (1.5) * food reduction rate (0.8).

This is purely a hypothetical example to illustrate the algorithm used in TIM 1.0. Results of simulations using these algorithms show that by allowing birds to compensate for a lower food ingestion rate on previous days, the probability of mortality increases compared to when birds do not compensate. Figure 7 shows results of model outcomes for baseline, reduced feed consumption and feed compensation for killdeer (insectivore) and mourning dove (granivore). Again, these conclusions should not be considered definitive given the uncertainties associated with the submitted study and the approach, in general.

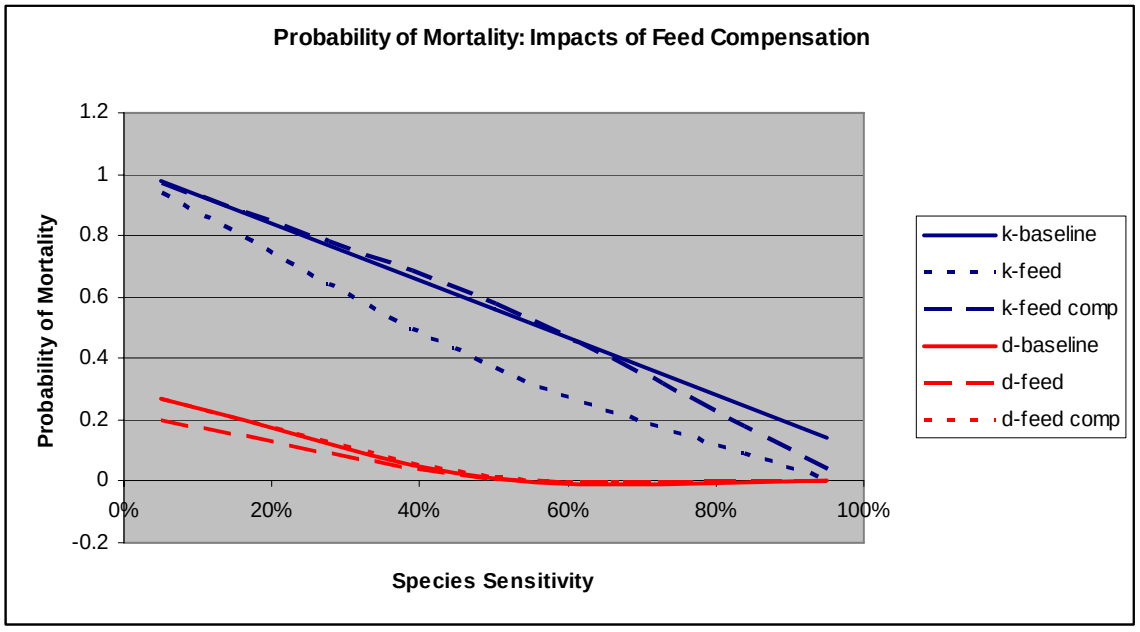

Figure 7. Effect of feed compensation on probability of mortality. Baseline insectivore based on killdeer (k-baseline), feed reduced (k-feed) and compensation for previous reduction in food intake (k-feed comp). Baseline granivore based on mourning dove (d-baseline), feed reduced (d-feed) and compensation for previous reduction in food intake (d-feed comp).

The increase in probability of mortality associated with compensation in food ingestion rate is not surprising; birds are eating more and hence exposure is higher. In the case where birds may be compensating for an energy deficit, they would likely consume more food within a given time step. Because carbofuran is very acutely toxic to birds and acts quickly the probability of mortality may actually increase over baseline conditions due to hunger stress. This may be particularly true if non-lethal effects quickly subside.

Importantly, there is considerable uncertainty regarding the modeling of both a reduction in total food consumption and compensation for decreased feeding in previous time steps. The available data are probably not robust enough to significantly reduce uncertainties associated with the effect of carbofuran on total feed consumption or the fact that birds will likely compensate for a previous deficit in food consumption. These are complex behaviors that may be difficult to adequately characterize given the wide intra- and inter-species variability in feeding habits.

Effect of Food Matrix on Carbofuran Acute Toxicity

Study 3: Stafford, J.M. 2007. Assessment of the Differential Toxicity of Carbofuran to Northern Bobwhite When Dosed With a Single Aqueous Bolus Versus the Same Dose Mixed in Feed, Springborn Smithers Laboratories Protocol No.: 030907/comparative/tox/ bobwhite/Furadan 4F. Springborn Smithers Laboratories, 2900 Quakenbush Rd., Snow Camp, North Carolina 27349. Springborn Smithers Study Number 282.4113 and FMC Study Number A2007-6204-01. FMC Corporation, P.O. Box 8, Route 1 and Plainsboro Rd. Princeton, NJ 08543. May 15, 2007. Unpublished report. MRID 47152901

Study 4: Stafford, J.M. 2007. Assessment of the Differential Toxicity of Carbofuran to Mallard Ducks When Dosed as a Single Aqueous Bolus Versus the Same Dose Mixed in Feed, Springborn Smithers Laboratories Protocol No.:0309207/comparative/tox/ mallard/Furadan 4F. Springborn Smithers Laboratories, 2900 Quakenbush Rd., Snow Camp, North Carolina 27349. Springborn Smithers Study Number 282.4112 and FMC Study Number A2007-6204. FMC Corporation, P.O. Box 8, Route 1 and Plainsboro Rd. Princeton, NJ 08543. May 31, 2007. Unpublished report. MRID 47143706

Two studies were submitted that evaluated the differential toxicity of carbofuran to birds (Bobwhite quail and Mallard ducks) when dosed as a single aqueous bolus dose versus the same dose mixed in feed. The objective of these tests was to compare the toxicity of various dose levels of carbofuran to Northern Bobwhite (*Colinus virginianus*) and Mallard ducks (*Anas platyrhynchos*) under two exposure scenarios: 1) when dosed with an aqueous bolus after 15 hours of fasting and 2) when similar doses are mixed with feed and intubated into the crop of test birds fasted for at least 15 hours. The studies quantify the difference in mortality resulting from these two exposure scenarios.

All birds that received the aqueous bolus doses were given the test substance in a solution of distilled water introduced directly into the crop via syringe and dosing needle at a volume of < 5 mL solution / kg body weight. In the case of birds receiving a food slurry dose, the appropriate volume of test substance solution (< 5 ml solution / kg body weight) was added to the food portion of the slurry dose and mixed thoroughly in a 50-mL dosing syringe cylinder. Food slurry dose preparation proceeded by placing the pre-weighed feed into the dosing syringe cylinder, thoroughly stirring the test substance solution into the feed, then adding the pre-weighed aliquot of distilled water, again thoroughly stirring the mixture, and finally fitting the plunger and feeding needle to the syringe and expelling any excess air prior to delivery to the test animal.

Behavioral symptoms of intoxication and mortality were the endpoints measured during this study. Test animals were monitored immediately after dosing for evidence of regurgitation. Additionally, birds were observed at 10 minutes, 30 minutes, one hour, and two hours post-dosing, and once again late in the afternoon. Thereafter, the treated animals were observed at least once daily for five days. Behavioral symptoms of toxicity and time of death were recorded, in addition to body weights and dose calculations. All surviving birds were euthanized at the end of the study.

The relative toxicity of carbofuran resulting from the food slurry bolus doses versus that of the aqueous bolus doses can be approximated by comparing the dose that caused similar number of mortalities and by comparing the estimated LD50s. For Bobwhite quail, the dose that caused 10% mortality was 1.75 mg/kg for the aqueous bolus dose and 7.08 mg/kg for the food slurry bolus dose; this is a 4-fold reduction in toxicity when the carbofuran is in a food-slurry bolus. The aqueous bolus dose that caused 80-90% mortality was 3.53 mg/kg while the dose for the food slurry was 12.5 mg/kg; this is a 3.5-fold reduction in toxicity with the food slurry bolus dose. Although more dose groups would be beneficial in estimating an LD50, the available dataset when used to calculate and LD50 indicate that there is a 3.9-fold difference between the LD50 from the food slurry bolus dose and the aqueous bolus dose. For Mallard ducks, the results were less robust since many of the birds regurgitated the dose, suggesting that effects likely occurred at a lower functional dose. At the aqueous dose of 0.81 mg/kg, there was 100% mortality while for birds dosed with the food slurry bolus at the same dose there was 20% mortality. The data were inadequate for robust LD50 estimation, however, estimates using the moving average method indicated that the LD50 for the aqueous dose was 0.496 (95% CL: 0-0.81) and for the food bolus dose was 1.0 (95% CL: 0.46-1.61). There is a 2-fold difference between the LD50s although the confidence intervals overlap suggesting there is no difference. Hence for Mallard ducks it is difficult, based on the available data to estimate what, if any, effect the food bolus has on acute toxicity estimates.

These two studies provide limited insight into the effect of a food bolus dose on acute toxicity of carbofuran to birds. At face value, it seems that the effect of a food bolus could reduce toxicity up to 4-fold, although it may have no effect. Moreover, the studies offer no insight into how toxicity or exposure might be altered for birds consuming wild forage items.

EPA concludes that these two studies provide limited useful insight into the effect of food matrix on carbofuran acute toxicity, but should be interpreted with caution given the uncertainties regarding what may actually occur with wild birds. Because there are no guidelines for this study type they are classified SUPPLEMENTAL.

Implications of Food Matrix Studies for Avian PRA:

Although there is still considerable uncertainty regarding the effect of a food matrix on carbofuran toxicity, TIM 1.0 was used to explore the potential risk outcomes of food

matrix effects. Two numerical adjustments were used in addition to the baseline LD50; 3.9* LD50 from the Bobwhite quail study and 2.0*LD50 from the Mallard study (comparison of LD50s). The intent was to use a range of LD50 adjustments with the idea that if food matrix effects were operating, true risk outcomes would lie near upper (3.9), middle (2.0) and/or lower (no adjustment or 1x) food matrix adjustments. The approach used did not involve any adjustments to TIM 1.0 equations but instead consisted of multiplying the LD50 used for baseline risk outcomes by 2.0 and 3.9. As mentioned in the background section, the dietary route is the only exposure route considered and simplifies the modeling; including other routes of exposure would necessitate differential treatment of LD50 since the food matrix effects only apply to the dietary route.

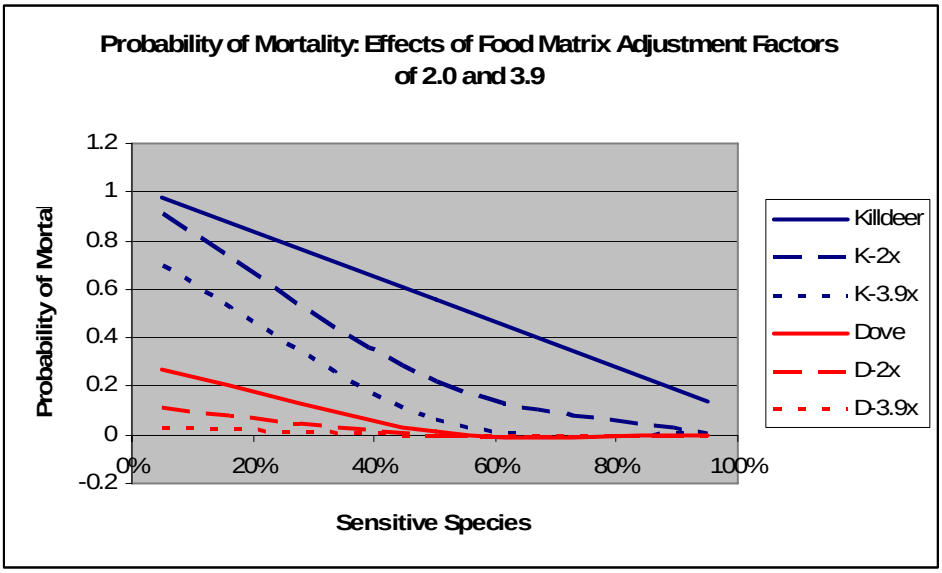

Figure 8. Effect of food matrix on acute toxicity of carbofuran: avian PRA output. Representative insectivore (killdeer) and granivore (mourning dove) LD50s adjusted by 2.0 (k-2x and d-2x for killdeer and dove, respectively) and 3.9 (k-3.9x and d-3.9x for killdeer and dove, respectively).

The output from simulations where the LD50 is adjusted to account for possible food matrix effects indicates that the probability of mortality is reduced (Figure 8). This result is unsurprising considering the increase in the LD50. While it is clear the the probability of mortality is reduced, for species or individuals that are more sensitive to carbofuran, the probability of mortality is still relatively high. For example, for the killdeer, the baseline probability of mortality for the 5th percentile sensitive species is approximately 0.97; increasing the LD50 by a factor of 2.0 reduces this to 0.91 and increasing it by 3.9 reduces the probability of mortality to 0.7. As sensitivity decreases, however, there is a proportionally larger impact of the food matrix effect on the probability of mortality.

Given the uncertainties regarding the studies, the results of this analysis should not be used quatantitatively. The actual range of effects was 4x to 1x change in LD50. Moreover, it seems unlikely that the two studies submitted represent the range of possible responses for all avian species. Hence, a reasonable intepretation might be that if food matrix effects exist, the above curves represent boundaries on possible outcomes for both less susceptible (dove) and more susceptible (killdeer) species. **Taken as a whole and**

keeping in mind that the dove and killdeer represent extremes in foraging and behavior, the potential risk for avian species can range from zero to upwards of 90%.

Aggregate Effect of the Four Avian Studies on Model Results

A review of the impacts of the four avian studies indicates that adjustments to the LD50 based on the food matrix studies likely has the greatest impact on the probability of mortality. Again, it's important to evaluate these data in light of the uncertainties presented by the study design itself and given the inherent variability in the response of wild birds to pesticide toxicity. These conclusions should not be considered definitive, given the shortcommings and uncertainties of the studies.

Simulations were conducted using: (1) the AChE recovery half-life for carry-over effects combined with (2) reduction in food consumption as a function of carbofuran exposure (with compensation). Given the uncertainties associated with the food matrix studies, simulations were conducted with the AChE recovery half-life and reduced food consumption but with the original LD50 and with an LD50 adjustment factor of 2.0 based loosely on the Mallard food matrix study; and with an LD50 adjustment factor of 3.9 based on the Northern bobwhite food matrix study. All these are compared to the baseline model outcomes which represent outputs from the original environmental fate and effects Science Chapter developed for the carbofuran IRED.

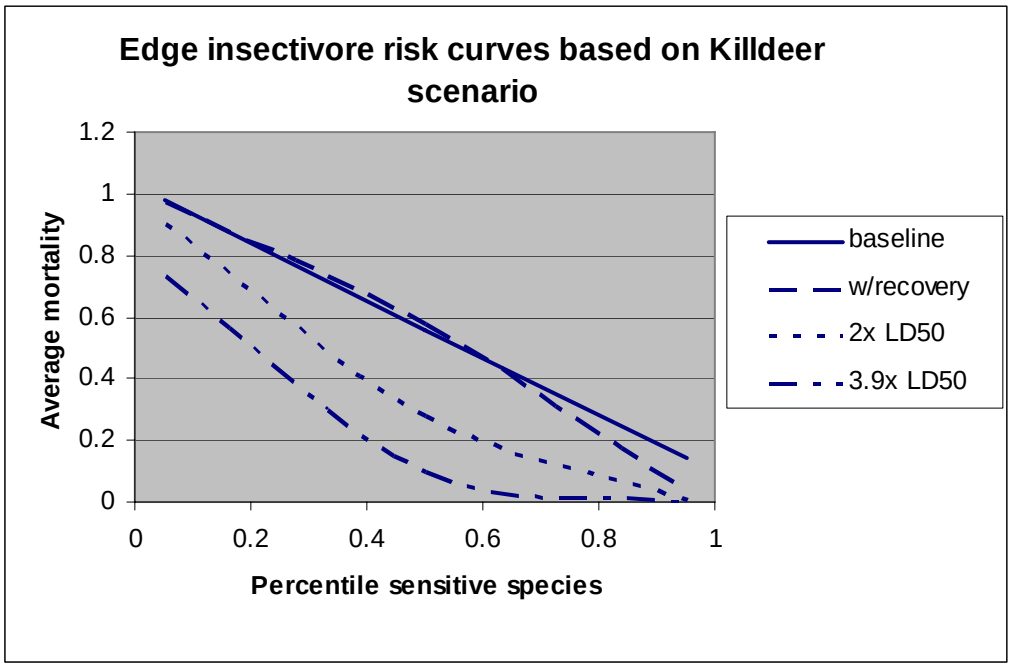

Figure 9. Combined model inputs; edge insectivorous bird species (killdeer scenario). Baseline represents input values from carbofuran RED chapter. Unadjusted LD50 simulations included AChE recovery half life and feed avoidance (with compensation) and the LD50 from the carbofuran RED. 2x LD50 is the same as Unadjusted LD50 except the LD50 is multiplied by 2 for the 5th, 50th and 95th percentiles. Similar to 2x LD50 but LD50 is multiplied by 3.9.

Figure 9 shows the average mortality for insectivorous birds (killdeer scenario) in and around corn fields treated with carbofuran for the simulations described above. Looking at the 20% and greater effect level, the baseline scenario indicates that for about 85% of species, there would be a 20% or greater average mortality. The unadjusted LD50 simulation, which includes the use of the AChE recovery half-life and reduced food consumption with compensation, shows that approximately 80% of species would have an average mortality of 20% or greater. For the 2x LD50 and 3.9x LD50 simulations, 60% and 40% of species are predicted to have average mortality of 20% or greater. For the 5th percentile sensitive species, the average mortality ranges from around 0.97 for the baseline and unadjusted LD50 simulations to approximately 0.7 for the 3.9x LD50 simulation.

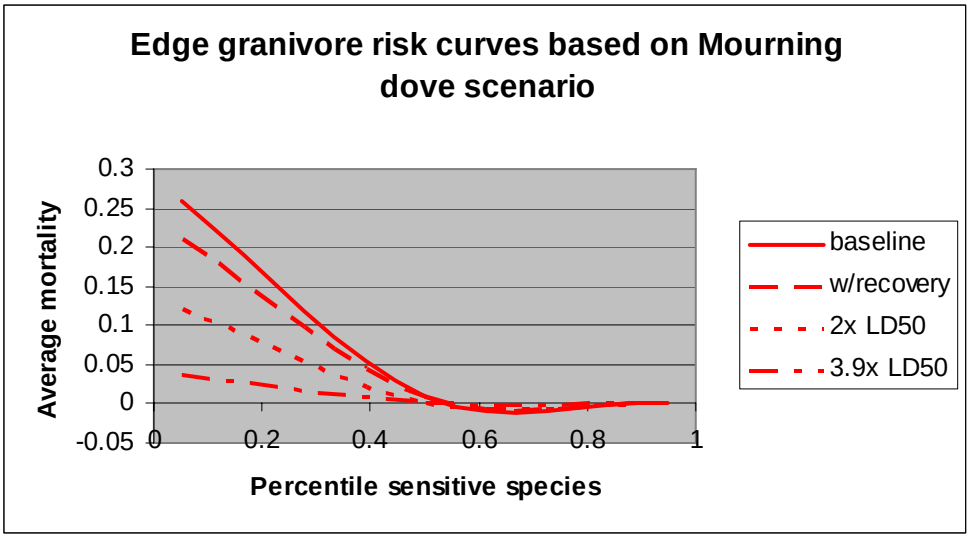

Figure 10. Combined model inputs; edge granivorous bird species (mourning dove scenario). Baseline represents input values from carbofuran RED chapter. Unadjusted LD50 simulations included AChE recovery half life and feed avoidance (with compensation) and the LD50 from the carbofuran RED. 2x LD50 is the same as Unadjusted LD50 except the LD50 is multiplied by 2 for the 5th, 50th and 95th percentiles. Similar to 2x LD50 but LD50 is multiplied by 3.9.

For granivorous species (mourning dove scenario), the impact of the adjustments based on the submitted studies is shown in Figure 10. Qualitatively, the pattern of results is similar to the insectivorous bird simulations shown in Figure 9 although the average mortality is generally lower. Here, only the baseline scenario and the unadjusted LD50 scenario show average mortality greater than 20%, and only for the most sensitive species. If we look at the an average mortality of about 5% only the most sensitive species shows an average mortality of close to 5% for the 3.9x LD50 treatment. For the 2x LD50 treatment, about 25% of species might be expected to have average mortality of 5% or greater. For both the baseleline and unadjusted LD50 simulations, approximately 40% of species would have an average mortality of 5% or greater. For the 5th percentile most sensitive species, average mortality ranges from about 4% for the 3.9x LD50 to approximately 27% for the baseline.

Thus far, the simulations presented have been based on representative insectivorous (killdeer) and granivorous species (mourning dove). The 5th, 50th and 95th percentiles for sensitivity (based on the average LD50 and slope) provide insight into how differences in sensitivity would effect risk projections. The representative species used are known to use agricultural areas (Best et al 1990) and can provide insight into the type of responses that may be expected for birds with similar feeding preferences. For omnivorous birds, risk projections would likely be between those presented for granivores and insectivores. One example is the red-winged blackbird, *Agelaius phoeniceus*, which is known to inhabit agricultural areas (Best et al 1990) and for which carbofuran acute toxicity data exist (Schafer et al 1983). Similar to the analyses conducted above, simulations were conducted using data from the four recently submitted avian toxicity studies to inform alternative inputs. Figure 11 shows the average mortality for red-winged blackbirds for several scenarios.

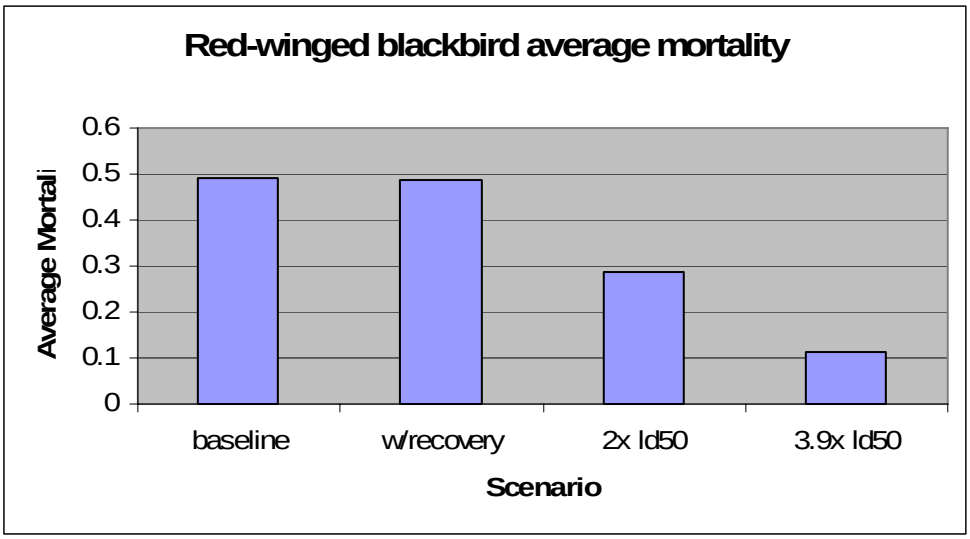

Figure 11. Average mortality of red-winged blackbirds using carbofuran-treated corn fields. Baseline represents input parameters from the original Carbofuran RED chapter.

The results for the red-winged blackbird are qualitatively similar to those for the representative edge insectivore and edge granivore presented above. Baseline average mortality is approximately 50%, which is similar to the unadjusted LD50 simulation which includes the AChE recovery half-life to describe carry-over effects and a reduction in per time step feed consumption (with compensation) based on carbofuran exposure in the preceding time step. Multiplying the LD50 by two (2x LD50), reduces the probability of mortality to approximately 30% while multiplying the LD50 by 3.9 (3.9x LD50) reduces the average mortality to approximately 10%.

In these simulations, red-winged blackbirds represent a species whose foraging preferences and behaviors lie between the edge insectivore and edge granivore scenarios presented above. The diet for red-winged black birds used in TIM 1.0 consists of 60% seeds (granivore) and 40% invertebrates (insectivore).

PRA Results Using TIM 2.1

In 2004, EPA presented an updated version of the avian PRA to the SAP. The version at that time, TIM 2.0, incorporated many of the previous SAP (2001) comments regarding TIM 1.0 including the use of an hourly time-step, a bimodal feeding pattern, a more sophisticated puddle model and the addition of dermal and inhalation exposure routes. TIM 2.0 represents an improvement in probabilistic modeling over TIM 1.0. Following the 2004 SAP, EPA further enhanced TIM 2.0 by accounting for multiple applications and further improving the puddle model; this version was named TIM 2.1. However, at the time the carbofuran ecological risk assessment was initiated, TIM 1.0 was the only available fully functional probabilistic model.

The original testing was conducted using TIM 1.0 as the new data primarily affect the dietary route of exposure represented in TIM 1.0, and to facilitate comparisons with the assessment provided in the IRED. We have conducted limited modeling of these new data using TIM 2.1, to determine whether the results continue to support the risk conclusions outlined in the carbofuran RED chapter. The approach follows that presented above, except that the study on avoidance behavior of Mallards was not evaluated due to its significant uncertainties, little effect on risk estimates of TIM 1.0 and because the laboratory derived data (collected daily) were not applicable to the hourly time steps incorporated by TIM 2.1.

TIM 2.1 uses representative species profiles instead of specific species used in TIM 1.0. To facilitate comparison, the "Edge Insectivore" species type in TIM 2.1 was adjusted to reflect the characteristics of the killdeer scenario in TIM 1.0. Similarly, the "Edge Granivore" species type in TIM 2.1 was adjusted to reflect the mourning dove scenario used in TIM 1.0. In both cases, scenarios are limited to the use of carbofuran on corn applied at a rate of 1 lb a.i./acre via foliar spray. Lastly, for brevity sake, only results from the aggregation of the inputs from the three submitted studies are presented.

Summary FMC Studies Used in TIM 2.1

Conclusions regarding the four avian studies are presented above and apply here as well. For the model runs using TIM 2.1, the AChE recovery half-life of 4.4 hours was used to estimate effects of carbofuran that may carry-over between time steps. Also, to evaluate the impacts of potential food matrix effects, the LD50 was increased by a factor of 2 and 3.9, in addition to baseline runs, where the LD50 was left unchanged.

TIM 2.1 Output: Dietary Route of Exposure Only(food only)

The first series of TIM 2.1 simulations were conducted considering only the dietary exposure route, to facilitate comparison to results above. This represents the narrowest estimation of potential risks and, also, accentuates the impact of the food matrix studies because risk is based only on exposure via the diet.

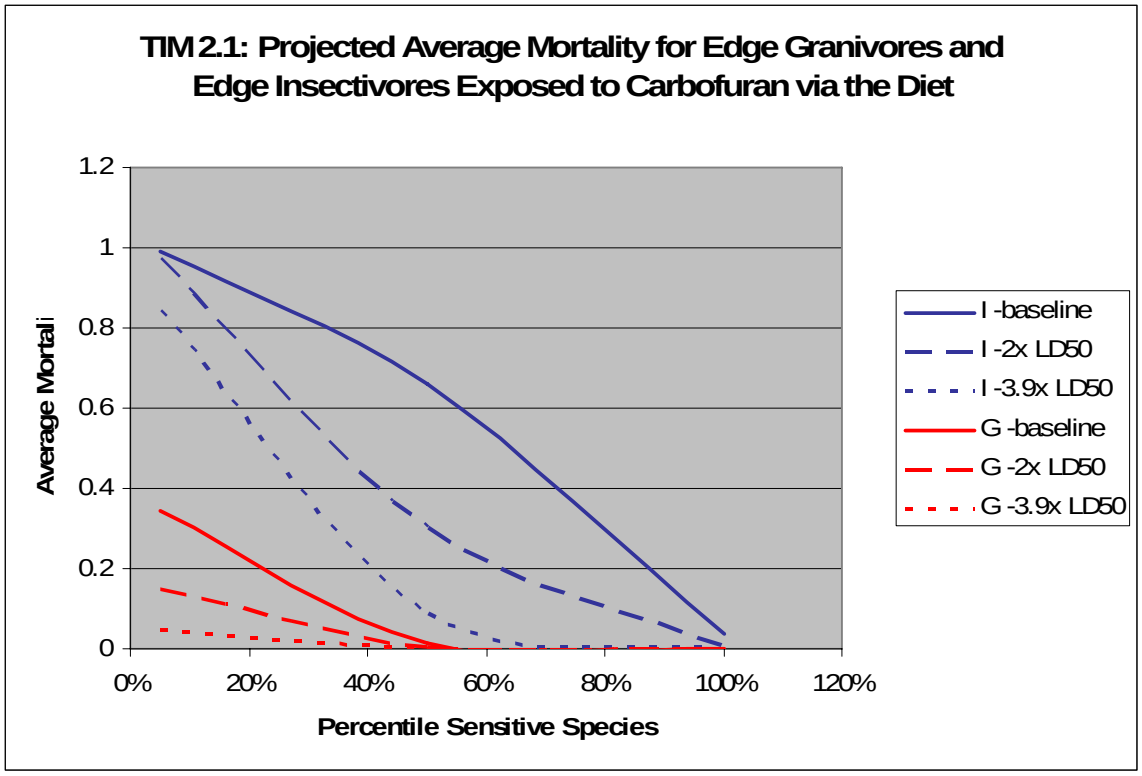

Figure 12. Combined model inputs; edge insectivorous (blue lines) and edge granivorous (red lines) bird species. Baseline represents input values from carbofuran RED chapter except using AChE recovery half-life. 2x LD50 is the same as baseline except the LD50 is multiplied by 2 for the 5th, 50th and 95th percentiles. 3.9x LD50 is similar to 2x LD50 but LD50 is multiplied by 3.9.

Figure 12 shows the risk curves, ranging from the most sensitive to least sensitive species for both an edge insectivore and an edge granivore. As expected, adjusting the LD50 upward by a factor of 2 and 3.9 reduces the average mortality. The effect of the food matrix is most pronounced with less sensitive species. For example, sensitive edge insectivores show an average mortality of 0.99, 0.97 and 0.84 for the baseline, 2x LD50 and 3.9x LD50, respectively while for species in the 50th percentile of sensitivity the average mortality is 0.66, 0.30 and 0.09 for the baseline, 2x LD50 and 3.9x LD50, respectively. The pattern is similar for edge granivores although risks, in general, are lower due to lower exposures; little mortality would be expected for species above the 40th percentile sensitivity.

Comparison of TIM 2.1 and TIM 1.0 Results

Table 1.0 presents the average mortality outputs from TIM 1.0 (Figures 2, 6-10) above and TIM 2.1 (Figure 12) based only on dietary exposures to carbofuran. Generally, the model versions produce similar results for the modeled scenarios, although there are slight differences in predicted mortalities. TIM 2.1 generally produced slightly higher estimates of average mortality for birds in the 5th and 50th percentile sensitivity categories but produced lower estimates of average mortality for species in the 95th percentile sensitivity category. Similar to conclusions presented above, the results indicate that food matrix effects can influence risk outcomes. However, given the uncertainties in

these data regarding applicability to a wide range of species and the application of these data to birds in the wild, EPA interprets these results as representing a range of potential risk outcomes. Importantly, risks to birds are not eliminated by the consideration of the additional data, particularly for sensitive species and those who's diet and behavior predispose them towards higher exposures.

Table 1.0. Results of Avian Probabilistic Modeling for the Use of Carbofuran On Corn (1 lb a.i./A)

Avian Species or Focal-type	Adjusted Inputs	Average Probability of Mortality		
		5th percentile (least sensitive)	50th percentile (medium sensitivity)	95th percentile (least sensitive)
Model Results Based on TIM v1.0: Dietary Exposure Only				
Killdeer	Baseline[1]	0.98	0.56	0.14
Killdeer	FMC data: AChE[2], Food matrix (2x)[3], Feed reduction[4]	0.90	0.28	<0.01
Killdeer	FMC data: AChE, Food matrix (3.9x), Feed reduction	0.73	0.1	<0.01
Mourning Dove	Baseline	0.27	0.01	<0.01
Mourning Dove	FMC data: AChE, Food matrix (2x), Feed reduction	0.12	<0.01	<0.01
Mourning Dove	FMC data: AChE, Food matrix (3.9x), Feed reduction	0.04	<0.01	<0.01
Model Results Based on TIM v2.1: Dietary Exposure Only				
Edge Insectivore	Baseline	0.99	0.66	0.04
Edge Insectivore	FMC data: AChE[2], Food matrix (2x)[3],	0.97	0.30	<0.01
Edge Insectivore	FMC data: AChE, Food matrix (3.9x),	0.84	0.09	<0.01
Edge Granivore	Baseline	0.34	0.01	<0.01
Edge Granivore	FMC data: AChE, Food matrix (2x),	0.15	<0.01	<0.01
Edge Granivore	FMC data: AChE, Food matrix (3.9x),	0.05	<0.01	<0.01

[1] Baseline conditions represent inputs presented in the carbofuran RED chapter
[2] AChE represents use of the brain cholinesterase recovery half life for estimating effects that carry-over between time steps
[3] The model LD50 was multiplied by 2 (2x) and 3.9 (3.9x) to account for potential food matrix effects
[4] Feed reduction with compensation as described above.

TIM 2.1 Output: Dietary Route + Avian Drinking Water Exposures

Although previous analyses are restricted to considerations of the dietary route of carbofuran exposure based on food alone, EPA acknowledges that other routes of exposure to birds are highly likely in carbofuran use areas. A potentially important route of exposure to birds is the consumption of carbofuran-contaminated water present on the treated field, either as dew or in puddles.

Drinking water consumption is based on an allometric equation for birds and, in the model, is adjusted for the water content of food items. Estimates of carbofuran concentrations in puddles are based on a varying volume puddle model. Importantly, TIM 2.1 allows specification of whether the rain event occurs before or after the application event. When rainfall creates puddles, higher exposure estimates are expected because of direct addition of pesticide to puddles, which are transient in nature. Simulations were conducted with rain occurring before and 24 h after application of carbofuran.

Figure 13 shows the projected average mortality for edge granivores and edge insectivores resulting from dietary exposures to carbofuran, including drinking water. Results show that, overall, the average mortality increases across species sensitivities and among the two bird species types compared to food exposures alone. For example, in comparison to the food only exposures for edge granivorous species, the projected average mortality for 50^{th} percentile species sensitivity went from about 0.002 up to 0.22 for the 2x LD50 scenario and from essentially 0 to 0.22 in the 3.9x LD50 scenario. The 2x LD50 and 3.9x LD50 scenarios are similar because the projected mortality is a result of drinking contaminated water only.

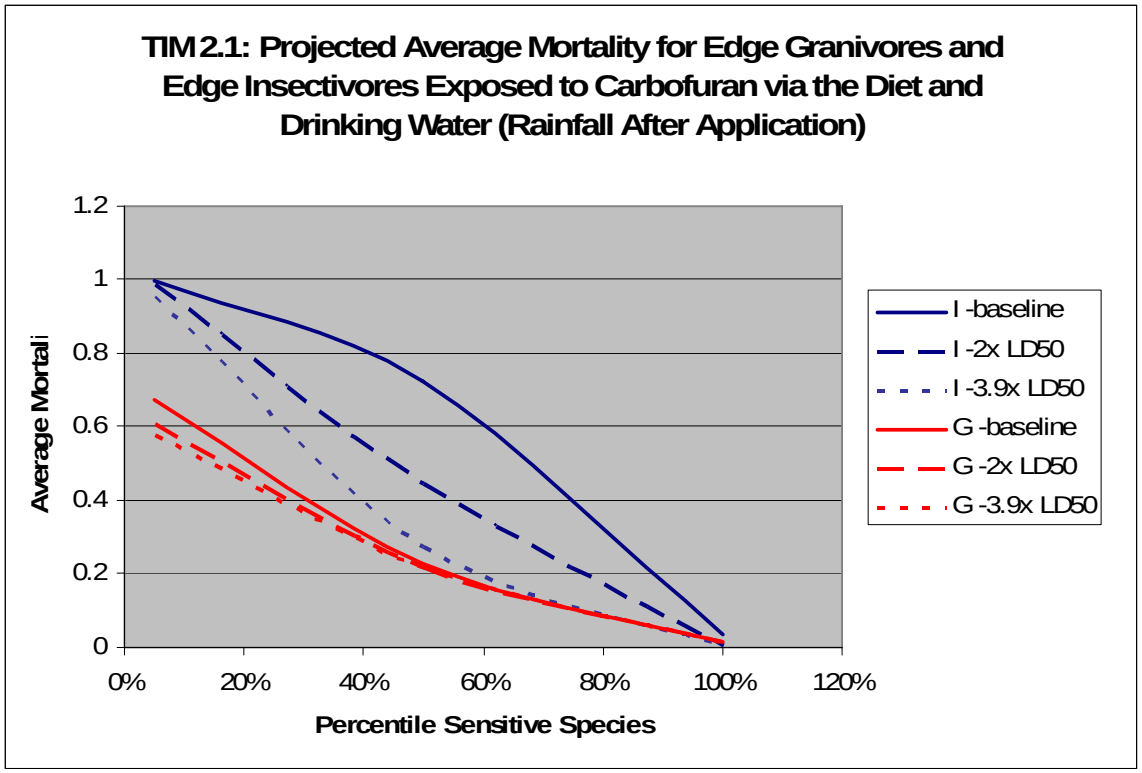

Figure 13. Combined model inputs; edge insectivorous (blue lines) and edge granivorous (red lines) bird species exposed to carbofuran via diet and drinking water. Baseline represents input values from carbofuran RED chapter except using AChE recovery half-life. 2x LD50 is the same as baseline except the LD50 is multiplied by 2 for the 5th, 50th and 95th percentiles. 3.9x LD50 is similar to 2x LD50 but LD50 is multiplied by 3.9.

A set of simulations were run to test the impact of the timing of rain events with respect to the application of carbofuran on exposure. Figure 14 shows the results of simulations where carbofuran application occurred 24 h after a rainfall event. In this case, puddles are already present on the field and direct application of pesticide to the puddles results in higher concentrations compared to when puddles form after carbofuran is applied. In this case, average mortality is high (>80%) for both types of species and with multiple adjustments to the LD50 for species that fall approximately below the 50th percentile in sensitivity. The increased probability of mortality associated with pesticide applications occurring after rainfall is driven by higher pesticide puddle concentrations.

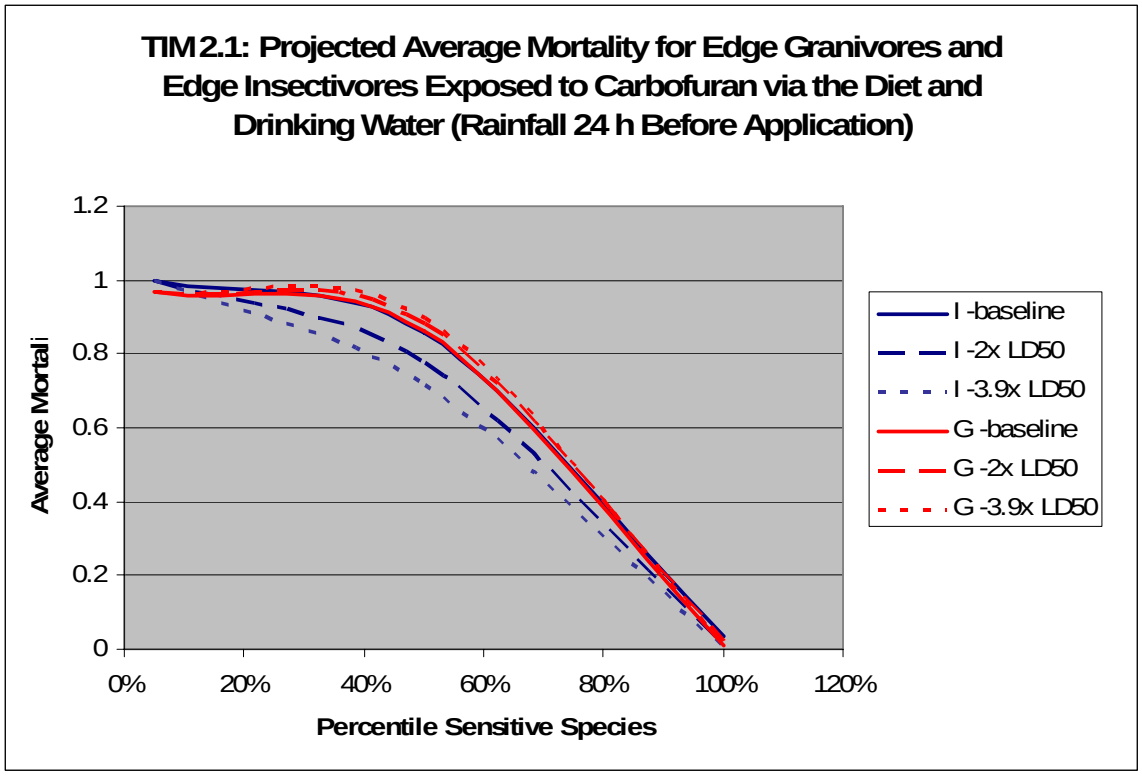

Figure 14. Combined model inputs; edge insectivorous (blue lines) and edge granivorous (red lines) bird species exposed to carbofuran via diet and drinking water. Baseline represents input values from carbofuran RED chapter except using AChE recovery half-life. 2x LD50 is the same as baseline except the LD50 is multiplied by 2 for the 5th, 50th and 95th percentiles. 3.9x LD50 is similar to 2x LD50 but LD50 is multiplied by 3.9.

Conclusions

Given the uncertainties and variability associated with assessing risks of carbofuran use to birds, the analysis presented here should be interpreted cautiously. The intent is to provide a sense of the range of possible risk outcomes associated with certain model assumptions that were informed by the four studies recently submitted by FMC. The results indicate that altering the model inputs based on information gleaned from the four studies broadens the range of possible risk outcomes but does not eliminate risk to avian species in and around carbofuran use areas. Indeed, for more sensitive species, the probability of mortality marginially changes when taking into account the AChE recovery half-life, reduced feed consumption and a four-fold upward adjustment of the LD50. Importantly, the results are similar based on both TIM 1.0 and TIM 2.1 suggesting also that PRA risk conclusions in the carbofuran RED would be the same even if the analysis were based on the most recent version of TIM. If anything, the results presented here lend further support for the conclusion that the use of carbofuran results in the mortality of some avian species in agro-ecosystems. Moreover, it should be emphasized that simulation results presented here are based on exposures limited to food and water intake which likely underestimates true exposures. Studies have shown that

dermal and inhalation routes can contribute to total exposures of pesticides (For example, Driver et al 1991; Mineau 2002) TIM 2.1 allows for inclusion of inhalation and dermal exposure routes; when these are included, average mortality increases. For example, the projected average mortality for edge insectivorous birds exposed via food ingestion, drinking water and dermally in the 50^{th} percentile sensitivity is 0.32 when using the LD50 multiplied by 3.9. The average mortality for the same scenario but for birds in the 5^{th} percentile sensitivity is in excess of 90%.

Overall, EPA concludes that the four avian studies submitted by FMC in 2007 provide limited insight into the potential risks of carbofuran to avian species. However, there still remains considerable uncertainty regarding some elements of study design and how results from these laboratory toxicity studies apply to birds in field conditions. Birds in the field are coping with a number of environmental conditions and variables that will impact the potential for adverse effects associated with pesticide use. In addition, there can be considerable inter-species variability in sensitivity to toxicants and in behavioral patterns further complicating study interpretation and risk projections. Specifically, EPA does not believe that the four studies recently submitted by FMC thoroughly address uncertainties associated with the risks of carbofuran to avian species or alter the conclusions that carbofuran presents a serious risk to avian species in and around use areas.

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