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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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SUBJECT: **Carbofuran.** HED Revised Risk Assessment for the Reregistration Eligibility Decision (RED) Document (Phase 6). PC 090601. DP # D330541.

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The following human health risk assessment for carbofuran supersedes the previous assessment, *HED Revised Risk Assessment for the Reregistration Eligibility Decision (RED) Document (Phase 4), 3/9/06, D327359*. This revision specifically addresses the conclusions of the Human Studies Review Board (HSRB) regarding the use of toxicological data from studies involving human subjects in the carbofuran risk assessment and incorporates, where appropriate, comments received during Phase 5 of the reregistration process. Additionally, a more refined dietary assessment was performed as the previous assessment may have overestimated exposures for certain food crops.

The Agency presented the three studies listed below, which are intentional human dosing toxicity studies (one oral and two dermal) to the Human Studies Review Board (HSRB) at a meeting on May 2-3, 2006 for scientific and ethical review. The HSRB discussed the studies extensively during this meeting. While the final written report is not available yet, the Agency believes that the oral comments of the HSRB provided a sufficient indication of the conclusions likely to appear in the HSRB's final report such that EPA could confidently move ahead in assessing risk. Accordingly, because EPA has a statutory deadline for completing its review of carbofuran, the Agency has decided to issue this risk assessment prior to receiving the final written report of the HSRB. The Agency will carefully review the HSRB's final report on carbofuran prior to issuing its final reregistration eligibility decision to determine whether the HSRB's report contains conclusions that warrant reconsideration of this risk assessment.

Arnold, J.D. 1976. Evaluation of safe exposure levels to carbamate, administered orally to healthy adult normal volunteers. Final Report. Quincy Research Center, Kansas City, MO.

Arnold, J.D. 1977. Carbamate (carbofuran) human dermal study. Final Report. Quincy Research Center, Kansas City, MO.

Arnold, J.D. 1978. Comparison of cholinesterase inhibition effects of furadan 4F and FMC 35001 4EC. Final Report. Quincy Research Center, Kansas City, MO.

The HSRB did not recommend the use of any of the oral or dermal studies conducted with carbofuran in human subjects for the single chemical assessment or in informing the interspecies uncertainty factor for the cumulative assessment. There were significant scientific deficiencies found in both the oral and dermal human studies, as well as some ethical deficiencies associated with the human dermal studies. The current carbofuran risk assessment, taking into consideration the HSRB recommendations, does not rely on these data.

1.0 EXECUTIVE SUMMARY

Background:

This human health risk assessment is being conducted to support the reregistration of the pesticide active ingredient carbofuran.

Carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl-N-methylcarbamate) - CAS Registry number 1563-66-2; Chemical number is 090601) is a broad spectrum carbamate insecticide and nematicide registered for control of soil and foliar pests on a variety of field, fruit, and vegetable crops. Carbofuran may also be used on ornamentals. There are no residential uses.

The registered formulation classes of carbofuran, granular and flowable concentrate, are typically applied to the soil at planting (banded, in-furrow, or injection treatment), postplanting (banded, sidedress, or basal spray treatment) or applied foliarly using ground or aerial equipment.

The residues of toxicological concern for all exposure analyses are parent carbofuran and its metabolite 3-hydroxycarbofuran.

Hazard Characterization:

The primary toxicologic effect seen following carbofuran exposure is neurotoxicity resulting from inhibition of the enzyme acetylcholinesterase. Carbofuran is a member of the N-methyl carbamate common mechanism group who share the ability to inhibit AChE by carbamylation. Following maximal inhibition, recovery is rapid (minutes to hours). Cholinesterase (ChE) inhibition and associated clinical signs have been demonstrated in laboratory animals exposed to carbofuran and in persons involved in the application and use of carbofuran. The repeated exposure studies in dog, rat, and mouse indicated that there was no accumulation of toxicity from repeated days of carbofuran exposure.

Consideration of all available toxicity data was used to determine the toxicity endpoints and reference doses appropriate for the carbofuran risk assessment. Criteria utilized in determining the appropriate toxicity endpoints and reference doses to use include the quality and reliability of the studies. EPA presented the carbofuran oral and dermal human toxicity studies to the Human Studies Review Board (HSRB) in May 2006. The HSRB found the dermal toxicity studies to be unethical and the oral study to be scientifically deficient primarily due to the small sample size and large variability seen in the ChE data. The HSRB concluded that none of the carbofuran human toxicity studies should be used in the human health risk assessment. The team considers the

comparative ChE rat study in adult and juvenile rats to be the most suitable for extrapolating dietary risk to carbofuran and the FMC time course study the most appropriate for extrapolating risk to occupational workers.

Acute RfD

There are several studies available where acute ChE inhibition was measured at or near peak time of inhibition (15-45 min) and which inform the derivation of the acute RfD and acute PAD. These include two studies performed by the registrant: 1) a time course study where male and female rats were dosed at 0.5 and 1.0 mg/kg and 2) a recently submitted comparative ChE study where adult and juvenile (post-natal day 11, PND11) rats were dosed at 0.3, 0.6, and 1.0 mg/kg (FMC 2005). Clinical signs (tremors) were also reported for adults and PND11 pups in the comparative ChE study. In another study, done in support of the Agency's cumulative risk assessment for the N-methyl carbamates, scientists from the National Health and Environmental Effects Research Laboratory (NHEERL) performed time course and dose-response studies in male rat where brain and RBC ChE inhibition along with motor activity were measured. For carbofuran, the Agency's study included doses ranging from 0.1 mg/kg up to 1.5 mg/kg (USEPA, 2005).

In order to evaluate the appropriate point of departure (PoD) for ChE inhibition, the Agency considered benchmark dose (BMD) estimates developed from the comparative ChE study in adult and PND11 rats along with BMD estimates provided in the preliminary cumulative risk assessment for carbofuran derived from the FMC time course study and the EPA studies. Dose-response modeling is preferred over the use of NOAEL/LOAELs (i.e., no or low observed adverse effect levels) since NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, but instead reflect dose selection (USEPA, 2000). The estimated dose at which 10% ChE is observed (BMD10) and the lower 95% confidence intervals (BMDL10) were estimated by fitting the ChE data to an exponential dose-response model using generalized nonlinear least squares. The BMD10 was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity across the brain compartment and is a response level close to the background ChE. Moreover, the Agency believes that 10% is likely to be protective to other toxicities, such as clinical signs and/or behavioral endpoints including tremors and changes in motor activity seen in carbofuran studies. For the acute RfD, the Agency has used a BMDL10 of 0.03 mg/kg calculated from data in pup brain ChE from the comparative ChE study.

Brain ChE inhibition has shown to be a sensitive endpoint for carbofuran in the studies considered. Regarding RBC ChE inhibition, the Agency's dose-response data and the registrant's time course study show that RBC ChE inhibition is also a sensitive endpoint, and actually, available data suggests the RBC ChE inhibition may be more sensitive than brain ChE inhibition; therefore, a point of departure based on RBC ChE inhibition (peripheral effect) would be protective of any effects in the target tissue (brain). In the comparative ChE study (FMC 2005),

however, no inhibition of RBC ChE was observed at any tested dose, including those doses which did result in blood ChE inhibition in the registrant's time course study and those that resulted in more than 50% brain ChE inhibition. The lack of dose-response relationship for RBC ChE data is also inconsistent with other studies in the dog and rat which show RBC ChE measures to be sensitive. The lack of RBC ChE inhibition is further questioned by the motor activity data and incidence of clinical signs, particular tremors.

Motor activity was compared with brain and RBC ChE inhibition data. Decreases in motor activity coincide with decreases in both RBC and brain ChE inhibition, particularly at the low end of the dose-response curve. Regarding clinical signs, in PND11 pups, every pup at each dose level exhibited tremors. It is unknown whether changes in motor activity and/or tremors are related to brain or peripheral ChE inhibition; consequently, the Agency can not discount the potential that peripheral ChE inhibition may be inhibited by carbofuran. Given that studies have shown RBC ChE inhibition to be a sensitive measure and that dose-related changes in behavioral endpoints and clinical signs have been observed at low doses of carbofuran, at this time, *the Agency does not consider the RBC ChE inhibition data from the comparative ChE study to be sufficiently reliable for developing a point of departure for risk assessment purposes.*

Overall, each of the available acute rat studies with carbofuran has some uncertainty. As stated above, the RBC ChE data from the comparative ChE study are considered unreliable. Brain ChE was not measured in the FMC time course study. The comparative ChE study and the FMC time course studies only included relatively high doses. EPA's dose-response study includes data at low and high doses but may have missed the peak inhibition. Because of the existing uncertainty regarding the database of toxicity studies with carbofuran, the Agency believes that an FQPA factor is required. The Agency's BMD analysis for the preliminary cumulative risk assessment was presented to the FIFRA SAP in February and August, 2005. At those meetings, the panel supported the Agency's approach for developing BMD estimates for the N-methyl carbamates. In this analysis, the Agency used data from both the registrant's time course study and from the Agency's dose-response study. The Agency believes that use of data from multiple studies provides a more robust analysis than a single study. The results of the combined analysis, provided in Table 5, indicate that, in adult rats, when using data from the FMC time course and the EPA dose response study that RBC ChE inhibition may be 5X more sensitive compared to that of brain ChE inhibition (ie, 0.03 mg/kg compared to 0.15 mg/kg.

Given that 1) pups are more sensitive than adult rats (brain ChE inhibition), 2) RBC ChE inhibition may be a more sensitive point of departure compared to brain ChE inhibition (and may be considered an appropriate surrogate for the peripheral nervous system), and 3) the lack of reliable RBC data in pups, there is residual uncertainty in the available toxicology database. The Agency has applied an FQPA factor (for database uncertainties) in the derivation of the carbofuran acute RfD. The magnitude of this factor is 5X based on the observed 5-fold difference between brain ChE inhibition and RBC ChE inhibition in adult rats, i.e, it is assumed that pups will also be 5 times more sensitive to RBC ChE inhibition than that of brain. The registrant should submit

additional comparative cholinesterase data which measures RBC and brain ChE inhibition in pups and adults. This comparative ChE study should also include a range-finding study and well-conducted time course study such that the definitive study is performed at the time of peak effect for ChE inhibition. After submission of this study, the Agency will refine its BMD analysis and reconsider the FQPA database uncertainty factor.

Therefore, the FQPA factor of 5X , along with the typical intraspecies (10X) and interspecies (10X) factors, is applied to the pup BMDL10 (0.03 mg/kg; brain ChE inhibition) and results in an acute PAD of 0.00006 mg/kg/day for the general population and all population subgroups.

Chronic RfD

Carbofuran-induced inhibition of ChE activity is rapidly reversible (less than 24 hours). Therefore, chronic exposures to carbofuran could be considered as a series of acute exposures and a separate chronic assessment is not necessary, i.e., the acute exposure assessment will be protective of longer exposure durations.

Dermal and Inhalation

There are no suitable dermal or inhalation toxicity studies for carbofuran risk assessment purposes. The BMDL10 value of 0.01 mg/kg/day calculated for the adult RBC ChE inhibition data (combined analysis of the FMC time course study and the EPA dose response study; USEPA 2005) is appropriate for assessing dermal and inhalation exposure risks (all durations) for occupational workers (the most sensitive effect in the population of concern, adults). There are no residential uses of carbofuran so a residential exposure assessment is not warranted

A dermal absorption factor of 6%, from a rat dermal penetration study is used in this risk assessment for route-to-route extrapolation. A default 100% inhalation absorption rate, relative to oral exposures, is applied for route-to-route extrapolation.

FQPA Considerations

There was evidence of qualitative increased susceptibility in the rat multi-generation reproduction study and the rat developmental neurotoxicity study. BMD analyses of the comparative ChE rat study revealed that the BMD values for the PND11 pups were lower (i.e., more sensitive) than those of adult rats. The Agency has applied an FQPA factor (for database uncertainties) in the derivation of the carbofuran acute RfD. The magnitude of this factor is 5X based on the observed 5-fold difference between brain ChE inhibition and RBC ChE inhibition in adult rats, i.e, it is assumed that pups will also be 5 times more sensitive to RBC ChE inhibition than that of brain.

Cancer

Carbofuran is classified as "Not Likely" a human carcinogen.

Dietary (food and water) Exposure and Risk Assessment:

HED considered potential acute exposure to carbofuran residues from dietary sources (food and water). A chronic assessment is not necessary as chronic exposures to carbofuran can be considered as a series of acute exposures because of the rapid reversibility of cholinesterase inhibition. A cancer risk assessment was not performed as carbofuran is classified as "Not Likely" a human carcinogen.

Food

HED conducted an acute dietary (food only) exposure analysis using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.00-2.02). Exposures (residue consumption) were compared to the population adjusted dose (PAD). Risk estimates that are less than 100% of the PAD do not exceed HED's level of concern.

A refined (Tier 3), acute probabilistic dietary exposure assessment was conducted for all supported carbofuran food uses. Combined anticipated residues of carbofuran and 3-hydroxycarbofuran on food were included in the assessment. Acute anticipated residues for many foods (artichoke, cucumber, melons, milk, peppers, potatoes, pumpkin, squash, strawberry and sweet corn) were derived using USDA Pesticide Data Program (PDP) monitoring data from recent years (through 2003 for all commodities except milk, for which recently available 2004 data were used). Anticipated residues for bananas and grapes were derived using monitoring data from the 2000 Carbamate Market Basket Survey. Most of the samples analyzed by the PDP and the Carbamate Market Basket Survey Task Force contained no detectable residues of carbofuran or its 3-hydroxy metabolite. A value equal to ½ the combined limits of detection (LODs) of carbofuran and 3-hydroxycarbofuran was assumed for samples with non-detectable residues (with zero values incorporated for percent of crop not treated). For commodities with no monitoring data available (cranberries, coffee, sugar beets, sugarcane and sunflowers) and for field crops that are typically blended during marketing (barley, field corn, oats, rice, soybean, and wheat), anticipated residues were based on field trial data (or, for coffee, on processing study data). PDP data were previously used to develop anticipated residues for barley, field corn, oats, rice, soybeans and wheat. Although PDP data are generally assumed to provide more refined estimates of exposure than field trial data, they may sometimes overestimate exposure, particularly for blended commodities, such as those listed above, with low percent crop treated estimates, no detections in the PDP data and

relatively high ½ LOD values. Therefore, in the current assessment, field trial data were used to provide more refined exposure estimates for these commodities.

BEAD provided average and maximum percent crop treated (%CT) estimates for most crops. The maximum %CT estimates were used to refine the acute dietary exposure estimates. Maximum %CT estimates were low for most crops but ranged up to 30% (artichokes). The estimated % crop imported was used in conjunction with information on the % imports treated with carbofuran (on a country-by-country basis) to develop %CT estimates for crops with tolerances maintained for import purposes (cranberry, rice, strawberry) and other crops (bananas, coffee and sugarcane) which are imported in significant amounts into the U.S.

Processing data are available for certain crops, including sugar beets (1x), grape juice(1x) and sugarcane (0.2x). Processing factors derived from these data were incorporated in the acute analyses. The data for grape juice were translated to cranberry juice. In addition, a cooking factor of 0.75X from a literature study was applied to all boiled/cooked/baked/fried vegetables (not fruit) such as artichokes, squash, peppers, potatoes, pumpkins, cucumbers, and sweet corn. For all other commodities, DEEM default processing factors were used.

The resulting acute dietary exposure estimates for food exceed HED's level of concern for the U.S. population and all reported population subgroups at the 99.9th percentile of exposure. Carbofuran dietary exposure at the 99.9th percentile was estimated at 0.000154 mg/kg/day for the U.S. population (260% of the aPAD) and 0.000292 mg/kg/day (490% of the aPAD) for children 1-2 years old, the most highly exposed population subgroup. [Estimated dietary exposure to carbofuran also exceeds HED's level of concern for children's subgroups at the 99th percentile of exposure. Estimated exposure for all populations is below HED's level of concern at the 95th percentile.]

The foods contributing most heavily to acute exposure at the 99.9th percentile of exposure for the subgroup having the highest estimated exposures (children, 1-2 yrs.) are cranberry (approximately 32% contribution to total exposure), cucumber (19%), watermelon (19%), and squash (11%).

Uncertainties in Dietary Assessment

Exposure estimates for all of the major food contributors, except cranberry, were based on PDP monitoring data adjusted to account for the percent of the crop treated with carbofuran and, therefore, may be considered fairly highly refined. Carbofuran is not registered in the U.S. for use on cranberries, however, and monitoring data are not available for this commodity. The exposure estimates for cranberry were based on field trial data and conservative assumptions about the percent of imported cranberries that could be treated. Therefore, exposures from cranberries are likely overestimated in this assessment. The availability and use of monitoring data and/or additional information on carbofuran use on imported cranberries would allow HED to refine

exposure estimates for cranberries.

The percent crop treated data provided by BEAD are screening level usage estimates. The screening level estimates for most crops are low, and, ordinarily, further refinement would not be expected to alter the dietary risk assessment significantly. However, the level of concern for carbofuran (0.00006 mg/kg body wt) is very low, and slight adjustments in %CT estimates might have a significant impact, particularly for crops, such as cucurbits, that contribute heavily to exposures at the 99.9th percentile.

Cooking and processing factors were incorporated into the assessment to the extent that they were available. However, additional data on the concentration and/or reduction of residues of carbofuran in foods during cooking or processing would allow HED to further refine dietary exposure estimates.

Sensitivity Analysis for Acute Dietary Exposures (food only)

PDP and Market Basket monitoring data were used to estimate carbofuran exposure for many food commodities. Most of the samples analyzed by the PDP and Carbamate Market Basket Survey Task Force (and many field trial samples as well) contained no detectable residues of carbofuran or its 3-hydroxy metabolite. In the acute exposure assessment, samples with non-detectable residues were assigned a residue value equal to ½ the combined Limits of Detection (LOD) for carbofuran and its metabolite, with zeros incorporated to account for the percent of the crop not treated with carbofuran. Generally, assigning ½ LOD to non-detectable residues is not expected to significantly affect the outcome of a risk assessment. In this case, because of the relatively high combined LODs and the low aPAD (0.00006 mg/kg/day), HED conducted sensitivity analyses which showed that the risk assessment for carbofuran is sensitive to assumed concentrations (i.e., ½ LOD) for non-detectable residues.

However, even when *all* non-detectable residues are assumed to be zero and crops for which monitoring data are unavailable (cranberries, etc.) are excluded from the assessment, estimated food exposures at the 99.9th percentile still exceed HED's level of concern for children.

This highlights an important point regarding the carbofuran risk assessment: At the upper percentiles of exposure, relatively low residues found in a small percentage of food samples (<1%), result in estimated exposures that are above HED's level of concern for children's subgroups**.** As a result of this finding, HED performed additional calculations to determine the risk to children consuming median (50th percentile) amounts or upper (90^{th} percentile) amounts of a single commodity (either cucumbers or summer squash) containing actual residues of carbofuran at the levels detected by the PDP. For example, a child eating a serving (~0.2 ounces) of cucumber with a mid-value residue (from PDP) of 0.147 ppm would result in a risk estimate of 75% of the

aPAD, at the 50th percentile of consumption. Overall, at the 50th percentile of consumption, %aPAD utilized ranged from about 15% for the lower PDP residue values to over 200% for the higher PDP residue values. At the 90th percentile of consumption, or up to 2 ounces consumed, %aPADs ranged from 120% to over 2000%. The consumption of summer squash by children is greater than that of cucumbers and the resulting risk estimates for squash at the 50th percentile of consumption ranged from about 45% to over 800%, and from >200% to >4000% at the 90th percentile of consumption.

These calculations demonstrate that although residues of carbofuran and/or its hydroxy metabolite may be found in only a few food samples (less than 1% of cucumbers, for instance), children who eat even moderate amounts of a food with measurable residues could have exposures in excess of HED's level of concern.

Water

The Environmental Fate and Effects Division (EFED) has completed a water resources analysis to determine the potential for carbofuran to contaminate surface and ground water.

The environmental fate characteristics of carbofuran indicate that it is mobile in many types of soils and persistent in acidic and neutral environments. Base hydrolysis is the most significant route of degradation of carbofuran in water and soil. These characteristics make carbofuran transportable to surface water and ground water in some environments and indicate the potential for carbofuran contamination of ground water and surface water in areas where it has a tendency to persist (e.g., neutral to low pH waters). HED has determined that the degradate 3-hydroxycarbofuran should be regulated along with carbofuran. However, available environmental fate studies do not show formation of 3-hydroxycarbofuran through most environmental processes except soil photolysis, where in one study it was detected in very low amounts. Even though 3-hydroxycarbofuran was not explicitly considered as a separate entity in the EFED exposure assessment, it would not be expected to significantly add to exposure estimates.

Surface Water

Nine different crop/location scenarios, which represented 80% of total carbofuran use from 1987 to 1997, were used in the modeling studies. For each crop/location scenario, two application rates were investigated: one application rate represented the lowest label rate that would be used (as determined by the US EPA, Office of Pesticide Program, Biological Economic Analysis Division), and one rate represented a high labeled rate allowed on either the federal or a state label. The use of the high and low rates allows bracketing of carbofuran aquatic concentrations. Bracketing was also achieved by using a range of PCAs (percent of area cropped)– using default regional PCAs and crop-specific PCAs , when available.

Using the PRZM/EXAMS model, the acute EDWCs (estimated drinking water concentrations) in surface water vary greatly across use areas (0.11 to 75 ppb) and take into account variability in application rates and in percent cropped areas in the watershed. The highest acute EDWCs occurred when the highest application rates (maximum label rates) were used for Texas sorghum followed by Illinois corn and Mississippi cotton. The lowest acute EDWCs occurred using the lower application rates for California and Pennsylvania alfalfa and Maine potato.

The acute surface water EDWCs may be considered somewhat conservative. The PRZM-EXAMS models used to estimate concentrations of carbofuran in surface water are based on an actual reservoir/watershed which is known to be a highly vulnerable configuration. Additionally, EDWCs based on the crop scenarios which generated the highest exposures (applications were at maximum rates; the entire crop within the watershed was treated every year for 30 years; and a high percentage of the watershed was cropped with corn or sorghum) would result in geographically localized, high-end exposure assessments for a potential subpopulation of individuals who derive their water from watersheds cropped in sorghum in TX or corn in the mid-west. Although the EDWCs are not expected to be representative of the rest of the country, they will be protective of the lower exposures anticipated for other individuals. Individuals whose drinking water comes from sources where lower EDWCs may occur, such as watersheds cropped in alfalfa in CA or PA, would be expected to have much lower exposures to carbofuran through drinking water.

Groundwater

Following detection of carbofuran in ground water in Long Island, NY, FMC voluntarily conducted a prospective groundwater (PGW) monitoring study (1981-1983; Maryland) to assess impacts from the labeled use of carbofuran. A corn plot had one application of Furadan 10G (totaling 3.0 lbs a.i./A; the labeled rate has since been reduced to 1 lbs a.i./A on corn for these soils for local pests), and a potato plot had eight foliar applications of Furadan 4F at one week intervals (totaling 1.0 lbs a.i./A). Only the corn plot was used to derive estimates of groundwater concentrations

Because this prospective ground water study was conducted over only one growing season, the reported ground water concentrations do not represent impacts from long-term use of carbofuran (applied in multiple years). For this reason, direct use of the PGW data may not be appropriately conservative. Thus, EFED used superpositioning techniques to provide estimates of concentrations following long-term use of carbofuran. These techniques apply if chemical transformation processes and all transport and interaction mechanisms are assumed to be linear with respect to concentration. Based on these assumptions, *EDWCs for ground water, based on PGW monitoring data, range from 1.4 ppb (low application to alfalfa) to 110 ppb (high application to grapes).*

Aggregate Exposure and Risk Assessment:

Potential exposure from residential settings was not considered as carbofuran is a restricted use pesticide and does not have residential uses or uses that could result in significant exposure via the residential pathway. Therefore, in assessing aggregate risk, HED need only consider potential acute exposure to carbofuran residues from food and drinking water.

Acute dietary exposure and risk from *food alone* was above HED's level of concern (i.e., >100% aPAD). For the most highly exposed subpopulation (children, 1-2 yrs) the acute dietary (food only) risk estimate is 490% of the aPAD. Since acute exposures exceed the aPAD for food alone, exposure from drinking water was not aggregated with food in the dietary assessment. However, HED is concerned about any additional exposure (to all subpopulations) through drinking water.

EFED provided Estimated Drinking Water Concentrations (EDWCs) for surface and ground water. Using the PRZM/EXAMS model, the acute EDWCs in surface water range from **0.11ppb** (low application to CA alfalfa) to **75 ppb** (maximum label application to TX sorghum) for nine crop/location scenarios. EDWCs for ground water, based on prospective ground water monitoring data, range from **1.4 ppb** (low application to alfalfa) to **110 ppb** (maximum application to grapes) (see Section 4.3, Table 9 and Table 10 for all values).

Assuming there is no acute dietary food exposure to carbofuran, and *all* of the allowable exposure occurred through water sources (i.e., assuming the aPAD of 0.00006 mg/kg/day is completely allotted to exposure to residues in water), the DWLOC (Drinking Water Level of Concern) for the general US population would be **2.1 ppb** and for infants and children the DWLOC would be **0.6 ppb**. These values are based on daily water consumption estimates of 2 liters for adults and 1 liter for infants and children. DWLOCs based on consumption of a single 8 ounce serving of water would be **2.6** ppb for infants and children and **18** ppb for adults. Therefore, even if all of the allowable dietary exposure (i.e, entire aPAD, or "risk cup") occurred through drinking water, HED would have concerns for acute exposure to carbofuran, particularly for individuals (both adults and children) who may derive their water from watersheds that are highly cropped and where carbofuran applications may be made up to the maximum label rates (representative scenarios include TX sorghum, IL corn, MS cotton, NC tobacco, ID potato, CA and PA alfalfa, CA grape, and ME potato). Exposure to individuals (adults) whose drinking water comes from sources where crop/location scenarios result in lower EDWCs (scenarios with lower applications including ME potato, CA grape and CA alfalfa) may not be of concern, if the entire risk cup were available for water exposures (for infants and children, of the nine representative crop/location scenarios, only low applications to CA grape would result in EDWCs that are below the DWLOCs; again, this assumes 100% of the risk cup would be available for water).

Occupational Exposure and Risk Assessment:

HED considered short- term exposures to pesticide handlers, mixers, loaders, applicators and short-term exposures to postapplication workers through dermal and inhalation routes. Intermediate-term and long-term exposures were not assessed as ChE inhibition does not increase with continued exposure to carbofuran and because of the rapid reversibility of ChE inhibition. Additionally, exposures more than 90 days in duration are not expected for carbofuran use.

Handler Exposure: Estimated total MOEs (dermal plus inhalation) are a short- term risk concern (i.e MOEs less than 100) at the *maximum* mitigation level (engineering controls) for almost all handler scenarios. The exceptions are mixing/loading granulars for tractor-drawn spreader application (rice, cucurbits, spinach) and flagging for spray application (corn, sugarcane). Additionally, total MOEs for mixing/loading/ applying liquids for backpack sprayer were greater than 100 with baseline protection. Total MOEs for mixing/loading/ applying liquids for low-pressure handwand application were also greater than 100, but with PPE2 protection (single layer protection, gloves, PF5 respirator).

It should be noted that for all the scenarios with MOEs below 100, more than half had total MOEs less than 10 and more than three-quarters had MOEs less than 20. None had MOEs greater than 52. Factors that should be considered in the interpretation of these results include (1) no carbofuran-specific data were available for handler exposure. Surrogate exposure data from PHED were used for all handler exposure estimates, (2) estimated occupational exposures in this assessment represent central to high-end values. Average daily exposures were estimated based on maximum label rates with average values for handler unit exposures, exposure duration, area treated, and other exposure factor inputs, (3) risk estimates from dermal exposure were greater (lower MOEs) than those for inhalation exposure. A dermal absorption factor of 6% has been used based on a 24 hour exposure duration from a dermal penetration study. Ideally, thedermal absorption factor would be selected from results seen after 10 hours of exposure to simulate an average worker exposure/day. However, since this time point (10 hours) was not evaluated in this study, the absorption factor of 6% noted at 24 hours was selected and is considered protective of workers, (4) a default 100% inhalation absorption rate (relative to oral exposure) was assumed as a suitable inhalation toxicity study was not available.

Postapplication (Reentry Exposure): Dislodgeable foliar residue (DFR) data for carbofuran applied to corn, cotton and potatoes were used to estimate exposure from postapplication activities. Most crops with postapplication activities failed to reach MOEs of 100 within the currently prescribed REIs. The crops with postapplication activities with estimated MOEs that conflict with current REIs (reintry intervals) are: soybeans and small grains (wheat, barley, oats) (currently 48 hours REI; MOEs reached in 12 days); alfalfa, sugar beets, sugarcane, and potatoes (currently 48 hours; MOEs not reached within 14 days, i.e. the duration of the relevant study); sweet corn, and field and pop corn (currently 14 days; MOEs not reached within 32 days/duration of relevant study). Only sunflower and sorghum had postapplication MOEs of 100 within the label REI of 14 days (MOEs reached in 13 days).

Tobacco-based Exposure and Risk Assessment:

A short-term inhalation risk assessment for adult smokers has been completed since carbofuran is registered for use on tobacco. Based on the short-term inhalation BMDL10 of 0.01 mg/kg/day (based on red blood cell cholinesterase inhibition in adult male rats), the short-term MOE for carbofuran exposure from the use of tobacco is estimated to be 12. This conservative risk estimate is above HED's level of concern for inhalation exposure to carbofuran (less than the short-term inhalation MOE of 100).

Incident Reports

HED conducted a review of occupational and non-occupational incidents as reported in the following databases: Incident Data System (IDS) (1992- 2003), Poison Control Center (PCC)(1993-2001), California Department of Pesticide Regulation (1982-2002), National Pesticide Telecommunications Network (NPTN)(1984-1991), National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR)(1998 - 2002). In all, from the period between 1992 and 2003, more than 700 possible carbofuran poisoning incidents were reported.

In the IDS, from 1996 through 2003, there have been 42 reported incidents from carbofuran exposure. Common among these reports is evidence that carbofuran is a prevalent cause of eye problems which was reported in about one-quarter of all the cases. Some of the cases involved single workers or groups of workers reentering a field shortly after application and being exposed to carbofuran residues. Fifty percent of these cases involved exposure to the applicator during spray operations. Although data were often limited, most cases involved failure to wear proper protective equipment, or they occurred when workers were cleaning or repairing spray equipment. There were three reports of deaths, all due to ingestion, where homicide was suspected.

PCC results for the years 1993 through 2001 for occupational and non-occupational incidents involving adults and older children and for children under age six were compared between carbofuran and all other reported pesticides. The PCC data indicate that carbofuran exposure is likely to result in more serious medical outcome and serious medical care than exposure to other pesticides. Most of the reported symptoms for carbofuran incidents were specific to cholinergic poisoning and most resulted from dermal and inhalation exposure rather than oral exposure. While approximately four percent of the non-occupational incidents could be attributed to misuse, or misreading of the label, it was not possible to determine what percentage of occupational incidents were attributable to misuse.

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, carbofuran was ranked 37th with 103 incidents in humans reported.

In the NIOSH/SENSOR data (surveillance in seven states) there were nineteen reports due to carbofuran alone out of 4,221 reports. Eleven of the cases occurred in Texas. The pattern of incidents is similar to those reported for California.

A 1997 HED incident review stated that, overall, carbofuran was judged second among 28 pesticides on measures of hazard derived from California and Poison Control Center data. Most of the risk from this product is due to use by pesticide handlers, especially mixer/loaders who handle the concentrated material. Less often, groups of people have been poisoned from spray drift or from exposure to field residue. A 1998 case in California illustrates the effects from field residues when workers reentered treated cotton fields two hours, instead of the required 48 hours, after application. Such residues are capable of causing moderate to relatively serious effects which require medical treatment.

Detailed descriptions of incidents reported to the California Pesticide Illness Surveillance Program from 1982 through 2002 identified a total of 88 cases in which carbofuran was either used alone or in combination with other chemicals but was judged to be responsible for the reported health effects. The majority of the illnesses were of a systemic type. The majority of incidents occur among handlers who mix, load, and apply carbofuran in agricultural fields.

The number and rate of poisoning cases due to carbofuran exposure is sufficient to warrant priority attention to risk reduction measures for this pesticide.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

TABLE 1. Nomenclature of Carbofuran and Metabolite

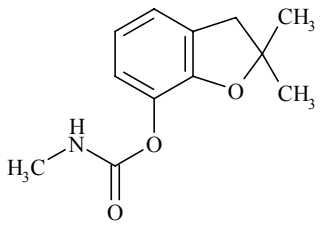
Test Compound	
Common name	Carbofuran
Company experimental names	FMC 10242
IUPAC name	2,3-dihydro-2,2-dimethylbenzofuran-7-yl methylcarbamate
CAS name	2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate
CAS #	1563-66-2
End-use products/EP	4 lb/gal FlC

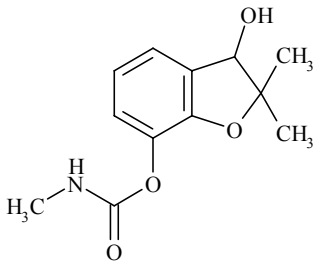
TABLE 1. Nomenclature of Carbofuran and Metabolite	
Metabolite	
Common name	3-Hydroxy-Carbofuran
Company experimental names	FMC 18209
IUPAC name	2,3-dihydro-3-hydroxy-2,2-dimethylbenzofuran-7-yl methylcarbamate
CAS name	2,3-dihydro-3-hydroxy-2,2-dimethyl-7-benzofuranyl methylcarbamate
CAS #	16655-82-6

TABLE 2. Physicochemical Properties		
Parameter	**Value**	**Reference**
Melting point/range	150-153° C	Accession #255050
pH	not dispersible in water	
Density (20°C)	1.18	
Water solubility (25°C)	0.035%	
Solvent solubility (25°C)	acetone 15%; xylene 1%	
Vapor pressure at 25°C	8.7×10^{-7}	
Dissociation constant (pK_a)	not dispersible in water	
Octanol/water partition coefficient Log(K_{OW})	17 for 1 ppm @ 20°C; 26 for 10 ppm @ 20°C	
UV/visible absorption spectrum (λmax, nm)	neutral and acidic methanol: 216nm and 277nm alkaline methanol: 292nm	MRID 44604101; MRID 44656801

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl-N-methylcarbamate) is a broad spectrum N-methyl carbamate that can cause cholinergic toxicity through inhibition of the acetylcholinesterase(s) of the peripheral and/or central nervous system. Similar to other N-methyl carbamate pesticides, inhibition is followed by rapid recovery of acetylcholinesterase. Animal toxicity studies reveal that the primary toxicologic effect following carbofuran exposure by the

oral route is cholinesterase (ChE) activity inhibition, the most sensitive endpoint. This is to be expected given that carbofuran is an N-methyl carbamate insecticide. In a special toxicokinetic study, inhibition and recovery of red blood cell and plasma ChE activities were observed in rats following single-oral, gavage doses of carbofuran. ChE inhibition was also observed in a comparative ChE study in adult and pup rats. ChE inhibition and associated clinical signs have been observed in humans exposed to carbofuran through application and use of this pesticide. Chronic oral studies in three separate species (dog, rat, mouse) have also demonstrated significant inhibition of ChE activity. Results of chronic studies in dog, rat, and mouse indicated that there was no cumulative effect of carbofuran on ChE inhibition.

Consideration of all available toxicity data was used to determine the toxicity endpoints and reference doses appropriate for the carbofuran risk assessment. Criteria utilized in determining the appropriate endpoints and reference doses to use include the quality and reliability of the studies. EPA presented the carbofuran oral and dermal human toxicity studies to the Human Studies Review Board (HSRB) in May, 2006. The HSRB found the dermal toxicity studies to be unethical and the oral study to be scientifically deficient primarily due to the small sample size and large variability seen in the ChE data. The HSRB concluded that none of the carbofuran human toxicity studies should be used in the human health risk assessment. The team considers the comparative ChE rat study in adult and juvenile rats to be the most suitable for extrapolating dietary risk to carbofuran and the FMC time course study the most appropriate for extrapolating risk to occupational workers.

Carbofuran has low acute toxicity in the acute dermal, primary skin and primary eye studies (Toxicity Category III or IV) and is not a skin sensitizer. Acute oral and inhalation assays showed carbofuran to have high acute toxicity (Toxicity Category I for both).

Carbofuran does not appear to possess mutagenic activity and was negative in both rat and mouse oncogenicity assays. Carbofuran is classified as a "Not likely" human carcinogen based on the lack of evidence of carcinogenicity in mice or rats.

The dermal absorption data for carbofuran are adequate and indicate that carbofuran can be absorbed through dermal exposure. The Hazard Identification Assessment Review committee selected a dermal absorption factor of 6% based on the results of a study in rats published in the literature (Shah *et al.*, 1987. J. Tox. and Environ. Health 22:207-223).

Developmental toxicity studies in both the rat and rabbit showed no evidence of quantitative or qualitative increased susceptibility of the developing fetuses. There was evidence of a *qualitative* increased susceptibility in the rat multi-generation reproduction study since offspring toxicity was manifested as decreased pup survival between birth and PND 4 whereas parental toxicity was limited to decreased body weight gain.

The rat developmental neurotoxicity study also provided evidence of a *qualitative* increase in offspring susceptibility. At the LOAEL of 75 ppm, maternal toxicity was manifested as decreases in body weight gain and food consumption, whereas offspring toxicity at this dose was manifested as increased mortality, decreased pup viability and decreased fetal weight. Additionally, offspring also exhibited delayed vaginal patency and preputial separation - which may be taken as developmental delays and possible indications of endocrine disruption. However, the changes were minimal and may have been due to decreased body weights.

BMD analyses of the comparative ChE rat study revealed that the BMD values for the PND11 pups were lower (i.e., more sensitive) than those of adult rats [memo dated January 19, 2005: Benchmark dose analysis of cholinesterase inhibition data in neonatal and adult rats (MRID no. 46688914) following exposure to carbofuran PC Code: 090601. DPBarcode D325342. TXR No. 0054034].

At least two studies from the open literature (Pant et al., Toxicol. 14[11]:889-894, 1985; Pant et al., Hum. Exp. Toxicol. 16[5]:267-272 1997) have indicated that carbofuran at relatively low doses (0.2 mg/kg/day) causes adverse effects in the rat male reproductive system. The HIARC had previously recommended that a new multi-generation reproduction study be conducted (with special protocols to examine the effects seen by Pant et al.). The Pant et. al. studies did not report details on the purity of the test material, and no information on confirmation of the concentration and homogeneity of doses. However, a recently submitted study (special male reproduction in the rat (MRID 46688911), designed and conducted similarly to that of Pant et al., did not support the findings of testicular/spermatoxic effects. In addition, the recent study adhered to GLP standards.

A non-guideline comparative cholinesterase assay (adult vs. young) has been submitted to address potential concerns that children may be more sensitive to ChE inhibition than adults. The HIARC has previously requested that an acute neurotoxicity study be performed. Based on the primary review of the comparative study, HED is not requiring an acute neurotoxicity study at this time. The current risk assessment relies on the doses and endpoints from the comparative study, which reflects the most sensitive effect in the most sensitive species/population. Because of a lack of reliable RBC ChE inhibition data, this comparative ChE study in adult and juvenile animals must be repeated. A 28-day inhalation study in rats remains outstanding.

Carbofuran is primarily metabolized into three phenolic carbamate metabolites (7-phenol carbofuran, 3-keto-7-phenol carbofuran and 3-hydroxy-7-phenol carbofuran) and into 3-hydroxy carbofuran. The trio of phenolic metabolites are not deemed to be of toxicologic significance, and 3-hydroxycarbofuran is considered to be at least equitoxic compared to parent carbofuran.

Table 3. Acute Toxicity of carbofuran technical

Guideline No./ Study Type	Species	MRID No.	Results	Toxicity Category
870.1100 Acute oral toxicity	Rat	Gronning and Kimmerle, 1974	LD_{50} = 7.8 mg/kg _ 6.0 mg/kg _	I
870.1200 Acute dermal toxicity	Rabbit	44671601	LD_{50} = 4403 (2900 - 6685) mg/kg - intact skin	III
870.1300 Acute inhalation toxicity	Rat	Gronning and Kimmerle, 1974	LC_{50} = 0.08 mg/L	I
870.2400 Acute eye irritation	Rabbit	00070347	Minimal irritation	III
870.2500 Acute dermal irritation	Rabbit	00054336	Primary Irritation Score = 0.25	IV
870.2600 Skin sensitization	Guinea pig	44827101	Non sensitizer	N/A
870.6100 Delayed Neurotoxicity (hen)		-	Not required for a carbamate	-
870.6200 Acute Neurotoxicity		-	not required at this time	-

Table 4. Toxicity Profile of carbofuran technical.[1] (Only studies classified Acceptable are shown.

Guideline No./ Study Type	MRID No. (year) /Doses	Results
870.3100 90-Day oral toxicity rodents	Not Available	---

Guideline No./ Study Type	MRID No. (year) /Doses	Results
870.3150 90-Day oral toxicity in nonrodents	Not Available	---
870.3200 21/28-Day dermal toxicity	00155429 (1991) 0, 10, 100, 1000 mg/kg/day (rabbit)	Systemic NOAEL = > 1000 mg/kg/day ; LOAEL = none found ChE NOAEL = > 1000 mg/kg/day ; LOAEL = none found
870.3250 90-Day dermal toxicity	Not Available	---
870.3465 90-Day inhalation toxicity	Not Available	---
870.3700a Prenatal developmental in rodents	00058609 (1980) 0, 0.25, 0.5, 1.2 mg/kg/day	**Maternal** NOAEL = > 1.2 mg/kg/day (HDT) LOAEL = none found **Developmental** NOAEL = > 1.2 mg/kg/day (HDT) LOAEL = none found ChE activity not measured
870.3700b Prenatal developmental in nonrodents	00076762 (1981) 0, 0.12, 0.5, 2 mg/kg/day	**Maternal** NOAEL = 0.5 mg/kg/day LOAEL = 2 mg/kg/day based on decreased body weight and red/brown staining in anogenital region **Developmental** NOAEL = 2 mg/kg/day (HDT) LOAEL = None found ChE activity not measured
870.3800 Reproduction and fertility effects	00030514, 00030570 (1979) 0, 1, 5 mg/kg/day	**Parental/Systemic** NOAEL = 1 mg/kg/day LOAEL = 5 mg/kg/day based on decreased body weight gain and food consumption **Reproductive** NOAEL = 1 mg/kg/day LOAEL = 5 mg/kg/day based on decreased pup survival and body weight ChE activity not measured

Guideline No./ Study Type	MRID No. (year) /Doses	Results
870.4100a Chronic toxicity rodents	00030516, 00030498, 00043745, 00043746, 00058736, and 00085498 (1979) 0, 0.5, 1, 5 mg/kg/day	Systemic NOAEL = 1 mg/kg/day LOAEL = 5 mg/kg/day based on decreased body weight ChE NOAEL = 1 mg/kg/day LOAEL = 5 mg/kg/day based on significant decreases in plasma, RBC, and brain cholinesterase in males and plasma and brain cholinesterase in females rats.
870.4100b Chronic toxicity dogs	00129507 (1983) 0, 0.25, 0.5, 12.5 mg/kg/day	Systemic NOAEL = 0.5 mg/kg/day LOAEL = 12.5 mg/kg/day (LDT) based on toxic signs, decreased body weight and food consumption in both sexes, anemia in males, decreased absolute brain and heart weight in males, and lung inflammation in 5/5 males and 2/6 females. ChE NOAEL= none found LOAEL= 0.25 mg/kg/day based on plasma ChE inhibition
870.4200 Carcinogenicity rats	See above under "Chronic toxicity rodents"	The combined chronic toxicity/oncogenicity study described above under "Chronic toxicity rodents" showed **no evidence of carcinogenicity**
870.4300 Carcinogenicity mice	00031512, 00030513 and 00030515 (1980) 0, 2.9, 18, 71 mg/kg/day	Systemic NOAEL = 18 mg/kg/day LOAEL = 71 mg/kg/day based on body weight and food consumption decreases **No evidence of carcinogenicity** ChE NOAEL= 2.9 mg/kg/day LOAEL= 18 mg/kg/day based on decreased brain cholinesterase in both sexes
870.5100 Gene Mutation	MRID 00133510 (1983) Highest dose tested was 10,000 µg/plate. Test material was insoluble at this level. *Carbofuran produced from catechol*	*Salmonella typhimurium* reverse gene mutation assay: A weak non-dose related positive response (≈2-fold increases) in *S. typhimurium* TA 1535 at 5000 and 10,000 µg/plate -S9. Negative in strains TA 98, TA 100, TA 1537, and TA 1538 up to 10,000 µg/plate +/-S9 and in *S. typhimurium* TA1535 (up to 10,000 µg/plate +S9). Test material purity not specified.

Guideline No./ Study Type	MRID No. (year) /Doses	Results
870.5100 Gene Mutation	00133511 (1983) Highest dose tested was 10,000 µg/plate. Test material was insoluble at this level. *Carbofuran produced from catechol*	*Salmonella typhimurium* reverse gene mutation assay: negative in strains TA1535, TA1537, TA1538, TA98 and TA100 up to the highest dose tested (10,000 µg/plate +/-S9). However, a 1.9-fold increase in mutant colonies was obtained at 10,000 µg/plate -S9 in strain TA1535. Test material purity not specified.
870.5100 Gene Mutation	00133512 (1983) Highest dose tested 5000 µg/plate *Carbofuran produced from catechol*	*Salmonella typhimurium* reverse gene mutation assay: Weak positive and dose-related response (1.6-2.1 fold increase) in *S.typhimurium* TA 1535 at 2500 and 5000 µg/plate -S9. Negative in TA 98, TA 100, TA 1537, and TA 1538 up to the highest dose tested (5,000 µg/plate +/-S9) and in *S. typhimurium* TA1535 up to 5,000 µg/plate +S9. Test material purity not specified.
870.5100 Gene Mutation	00133513 (1983) Highest dose tested was 10,000 µg/plate. Test material was insoluble at this level. *Carbofuran produced from catechol*	*Salmonella typhimurium* reverse gene mutation assay): Negative in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 up to the highest dose tested (10,000 µg/plate +/-S9. 1.7-fold increases in mutant colonies were obtained at 2500-10,000 µg/plate -S9 in strain TA1535. Test material purity not specified.
870.5100 Gene Mutation	00133514 (1983) Highest dose tested was 10,000 µg/plate. Test material was insoluble at this level. *Carbofuran produced from catechol*	*Salmonella typhimurium* reverse gene mutation assay: Weak positive response (1.97-fold increase) in *S. typhimurium* TA 1535 at 5000 and 10,000 µg/mL -S9. Negative in TA 98, TA 100, TA 1537, TA 1538 up to the highest dose tested. Test material purity not specified.
870.5100 Gene Mutation	00133515 (1983) Highest dose tested was 10,000 µg/plate. Test material was insoluble at this level. *Carbofuran produced from catechol*	*Salmonella typhimurium* reverse gene mutation assay: Negative in *S. typhimurium* strains TA1537, TA1538, TA98 and TA100 However, 1.9 and 1.7-fold increases in mutant colonies were obtained at 5000 and 10,000 µg/plate -S9, respectively, in strain TA1535. Test material purity not specified.
870.5100 Gene Mutation	00133516 (1983) Highest dose tested was 10,000 µg/plate. Test material was insoluble at this level. *Carbofuran produced from catechol*	*Salmonella typhimurium* reverse gene mutation assay: Negative in strains TA1535, TA1537, TA1538, TA98 and TA100 up to the highest dose tested. 97.5% purity.

Guideline No./ Study Type	MRID No. (year) /Doses	Results
870.5300 Gene Mutation	00133518 (1983) *Carbofuran produced from catechol*	Mouse lymphoma L5178Y $TK^{+/-}$ forward gene mutation assay: Positive in both the presence and absence of S9 activation. In the absence of S9 activation, dose-related increases in the mutation frequency (MF) were calculated over a dose range (67-211 µg/mL) that caused a 64-95% reduction in total cell growth, respectively. In the presence of S9-activation, increased MFs were observed only at severely cytotoxic doses (1780 and 2373 µg/mL). Lower levels (<67 µg/mL -S9; ≤1335 µg/mL +S9) were negative. Test material was 98% pure.
870.5275 Gene Mutation	00133520 (1983) High dose 10 ppm *Carbofuran produced from catechol*	*Drosophila melanogaster* sex-linked recessive lethal mutation assay: Negative in the germinal cells of male flies fed 10 ppm (assumed to be equivalent to ≈10 µg/mL) Overt toxicity (reduced survival) was observed at this level; no effects on fertility were reported. (purity unspecified)
870.5100 Gene Mutation	00134506 (1983) Test material was insoluble at highest dose tested of 10,000 µg/plate. *Carbofuran from ortho-nitrophenol*	*Salmonella typhimurium* reverse gene mutation assay: Negative in strains TA1535, TA1537, TA1538, TA98 and TA100 +/-S9. However, ≈1.7- fold increases in mutant colonies were obtained at 2500, 5000 and 10,000 µg/plate -S9 in strain TA1535. Purity not specified.
870.5100 Gene Mutation	00133517 (1983) Test material was insoluble at highest dose tested of 10,000 µg/plate. *Carbofuran from ortho-nitrophenol*	*Salmonella typhimurium* reverse gene mutation assay: Negative in strains TA1535, TA1537, TA1538, TA98 and TA100 up to the highest dose tested (10,000 µg/plate +/-S9). Purity not specified.
870.5300 Gene Mutation	00133519 (1983) Highest dose tested of 1780 µg/mL was severely cytotoxic *Carbofuran from ortho-nitrophenol*	Mouse lymphoma L5178Y $TK^{+/-}$ forward gene mutation assay: Positive in both the presence and absence of S9 activation. In the absence of S9 activation, dose-related increases in the MF were calculated at moderately cytotoxic (≤34% total survival) doses (75 and 100 µg/mL) and severely cytotoxic (≤9% total survival) concentrations (133-316 µg/mL). Dose-related increased MFs were also noted in the presence of S9-activation at moderately cytotoxic (1001 and 1335 µg/mL) and severely cytotoxic (1780 µg/mL) doses. Lower levels (≤56 µg/mL -S9; ≤751 µg/mL +S9) were negative. Test material of unspecified purity.

Guideline No./ Study Type	MRID No. (year) /Doses	Results
870.5275 Gene Mutation	00133521 (1983) Doses of 5 or 10 µg/mL *Carbofuran from ortho-nitrophenol*	*Drosophila melanogaster* sex-linked recessive lethal mutation assay: The test was negative in the germinal cells of male flies. Overt toxicity (reduced survival) and target cell interaction (reduced fertility) were observed at both assayed concentrations. 97.6% purity.
870.375 Cytogenetics	00133006 (1983) Highest dose tested 100 µg/mL -S9; 2500 µg/mL +S9 *Carbofuran produced from catechol*	*In vitro* Chinese hamster ovary (CHO) cell chromosome aberration assay): The test was negative up to the highest doses tested; higher nonactivated doses were cytotoxic.
870.5385 Cytogenetics	00133522 (1983) 0.6, 2.0 or 6.0 mg/kg/day *Carbofuran produced from catechol*	*In vivo* bone marrow cytogenetic assay: Negative in male Sprague Dawley rats receiving oral gavage administrations for 5 days. Death and other signs of severe toxicity, such as ataxia and convulsions, were seen at the high dose. The negative findings from this *in vivo* cytogenetic assay can be applied to females. 98% pure test material
870.5375 Cytogenetics	00133010 (1983) Highest dose tested 100 µg/mL -S9; 312.5 µg/mL +S9 *Carbofuran produced from catechol*	*In vitro* sister chromatid exchange in CHO cells assay: Negative up to the highest doses tested ; higher levels were cytotoxic. 98% pure test material
870.5375 Cytogenetics	00133007 (1983) Highest doses tested 1000 µg/mL -S9; 2500 µg/mL +S9 *Carbofuran from ortho-nitrophenol*	*In vitro* CHO cell chromosome aberration assay: Negative up to the highest non-cytotoxic doses tested. Purity unspecified.
870.5375 Cytogenetics	00133011 (1983) Highest doses tested 1000 µg/mL -S9; 2500 µg/mL +S9 *Carbofuran from ortho-nitrophenol*	*In vitro* CHO cell chromosome aberration assay: Negative up to the highest non-cytotoxic doses tested. Purity unspecified.
870.5550 Other Effects	00133008 (1983) Highest dose tested of 1000 µg/mL +/-S9 was insoluble *Carbofuran from ortho-nitrophenol*	UDS in WI-38 human fibroblasts: Negative with technical up to a high insoluble concentration (1000 µg/mL +/-S9). Purity unspecified.

Guideline No./ Study Type	MRID No. (year) /Doses	Results
870.5550 Other Effects	00133009 (1983) Highest dose tested 100 µg/mL *Carbofuran produced from catechol*	Unscheduled DNA synthesis (UDS) in primary rat hepatocytes: Negative up to the highest dose tested (100 µg/mL); higher concentrations were excessively cytotoxic. 98% pure test material
870.6200a Acute neurotoxicity screening battery	Not Available	---
870.6200b Subchronic neurotoxicity screening battery	43163401 (1994) 0, 50, 500, and 1000 ppm 2.4 - 4.7, 27.3 - 46.1, and 55.3 - 92.2 mg/kg/day males, 3.1 -4.8, 35.3 - 50.7 and 64.4 - 100.0 mg/kg/day females.	NOAEL = none found LOAEL = < 2.4 mg/kg/day. Increase in landing foot splay seen at lowest dose tested. ChE activity not measured
870.6300 Special non-guideline comparative ChE inhibition study in the rat	46688912; 46688913; 46688914 ≥0.3 mg/kg	Tremors seen in pups at all doses. LOAEL = 0.3 mg/kg. RBC ChE inhibition - no dose response Brain ChE inhibition - observed at all doses in pups and adults
870.6300 Developmental neurotoxicity	43378101 (1994) 0, 20, 75, or 300 ppm (1.70-1.73, 4.95-6.91, or 8.57-31.38 mg/kg/day)	**Maternal** NOAEL = 1.7 mg/kg/day LOAEL = 6 mg/kg/day based on decreased body weight and food consumption **Offspring** NOAEL = 1.7 mg/kg/day LOAEL = 6 mg/kg/day based on increased pup mortality, delayed preputial separation and vaginal opening and decreased pup body weight. ChE activity not measured
870.7485 Metabolism and pharmacokinetics	00047987 (1968)	Using ring-^{14}C labeled carbofuran, 92% of the radioactivity was found in urine (the majority of the residue was recovered in 32 hours).The major step in the oxidative metabolism of carbofuran was the formation of 2,3-dihydro-2,2-dimethyl-3-hydroxybenzofuranyl-7-methylcarbamate.
870.7600 Dermal penetration	Shah *et al.* (1987)	The dermal absorption seen at 24 hours following exposure of F344 rats to carbofuran was approximately 6%.

[1] 25 acceptable mutagenicity studies (14 with carbofuran produced from catechol [the starting material for the currently used manufacturing process], seven with carbofuran produced from ortho-nitrophenol as the starting material, and four with carbofuran impurities) were available for review. Column two of this table notes the starting

material for each of the mutagenicity studies shown in this table. The mutagenicity studies performed with carbofuran impurities are not shown in this table but can be found in HED Doc. nos. 004534 and 004978.

3.2 FQPA Considerations

ChE inhibition and related clinical symptomology have been observed in persons exposed from application and use of carbofuran. RBC and brain ChE inhibition has been observed in adult and pup rats.

There was no evidence of either quantitative or qualitative increased susceptibility of fetus/pups in the rat or rabbit developmental toxicity studies. There was evidence of qualitative increased susceptibility in the rat multi-generation reproduction study and the rat developmental neurotoxicity study.

As described in detail in Section 3.3 below, given that 1) pups are more sensitive than adult rats (brain ChE inhibition), 2) RBC ChE inhibition may be a more sensitive point of departure compared to brain ChE inhibition (and may be considered an appropriate surrogate for the peripheral nervous system), and 3) the lack of reliable RBC data in pups, there is residual uncertainty in the available toxicology database, Agency has applied an FQPA factor (for database uncertainties) in the derivation of the carbofuran acute RfD. The magnitude of this factor is 5X based on the observed 5-fold difference between brain ChE inhibition and RBC ChE inhibition in adult rats, i.e, it is assumed that pups will also be 5 times more sensitive to RBC ChE inhibition than that of brain. The registrant should submit additional data comparative cholinesterase data which measures RBC and brain ChE inhibition in pups and adults. This comparative ChE study should also include a range-finding study and well-conducted time course study such that the definitive study is performed at the time of peak effect for ChE inhibition. After submission of this study, the Agency will refine its BMD analysis and will reconsider the FQPA database uncertainty factor.

3.3 Dose Response Assessment

Acute RfD

There are several studies available where acute ChE inhibition was measured at or near peak time of inhibition (15-45 min) and which inform the derivation of the acute RfD and acute PAD. These include two studies performed by the registrant: 1) time course study (MRID no. 45675701) where male and female rats were dosed at 0.5 and 1.0 mg/kg and 2) recently submitted comparative ChE study where adult and juvenile (post-natal day 11, PND) rats were dosed at 0.3, 0.6, and 1.0 mg/kg (FMC 2005; MRID no. 46688914). Clinical signs were also reported for adults and PND11 pups in the comparative ChE study. In another study, done in support of the Agency's cumulative risk assessment for the N-methyl carbamates, scientists from the National Health and Environmental Effects Research Laboratory (NHEERL) performed time course and dose-response studies in male rat where brain and RBC ChE inhibition along with motor activity

were measured. For carbofuran, the Agency's study included doses ranging from 0.1 mg/kg up to 1.5 mg/kg (USEPA, 2005).

In order to evaluate the appropriate point of departure (PoD) for ChE inhibition, the Agency considered benchmark dose (BMD) estimates developed from the comparative ChE study in adult and PND11 rats (TXR no. 0054034) along with BMD estimates provided in the preliminary cumulative risk assessment for carbofuran (USEPA, 2005). Dose-response modeling is preferred over the use of NOAEL/LOAELs (i.e., no or low observed adverse effect levels) since NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, but instead reflect dose selection (USEPA, 2000). The estimated dose at which 10% ChE is observed (BMD10) and the lower 95% confidence intervals (BMDL10) were estimated by fitting the ChE data to an exponential dose-response model using generalized nonlinear least squares. The BMD10 was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity across the blood and brain compartments and is a response level close to the background ChE. Moreover, the Agency believes that 10% is likely to be protective to other toxicities, such as clinical signs and/or behavioral endpoints.

The exponential model was used in the Preliminary OP Cumulative Risk Assessment (USEPA, 2001) to determine relative potency factors and points of departure. The exponential model and statistical methods used to calculate the BMD10s and BMDL10s have been supported by the FIFRA Science Advisory Panel (FIFRA, 2002) for analysis of ChE inhibition data similar to that of OPs and N-methyl carbamates, including carbofuran. Technical description of the statistical methods can be found in the cumulative hazard assessment of the Preliminary OP Cumulative Risk Assessment (USEPA, 2001). The decreasing exponential model has also been used in the Preliminary N-Methyl Carbamate Cumulative Risk Assessment (USEPA, 2005). Model fits and model parameters specific to this analysis can be found in TXR no. 0054034 (Lowit, 2006). The exponential model used here can be downloaded by the public at www.epa.gov/pesticides/cumulative/EPA_approach_methods.htm. The Agency's preliminary cumulative risk assessment for the N-methyl carbamates can be found at http://www.epa.gov/oscpmont/sap/2005/index.htm#august.

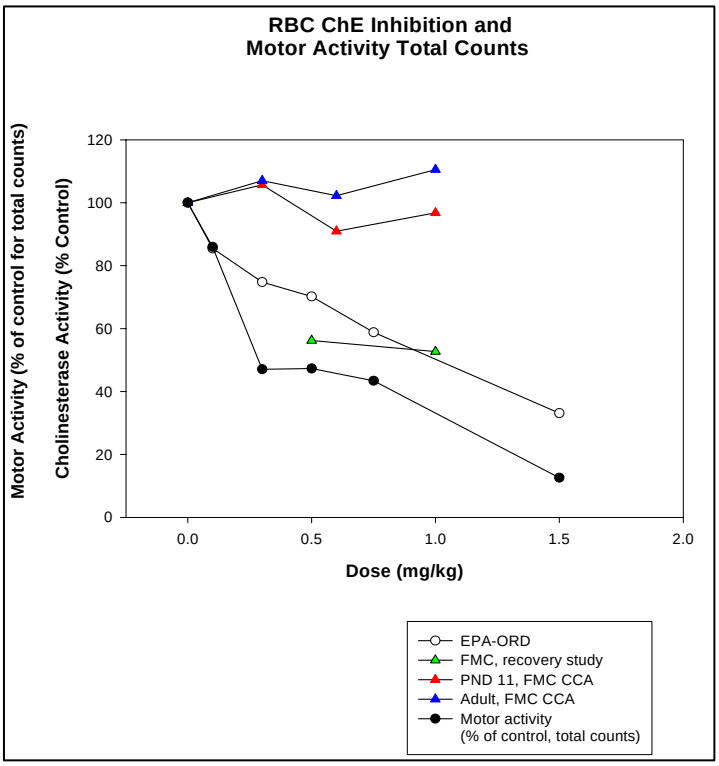
As shown in Table 5 below and Figure 1 below, brain ChE inhibition has shown to be a sensitive endpoint for carbofuran in each of studies considered. Regarding RBC ChE inhibition, the Agency's dose-response data and the registrant's time course study show that RBC ChE inhibition is also a sensitive endpoint. In the comparative ChE study (FMC 2005), however, no inhibition of RBC ChE was observed at any tested dose, including those resulting in blood ChE inhibition in the registrant's time course study and those that resulted in more than 50% brain ChE inhibition (See Figure 1 below). The lack of dose-response relationship for RBC ChE data is also inconsistent with other studies in the dog and rat which show blood ChE measures to be sensitive (See Table 4). The lack of RBC ChE inhibition is further questioned by the motor activity data and incidence of clinical signs, particular tremors.

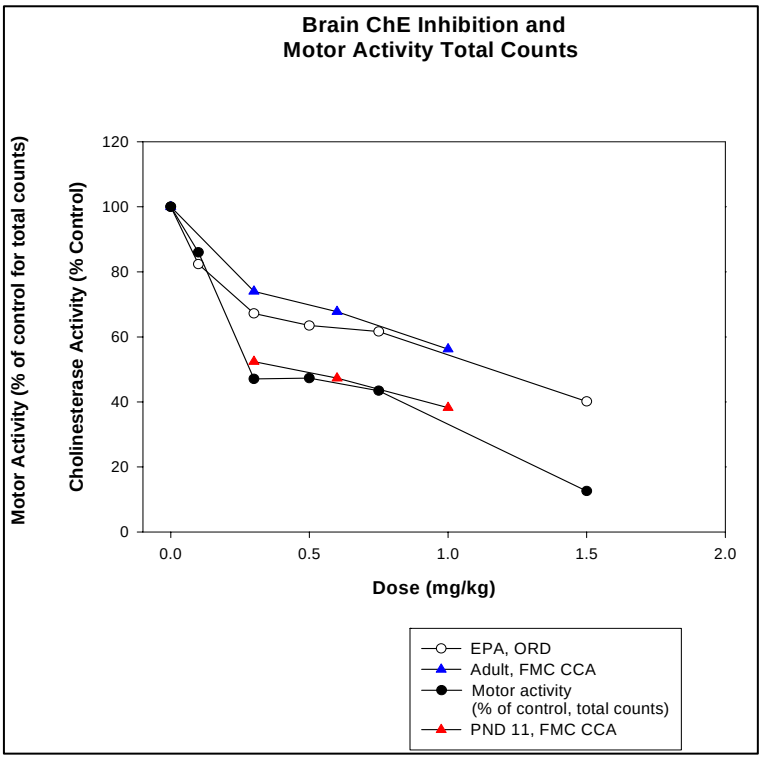
Figure 1 shows an overlay of motor activity (total counts) with brain and RBC ChE inhibition data. At the low end of the dose-response curve, although not statitistically signicant (see USEPA, 2005), there is a clear dose related decrease in total motor activity counts at 0.1 mg/kg. Motor activity is further decreased (statistically significant) at 0.3 mg/kg and higher. These decreases in motor activity coincide with decreases in both RBC and brain ChE inhibition, particularly at the low end of the dose-response curve. Regarding clinical signs, in PND11 pups, every pup at each dose level exhibited tremors. In adult rats, tremors were also noted at the 0.6 and 1.0 mg/kg dose levels. It is unknown whether changes in motor activity and/or tremors are related to ChE inhibition in the central (ie, brain) or peripheral systems; the Agency can not discount the potential that peripheral ChE inhibition may be inhibited by carbofuran. Given that numerous studies have shown RBC ChE inhibition to a sensitive measure and that dose-related changes in behavioral endpoints and clinical signs have been observed at low doses of carbofuran, at this time, *the Agency does not consider the RBC ChE inhibition data from the comparative ChE study to be sufficiently reliable for developing a point of departure for risk assessment purposes.*

Table 5. Benchmark estimates for carbofuran from the comparative ChE study and the Preliminary Cumulative Risk Assessment for the N-methyl carbamate pesticides.

Source		**Brain**		**RBC**	
		Male	Female	Male	Female
PND11 (CCA)	BMD10	0.04	0.05	(data provide no dose-response relationship)	
	BMDL10	**0.03**	0.04		
Adult rat (CCA)	BMD10	0.11	0.12		
	BMDL10	0.05	0.06		
Adult rat (Preliminary Cumulative RA; EPA 2005)	BMD10	**0.15**	**N/A**	**0.03**	**N/A**
	BMDL10	0.13		0.01	

Figure 1. Plot of RBC and Brain ChE inhibition and motor activity data





The Agency's BMD analysis for the preliminary cumulative risk assessment was presented to the FIFRA SAP in February and August, 2005. At those meetings, the panel supported the Agency's approach for developing BMD estimates for the N-methyl carbamates. In this analysis, the Agency used data from both the registrant's time course study and from the Agency's dose-response study. The Agency believes that use of data from multiple studies provides a more robust analysis than a single study. The results of the combined analysis, provided in Table 5, indicate that, in adult rats, RBC ChE inhibition is 5X more sensitive compared to that of brain ChE inhibition (ie, 0.03 mg/kg compared to 0.15 mg/kg). Preliminary comparison of the upper and lower confidence limits on the BMD_{10}s for RBC and brain ChE inhibition provided in the cumulative risk assessment, suggests that the difference in sensitivity between RBC ChE and brain ChE inhibition could be as low as approximately 1-2 fold and up to approximately 15 fold. The Agency typically uses the central estimate (ie, the BMD_{10}) as the measure for comparing potencies and/or comparing relative sensitivity. As such, based on the data available to the Agency in 2005 for inclusion in the preliminary cumulative risk assessment, RBC ChE inhibition appears to be 5X more sensitive than brain ChE inhibition.

As noted above, the comparative ChE study did not provide reliable dose-response information for RBC ChE inhibition. The brain ChE inhibition data provided in the comparative ChE study are consistent with the data from EPA's dose-response study (Figure 1). Prior to the release of the revised cumulative risk assessment (expected in summer 2006), EPA will be revising its BMD estimates to include the adult brain ChE inhibition data from the comparative ChE inhibition study. Given the remarkable consistency between the new and existing data, the Agency does not expect the BMD and BMDL calculated for brain ChE inhibition to change significantly.

The Agency's analysis of the brain ChE inhibition data from the comparative ChE study suggests that PND11 pups are 2.5X more sensitive than adults (Table 5; 0.11 mg/kg and 0.12 mg/kg for male and female adult rats, respectively compared to 0.04 mg/kg and 0.05 mg/kg for male and female PND11 rats, respectively). Given that *1)* pups are more sensitive than adult rats (brain ChE inhibition); *2)* RBC ChE inhibition may be a more sensitive point of departure compared to brain ChE inhibition (and may be considered an appropriate surrogate for the peripheral nervous system); *3)* the lack of reliable RBC data in pups, there is residual uncertainty in the available toxicology database. Given this uncertainty, the Agency has applied an FQPA factor (for database uncertainties) in the derivation of the carbofuran acute RfD. The magnitude of this factor is 5X based on the observed 5-fold difference between brain ChE inhibition and RBC ChE inhibition in adult rats, i.e, it is assumed that pups will also be 5 times more sensitive to RBC ChE inhibition than that of brain.

The Agency considered two different approaches to deriving the acute RfD/PAD for carbofuran (See Table 6 below).

Table 6. Comparison of hazard identification approaches in deriving acute RfD/PAD

Step in Hazard Identification Process	**Approach #1**	**Approach #2**
Point of Departure	BMDL of 0.03 mg/kg based on brain ChE inhibiton from PND11 pups	BMDL of 0.01 mg/kg based on RBC in adult rats
Inter- and Intra-species extrapolation	Default 10X-10X	Default 10X-10X
FQPA	5X based on ratio of BMD from brain/RBC (ie, 0.15/0.03 = 5)	2.5x for lack of quality RBC data in comparative ChE study based on ratio of BMD from pup/Adult for brain (ie, 0.11/0.04 and 0.12/0.05 ~2.5)
aPAD	0.00006 mg/kg	0.00004 mg/kg

As shown by these calculations, the points of departure and uncertainty factors in the two approaches result in a similar acute PAD. The Agency as selected Approach #1 (using brain ChE inhibition as the point of departure) for risk extrapolation as data are available in the more sensitive population and as brain represents the target tissue (however, surrogate RBC ChE

inhibition data would be assumed to be protective of brain effects) for carbofuran. **As a result the acute PAD for the general population and all population subgroups is 0.00006 mg/kg.**

Chronic RfD

The acute RfD is considered protective of chronic exposures. Carbofuran-induced inhibition of ChE activity is reversible (within 24 hours). The longer-term exposures could be considered as a series of acute exposures.

Short-, Intermediate-and Long-Term Dermal and Inhalation Occupational Exposure

The risk assessment team recommends the use of the BMDL10 of 0.01 mg/kg/day based on adult RBC ChE inhibition from the special EPA study (USEPA 2005) for risk assessment purposes and for these occupational exposure scenarios. A margin of exposure (MOE) of 100 is applicable. At present, there are no residential uses. Although a 21-day dermal rabbit study was available, this toxicity study is not appropriate because the endpoint of concern (i.e., cholinesterase activity) was not measured. Data in rats and humans indicate inhibition of cholinesterase activity to be the endpoint of concern.

Since an oral dose was selected for all dermal scenarios, a 6% dermal absorption factor (based on a study in rats) is recommended for route-to-route extrapolation. A 100% absorption factor for inhalation exposure is assumed for all inhalation scenarios.

Table 7: Toxicology Endpoint Selection Table[1]

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA factor and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary all populations	BMDL10 = 0.03 mg/kg/day[2] UF = 100[3] **Acute RfD** = 0.0003 mg/kg/day	FQPA [4] = 5X **aPAD** = 0.00006 mg/kg/day	Comparative ChE Study BMDL10 = 0.03 mg/kg/day, based on cholinesterase inhibition in the brain of postnatal day 11 (PND11) male pups.
Dermal (Occupational; all durations)	BMDL10 = 0.01 mg/kg/day[2] UF=100[3] Dermal absorption rate (rat dermal study) = 6%	**MOE** $\geq$ 100 does not exceed level of concern	Special ChE Study (USEPA 2005) BMDL10 = 0.01 mg/kg/day, based on RBC cholinesterase inhibition in adult rat
Inhalation (Occupational; all durations)	BMDL10 = 0.01 mg/kg/day[2] UF=100[3] Inhalation absorption rate = 100%	**MOE** $\geq$ 100 does not exceed level of concern	Special ChE Study (USEPA 2005) BMDL10 = 0.01 mg/kg/day, based on RBC cholinesterase inhibition in adult rat
Cancer	"Not likely"		Risk assessment not required

[1] UF = uncertainty factor, FQPA SF = FQPA safety factor, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose.
[2] BMD10=The lower 95% confidence interval of the estimated dose at which 10% ChE is observed,
[3] UF (uncertainty factor):),10X for interspecies extrapolation and 10X for intraspecies variability.
[4] 5X (ratio of BMD for brainChE inhibition/RBC ChE inhibition)

3.4 Endocrine Disruptor Effects

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other endocrine effect..." . EPA has been working with interested stakeholders, including other government agencies, public interest groups, and industry and research scientists, to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disruptor Screening Program was published in the Federal Register on December 28, 1998 (63 FR 71541). The program uses a tiered approach and anticipates issuing a Priority List of chemical and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of carbofuran for endocrine effects may be required.

Offspring in the rat developmental neurotoxicity study on carbofuran displayed delayed vaginal patency and preputial separation - which may be taken as possible indications of developmental delays and endocrine disruption. However, the effects were minimal and may be due to decreased body weights.

4.0 DIETARY EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Carbofuran [2,3-dihydro-2,2-dimethyl-7-benzofuranyl-N-methylcarbamate] is a broad spectrum systemic insecticide and nematicide registered for control of soil and foliar pests for food/feed uses on a variety of field, fruit, and vegetable crops. Carbofuran may also be used on ornamentals. Carbofuran belongs to the carbamate class of compounds, which are known to be inhibitors of cholinesterase activity. The granular (G) and flowable concentrate (FlC) are the carbofuran formulation classes registered for use on food/feed crops. These formulations are typically applied to the soil at planting (banded, in-furrow, or injection treatment), post-planting (banded, side-dress, or basal spray treatment) or applied foliarly using ground or aerial equipment. Carbofuran is a restricted use pesticide and is not used in residential settings. Carbofuran does not have food-handling establishment uses.

The insecticide can be applied with aerial equipment, drencher, drip irrigation systems, groundboom sprayers, and tractor-drawn granular spreaders. Application rates vary from 0.25 to 10 pounds active ingredient per acre depending upon the application scenario. The approximate

range of % active ingredient in end-use products is 5 - 45% though % active ingredient in product for formulation can be as high as 75%. Carbofuran can be applied, depending on the specific crop, pre-emergent, post-emergent, at planting, or multiple foliar.

4.2 Residues of Concern

On July 28, 1997, the Metabolism Assessment Review Committee (MARC) met to evaluate the tolerance expression for carbofuran. The MARC decided that the three phenolic carbamate metabolites, 7-phenol carbofuran, 3-keto-7-phenol carbofuran and 3-hydroxy-7-phenol carbofuran, lack the carbamate moiety responsible for cholinesterase inhibition. The tolerance expression for carbofuran will include only the combined residues of carbofuran and 3-hydroxycarbofuran. The residue of concern for risk assessment in both food and drinking water consists of carbofuran and its metabolite, 3-hydroxycarbofuran (*Carbofuran. Reregistration Case No. 0101. Outcome of the 7/28/97 meeting of the HED Metabolism Committee*; David Miller; 08/28/97).

4.3 Water Fate and Estimated Environmental Concentrations

The Environmental Fate and Effects Division (EFED) has completed a water resources analysis to determine the potential for carbofuran to contaminate surface and ground water (email communication D.Young to D.Drew, 3/8/06).

The environmental fate characteristics of carbofuran indicate that it is mobile in many types of soils and persistent in acidic and neutral environments. Base hydrolysis is the most significant route of degradation of carbofuran in water and soil, with half-lives on the order of a year for pHs less than 7 and on the order of hours to weeks for pHs greater than 7. These characteristics make carbofuran transportable to surface water and ground water in some environments and indicate the potential for carbofuran contamination of ground water and surface water in areas where it has a tendency to persist (e.g., neutral to low pH waters). There are several major degradates of carbofuran, but HED has determined that only the degradate 3-hydroxycarbofuran should be regulated along with carbofuran. However, available environmental fate studies do not show formation of 3-hydroxycarbofuran through most environmental processes–for example, via hydrolysis, soil metabolism, field dissipation; the only study where it was detected resulted from soil photolysis, but in low amounts. Therefore, 3-hydroxycarbofuran was not explicitly considered as a separate entity in the EFED exposure assessment; however, in the exposure modeling, it was implicitly incorporated into the parent carbofuran estimated exposure concentrations (via non-inclusion of a carbofuran soil photolysis degradation mechanism). While estimation of potential exposure to 3-hydroxycarbofuran remains an uncertainty in this assessment it is not expected to significantly add to exposure estimates (maximum concentrations in monitoring were around 6% of parent concentrations).

Available studies indicate conventional water treatment does not significantly remove carbofuran concentrations. Softening, granular activated charcoal, reverse osmosis, and oxidation are effective to varying degrees in removing carbofuran. Softening, in one case removed 100% of carbofuran.

Surface Water: Nine different crop/location scenarios, which represented 80% of total carbofuran use from 1987 to 1997, were used in the modeling studies. For each crop/location scenario, two application rates were investigated: one application rate represented the lowest label rate that would be used (as determined by the US EPA, Office of Pesticide Program, Biological Economic Analysis Division), and one rate represented a high labeled rate allowed on either the federal or a state label. The use of the high and low rates allows bracketing of carbofuran aquatic concentrations. Bracketing was also achieved by using a range of PCAs (percent of area cropped)– using default regional PCAs and crop-specific PCAs , when available. The rates used in the modeling are given in Table 8.

Table 8. PRZM/EXAMS Crop Scenarios

Location/Crop	Percent of Area Cropped[1] (PCA)	Low Application Rate on label and Method	High Application and Method
PA Alfalfa	46 (R)	1 foliar application at 0.125 lb a.i./A	1 foliar application at 1 lb a.i./A
CA Alfalfa	56 (R)	1 foliar application at 0.125 lb a.i./A	1 foliar application at1 lb a.i./A
CA Grape	56(R)	2 lb a.i./A by drip irrigation	1 broadcast at 10 lb a.i./A
IL Corn	46 (C)	1 foliar application at 1 lb a.i./A	2 applications at 1 lb a.i./A
ME Potato	14 (R)	1 foliar at 0.125 lb a.i./A	2 foliar at b 1 a.i./A
ID potato	63(R)	no lower range given	3 lbs a.i./A at planting, soil applied, incorporated with irrigation water
MS Cotton	20 (C)	1 foliar at 0.25 lb a.i./A	1 application in furrow at 1 lb a.i./A
TX Sorghum	67 (R)	1 foliar application at 0.25 lb a.i./A	1 in-furrow application at 1 lb a.i./A plus 2 foliar applications at 0.5 lb a.i./A
NC tobacco (flue cured)	38 (R)	1 application at 4 lb a.i./A incorporated to 3"	1 application at 6 lb a.i./A incorporated to 3"

[1]Percent Cropped Area = the percent of watershed that contains pesticide-treated crops. The (C) signifies that the value is crop specific; the (R) signifies that the value is region specific, which is used when crop-specific PCAs are not available. PCAs are used for drinking water analyses only.

Results of the modeling runs are summarized in Table 9. These values represent the range of concentrations that are expected to result from the annual use of carbofuran over a 30-year period at lowest and maximum application rates. Acute values in the table represent the 90th percentile of the cumulative distribution of the highest annual concentrations simulated over 30 years.

In summary, using the PRZM/EXAMS model, the acute EDWCs (estimated drinking water concentrations) in surface water vary over several orders of magnitude across use areas (0.11 to 75 ppb) and take into account variability in application rates and in percent cropped

areas in the watershed (Table 9). The highest acute EDWCs occurred when the highest application rates (maximum label rates) were used for Texas sorghum followed by Illinois corn and Mississippi cotton. The lowest acute EDWCs occurred using the lower application rates for California and Pennsylvania alfalfa and Maine potato.

Table 9. Surface Water Drinking Water Estimated Concentrations from PRZM/EXAMS (ranges of acute concentrations take into account a distribution of default PCAs)

Location/Crop	Using Low Rate on label	Using High Rate
	acute concentration[1] (ppb)	acute concentration[1] (ppb)
ME Potato	0.5 (0.25 - 3.1)	3.2 (1.6 - 20)
CA Grape	0.4	4.3
PA Alfalfa	0.85 (0.13 - 1.5)	6.9 (1.1 - 12)
CA Alfalfa	0.85 (0.11 - 1.2)	6.9 (0.86 - 10)
ID potato	--	10
NC Tobacco	8 (8-17)	12 (12-26)
MS Cotton	4.2 (14-18)	17 (57-72)
IL Corn	19 (19-36)	26 (26-49)
TX Sorghum	6.0 (2.4-7.8)	58 (23-75)

1. One-in-ten-year annual peak concentration

Groundwater: Following detection of carbofuran in ground water in Long Island, NY, FMC voluntarily conducted a prospective groundwater (PGW) monitoring study during 1981-1983 near Salisbury, Maryland to assess impacts from the labeled use of carbofuran. A corn plot had one application of Furadan 10G (totaling 3.0 lbs a.i./A; the labeled rate has since been reduced to 1 lbs a.i./A on corn for these soils for local pests), and a potato plot had eight foliar applications of Furadan 4F at one week intervals (totaling 1.0 lbs a.i./A) (Burt, 1982,1983; USEPA, 1985). Only the corn plot was used to derive estimates of groundwater concentrations

Because this prospective ground water study was conducted over only one growing season, the reported ground water concentrations do not represent impacts from long-term use

of carbofuran (applied in multiple years). For this reason, direct use of the PGW data may not be appropriately conservative. Thus, EFED used superpositioning techniques to provide estimates of concentrations following long-term use of carbofuran. These techniques apply if chemical transformation processes and all transport and interaction mechanisms are assumed to be linear with respect to concentration. Based on these assumptions, EFED provided the following estimates of carbofuran concentrations in groundwater for various application rates (Table 10). EDWCs for ground water, based on PGW monitoring data, range from 1.4 ppb (low application to alfalfa) to 110 ppb (high application to grapes).

Table 10. Ground water concentrations for a range of application rates, based on PGW study.

Application Rate (lb a.i./A)	0.125	0.25 lb	1 lb	2 lb	4 lb	10 lb
Example Applicable Crop	low application to alfalfa	low application to cotton	low application to Corn	high application to corn	low application to tobacco	high application to grapes
GW EECs/EDWCs (ppb)	1.4	2.8	11	22	44	110

PDP monitoring data

Detectable residues of carbofuran (no 3-hydroxycarbofuran found) were found in 14 out of 1418 PDP water samples (data from 2001-2003). Carbofuran residues ranged from 0.001 ppb to 0.079 ppb. The concentrations seen in the PDP data are considerably lower than the EDWCs for surface and ground water. However, these data were not deemed appropriate for use in risk assessment as the data may not be reflective of drinking water concentrations in areas with significant carbofuran use. Also, The community water systems sampled by PDP are generally deep ground water or surface water systems. The PDP does not sample individual, private wells. Since the highest carbofuran concentrations are likely to occur in shallow, private wells in areas where carbofuran is used, use of the PDP data would not be protective of people whose drinking water comes from such wells.

4.4 Dietary Exposure and Risk Assessment

Magnitude of the Residue on Food/Feed

The reregistration requirements for magnitude of the residue in/on the following RACs have been fulfilled: alfalfa forage and hay; barley grain and straw; bananas; canola seed; coffee beans (green); field corn grain, forage, and stover; sweet corn (kernal plus cob with husk removed), forage, and stover; cottonseed; cotton gin byproducts; cranberries; cucumbers;

grapes; melons (including watermelon); oat grain and straw; peppers; potatoes; pumpkins; grain sorghum, forage, and stover; soybean seed, forage, and hay; sugar beets and sugar beet tops; spinach (grown for seed), squash; strawberry; sugarcane; sunflower seed; wheat grain and straw; and tobacco. Overall, adequate field trial data depicting carbofuran residues of concern following treatments according to the maximum registered use patterns have been submitted for the RACs listed above. Label revisions or modifications are required for some of the above-listed crops in order to reflect current Agency policies and/or to reflect the parameters of use patterns for which field trial data are available. Field trial data remain outstanding for barley hay; oat forage and hay; wheat forage and hay; and for the aspirated grain fractions of soybeans. Refer to the "Directions for Use" section for required label modifications and to the "Tolerance Reassessment Summary" in the Revised HED Product and Residue Chemistry Chapter of the RED (D. Drew, 1/13/05, D306796). Also see the attached table " Tolerance Reassessment Summary for Carbofuran", Appendix 1.

Based on the available dairy cattle feeding studies, HED concludes that tolerances for the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep are not required as there is "no reasonable expectation of finite residues" [Category 3 of 40 CFR §180.6(a)]. A tolerance for milk is required.

Recent USDA Pesticide Data Program (PDP) monitoring data are available for residues of carbofuran and 3-hydroxycarbofuran in a variety of foods and were used for deriving anticipated residues for banana, barley, corn, cucumber, grapes, melons, milk, oats, peppers, potatoes, pumpkin, rice, sorghum, soybean, spinach, squash, strawberry and wheat in the previous 3/09/06 risk assessment. HED has since concluded that use of PDP data for certain foods (barley, corn/sorghum, oats, rice, soybeans and wheat) have likely overestimated carbofuran exposures from consumption of these foods. Therefore, in the current assessment, HED is basing exposure estimates for these commodities on field trial data, as explained in more detail below. Certain other foods (corn syrup, sorghum syrup and spinach) for which PDP data were previously used have been removed from the revised risk assessment, based on a determination that residues will not occur in these foods.

The Carbamate Market Basket Survey Task Force (CMBSTF) conducted a year long national survey of carbamate residues on selected food commodities, including carbofuran on bananas and grapes, purchased at grocery stores. These data were not used in the previous dietary analysis because HED did not expect exposure estimates for bananas and grapes based on these to differ significantly from exposure estimates based on PDP monitoring data. HED's assumption was incorrect, since the combined Limits of Quantitation (LOQs) for carbofuran and its metabolite in the Market Basket Survey (0.001 ppm) were 10- to 20-fold lower than the combined LODs in the PDP monitoring data (0.02 ppm for bananas and 0.0125 ppm for grapes). The Market Basket Survey data for bananas and grapes were used in this revised assessment to provide more refined exposure estimates for these commodities.

4.4.1 Acute Dietary Risk Assessments

An acute probabilistic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID, Version 2.00-2.02), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. HED has determined that the acute assessment would be protective of any chronic exposures from dietary exposure to carbofuran; therefore, a separate chronic dietary exposure assessment was not conducted. [See memorandum dated 3/7/06, D327358, S. Stanton and revised dietary assessment dated 7/20/06, D330841, S. Stanton for full details of the dietary assessment.]

A revised, refined (Tier 3), acute probabilistic dietary exposure assessment was conducted for all supported carbofuran food uses. Combined anticipated residues of carbofuran and 3-hydroxycarbofuran on food were included in the assessment.

Residues Used in the Revised Assessment:

Acute anticipated residues for many foods (artichoke, cucumber, melons, milk, peppers, potatoes, pumpkin, squash, strawberry and sweet corn) were derived using USDA Pesticide Data Program (PDP) monitoring data from recent years (through 2003 for all commodities

except milk, for which recently available 2004 data were used). Anticipated residues for bananas and grapes were derived using monitoring data from the 2000 Carbamate Market Basket Survey. Most of the samples analyzed by the PDP and the Carbamate Market Basket Survey Task Force contained no detectable residues of carbofuran or its 3-hydroxy metabolite. A value equal to ½ the combined limits of detection (LODs) of carbofuran and 3-hydroxycarbofuran was assumed for samples with non-detectable residues (zero values were used to incorporate percent of crop not treated). For commodities with no monitoring data available (cranberries, coffee, sugar beets, sugarcane and sunflowers) and for field crops that are typically blended during marketing (barley, field corn, oats, rice, soybean, and wheat), anticipated residues were based on field trial data (or, for coffee, on processing study data).

PDP data were previously used to develop anticipated residues for barley, field corn, oats, rice, soybeans and wheat. Although PDP data are generally assumed to provide more refined estimates of exposure than field trial data, they may sometimes overestimate exposure, particularly for blended commodities, such as those listed above, with low percent crop treated estimates, no detections in the PDP data and relatively high ½ LOD values. PDP data are assumed to reflect residues after blending of treated and untreated portions of the crop has already occurred; therefore, the average of all PDP residues is calculated and used directly in the assessment as a point estimate without further adjustment for %CT. Since non-detectable PDP residues are assigned a value equal to ½ LOD, a residue estimate equal to at least ½ the combined LOD is assumed even in cases where there are no detectable residues in the PDP data. HED has concluded that this approach has likely overestimated exposures for these crops in the previous assessment; therefore, field trial data were used to provide more refined exposure estimates for these commodities in the current assessment. No detectable residues of carbofuran or 3-OH carbofuran were found in or on the grain of barley, field corn, popcorn, oats, rice or wheat in the submitted field trials for these crops. In the revised assessment, HED calculated an anticipated residue for these commodities based on ½ LOD adjusted for the estimated maximum %CT. The raw field trial data for soybeans were not readily available. However, a summary of the data (L. Propst, 4/4/83) indicated that carbamate residues in the field trials ranged from non-detectable (0.01 ppm) to 0.06 ppm. HED calculated a high-end anticipated residue for soybeans based on the highest detected residue (0.06 ppm), adjusted for %CT.

In the previous assessment, anticipated residues for artichokes were based on field trial data, an approach that HED believes significantly overestimated exposures for this crop. To provide a more realistic exposure estimate, HED is translating PDP monitoring data for peppers to artichokes in the current assessment. Peppers were selected as a surrogate for artichokes for several reasons: (1) The highest number of PDP detections were found in peppers; (2) ½ the combined LOD for peppers is low (0.0016 ppm); therefore, the use of ½ LOD for non-detectable residues is less likely to overestimate actual dietary exposure; (3) the pre-harvest intervals (PHIs) for peppers and artichokes are similar (21-22 days); and (4) the maximum application rate for peppers is significantly higher than the rate for artichokes, providing a degree of confidence that the monitoring data for peppers are protective of exposures from

artichokes.

PDP data showing no detectable residues were used to estimate exposure from spinach in the previous assessment. HED has determined, however, that the use of carbofuran on spinach grown for seed (the only labeled use on spinach) will not result in residues of carbofuran or its metabolites on spinach produced from the treated seed crop. Therefore, this use is classified as a non-food use. Since residues of carbofuran are not expected on spinach, spinach has been removed from the assessment (Note: The contribution from spinach was negligible in the previous assessment, so this change does not significantly alter estimated dietary risk).

In the previous assessment, HED based exposure estimates for coffee on field trial data adjusted by a processing factor of 0.1x. No detectable residues of carbofuran or 3-hydroxycarbofuran were found in processed coffee (roasted or instant) in the submitted coffee processing study. Therefore, in this revised assessment, HED used the data for processed coffee directly (rather than using the field trial data modified by a processing factor). A point estimate was derived based on ½ the combined LOD (0.01 ppm) from the processing study, adjusted to account for percent crop treated.

Anticipated residues for corn syrup and sorghum syrup were included in the previous assessment but have been excluded from the revised assessment, based on HED's determination that finite residues will not occur in these commodities after processing. This conclusion is based on extensive PDP data for corn syrup showing no detectable residues.

BEAD provided average and maximum percent crop treated (%CT) estimates for most crops. The maximum %CT estimates were used to refine the acute dietary exposure estimates. Maximum %CT estimates were low for most crops but ranged up to 30% (artichokes). %CT estimates for several imported commodities (bananas, coffee, rice and sugarcane) have been revised since the 3/7/06 assessment based on additional information from BEAD and the registrant, FMC Corporation, regarding the percent of the crop that is imported and the percent of imports treated with carbofuran. For rice, the estimated maximum %CT in the current assessment (0.5%) is significantly lower than in the previous assessment (11%). For bananas (current 78.5% vs. previous 4%), coffee (current 58% vs. previous 1%) and sugarcane (current 7.3% vs. previous 5%), the estimated maximum %CT in the current assessment is higher.

Processing data are available for certain crops, including sugar beets (1x), grape juice(1x) and sugarcane (0.2x). Processing factors derived from these data were incorporated in the acute analyses. The data for grape juice were translated to cranberry juice. In addition, a cooking factor of 0.75X from a literature study was applied to all boiled/cooked/baked/fried vegetables (not fruit) such as artichokes, squash, peppers, potatoes, pumpkins, cucumbers, and sweet corn. For all other commodities, DEEM ver. 7.81 default processing factors were used.

4.4.2 Acute Dietary Exposure Results and Conclusions

The estimated acute dietary (food only) exposure exceeds HED's level of concern for the U.S. population and all reported population subgroups at the 99.9th percentile of exposure. Carbofuran dietary exposure at the 99.9th percentile was estimated at 0.000154 mg/kg/day for the U.S. population **(260% of the aPAD)** and 0.000292 mg/kg/day **(490% of the aPAD)** for children 1-2 years old, the population subgroup with the highest estimated dietary exposure. Estimated dietary exposure to carbofuran also exceeds HED's level of concern for children's subgroups at the 99th percentile of exposure. Estimated exposure for all populations is below HED's level of concern at the 95th percentile. (See results Table 11 below).

Table 11. Results of Acute Dietary Exposure Analysis for Food Alone							
Population Subgroup	aPAD (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.00006	0.000021	35	0.000046	77	0.000154	260
All Infants (< 1 year old)	0.00006	0.000023	39	0.000057	96	0.000182	300
Children 1-2 years old	0.00006	0.000048	80	0.000107	180	0.000292	490
Children 3-5 years old	0.00006	0.000041	68	0.000091	150	0.000290	480
Children 6-12 years old	0.00006	0.000027	45	0.000062	100	0.000202	340
Youth 13-19 years old	0.00006	0.000017	29	0.000042	70	0.000130	220
Adults 20-49 years old	0.00006	0.000015	25	0.000035	58	0.000107	180
Adults 50+ years old	0.00006	0.000015	25	0.000035	58	0.000124	210
Females 13-49 years old	0.00006	0.000015	24	0.000034	56	0.000109	180

The foods contributing most heavily to acute exposure at the 99.9th percentile of exposure are listed below for the overall U.S. population and the children's subgroups having the highest estimated exposures (children, 1-2 yrs. old and 3-5 yrs. old).

Table 12. Major Food Contributors to Carbofuran Acute Exposure at the 99.9th Percentile (The numbers in parentheses indicate the food's approximate contribution as a percent of total exposure.)

U.S. Population	Children, 1-2 Years Old[1]	Children, 3-5 Years Old
Cucumber (23)	Cranberry (32)	Cucumber (32)
Watermelon (22)	Cucumber (19)	Cranberry (25)
Cranberry (17)	Watermelon (19)	Watermelon (24)
Squash (10)	Squash (11)[2]	Squash (6)[2]
Potato (10)	Strawberry (7)	Strawberry (5)
Strawberry (7)	Sweet Corn (3)	Sweet Corn (2)
Sweet Corn (3)	Potato (3)[2]	Cantaloupe (2)
Cantaloupe (2)		

[1]The population subgroup with the highest estimated acute exposure from food alone.
[2]While squash is not one of the highest contributors to overall dietary exposure for children, it accounts for more than 50 percent of exposure for infants less than 1 year old, with potatoes accounting for another 21 percent.

Exposure estimates for all of the major food contributors, except cranberry, were based on PDP monitoring data adjusted to account for the percent of the crop treated with carbofuran and, therefore, may be considered fairly highly refined. Carbofuran is not registered in the U.S. for use on cranberries, however, and monitoring data are not available for this commodity. The exposure estimates for cranberry were based on field trial data and conservative assumptions about the percent of imported cranberries that could be treated. Therefore, exposures from cranberries are likely overestimated in this assessment. The availability and use of monitoring data and/or additional information on carbofuran use on imported cranberries would allow HED to refine exposure estimates for cranberries.

Characterization of Dietary Assessment Inputs/Outputs

The dietary assessment includes estimates of acute exposure to carbofuran and 3-hydroxycarbofuran from food only. A characterization of the inputs/outputs and uncertainties regarding the assessment is provided below.

- The assessment for food incorporates fairly refined anticipated residue estimates for most commodities that were derived from PDP monitoring or Market Basket Survey data and %CT data. The PDP and Market Basket Survey Task Force analyzed for parent carbofuran and its metabolite of concern, 3-hydroxycarbofuran. Therefore, the PDP and Market Basket data do not likely underestimate exposure to the carbofuran residues of toxicological concern.

- For several commodities (sugar beet, coffee, cranberry, sugarcane and sunflower) monitoring data were unavailable, forcing HED to rely on less refined, field trial data in developing anticipated residues for these crops. The availability and use of monitoring data for these commodities would result in a more refined estimate of dietary exposure. This is especially true for cranberry, which contributes heavily to estimated children's exposures at the 99.9th percentile.

- The percent crop treated data provided by BEAD are screening level usage estimates. The screening level estimates for most crops are low, and, ordinarily, further refinement would not be expected to alter the dietary risk assessment significantly. However, the level of concern for carbofuran (aPAD=0.00006 mg/kg body wt) is very low, and slight adjustments in %CT estimates might have a significant impact, particularly for crops that contribute heavily to exposures at the 99.9th percentile (cucurbits, etc.).

- Cooking and processing factors were incorporated into the assessment to the extent that they were available. However, additional data on the concentration and/or reduction of residues of carbofuran in foods during cooking or processing would allow HED to further refine dietary exposure estimates, as discussed below.

    - A cooking factor of 0.75X from a literature study (Beevi, S. Naseema, Mathew, Thomas Biju, and Visalshi, A. 1992. Residues of carbofuran in bittergourd applied at intervals of planting. *J. Environmental Biology* 13(4): 277-280) was applied to all cooked vegetables in the assessment; however, additional data are still required (D243338, 2/27/98, D.Miller) to confirm this reduction factor.

    - Although additional cooking studies exist for carbofuran residues on potatoes (Misra, S.S. and Agrawal, Hari Om. 1989. Persistence of aldicarb and carbofuran residues in potatoes grown in northwestern plains of India. *Tropical Pest Management*. 35(4): 371-374), indicating that residues on cooked potatoes are much less than those on the RAC, the resulting cooking factor of 0.06X was derived from *unwashed*, unpeeled potatoes to peeled, cooked potatoes, and cannot be applied to the PDP potato data, as potatoes are *washed* (but not peeled) prior to PDP analysis. The availability and use of data from applicable cooking studies for commodities generally cooked prior to consumption (wheat, potatoes, etc) would further refine the dietary exposure assessment.

- In exaggerated rate processing studies for some commodities, residues were non-detectable on both the raw agricultural commodity (RAC) and the processed commodity; therefore, no reduction factors could be calculated.

- The acute assessment for food assumed a concentration equal to ½LOD for monitoring and field trial samples with no detectable residues (with zeros incorporated to account for the percent of the crop not treated with carbofuran). Generally, assigning ½ LOD to non-detectable residues is not expected to significantly affect the outcome of a risk assessment; however, previously conducted sensitivity analyses for carbofuran indicate that the risk assessment is sensitive to the assumed concentrations (i.e., ½LOD) for non-detectable residues at the upper percentiles of exposure.

At the upper percentiles of exposure, relatively low residues in a small percentage of food samples result in estimated exposures that are above HED's level of concern for children's subgroups. As a result of this finding, HED performed additional calculations to determine the risk to children consuming typical (50th percentile) or high-end (90th percentile) amounts of a single commodity (either cucumbers or summer squash) containing residues of carbofuran at levels detected by the PDP. PDP monitoring data are not available for squash; however, the cucumber data are believed to provide a reasonable surrogate for residues in summer squash. The results are summarized in the table below.

Table 13: Risk to Children Consuming Typical or High-end Amounts of Cucumbers or Squash Containing Carbofuran Residues									
Food	Population Subgroup	Typical: 50th Percentile of Consumption				High-End: 90th Percentile of Consumption			
		Consumption (g/kg bw)	PDP Residue[1] (ppm)	Exposure (mg/kg bw)	% aPAD	Consumption (g/kg bw)	PDP Residue[1] (ppm)	Exposure (mg/kg bw)	% aPAD
Cucumber	Children 1-2	0.305009 (less than 5g of cucumbers for a 15 kg child)	0.029	0.000009	15	2.485074 (less than 40g for a 15 kg child)	0.029	0.000072	120
			0.117	0.000036	59		0.117	0.000291	480
			0.137	0.000042	70		0.137	0.000340	570
			0.147	0.000045	75		0.147	0.000365	610
			0.437	0.000133	220		0.437	0.001086	1800
			0.537	0.000164	270		0.537	0.001334	2200
	Children 3-5	0.293744 (approx. 6g of cucumbers for a 20 kg child)	0.029	0.000009	14	2.517696 (approx. 50 g or ½ cup for a 20 kg child)	0.029	0.000073	120
			0.117	0.000034	57		0.117	0.000296	490
			0.137	0.000040	67		0.137	0.000345	570
			0.147	0.000043	72		0.147	0.000370	620
			0.437	0.000128	210		0.437	0.001100	1800
			0.537	0.000158	260		0.537	0.001352	2300

[1] The PDP detected residues of carbofuran in 7 of 922 cucumber samples at levels ranging from 0.029 ppm (detected twice) to 0.537 ppm. These values were translated to summer squash. No adjustment was made to account for reductions of residues during cooking of squash. Application of the 0.75x reduction factor for cooked squsah would result in slightly lower exposure and risk estimates.

Detectable residues of carbofuran and/or its hydroxy metabolite were found in only a few samples of cucumbers in monitoring data (7/922 or less than one percent). However, if young children aged 1 to 5 consume moderate amounts of cucumbers (i.e., the median or 50th percentile of consumption, corresponding to approximately 0.2 ounces of cucumber) that contain observed levels of carbofuran, the percent aPAD utilized ranges from about 15 for the lower observed residue values to over 200 for the higher observed values. For children who consume larger amounts of cucumbers (i.e., the 90th percentile of consumption, corresponding to 1.5 to 2 ounces of cucumbers or roughly ½ cup), exposure increases approximately 10-fold (120 percent to over 2000 percent of the aPAD), which exceeds the Agency's level of concern based on the consumption of a single daily serving of one commodity.

The results from consumption of summer squash are even more dramatic. Although monitoring data are not available for summer squash, residue levels observed in monitoring data for cucumbers were translated to summer squash, based on the similarity of the commodities themselves and the similarity of carbofuran use patterns for these crops. Since children's squash consumption at the 50th (median) percentile is about three times higher than median cucumber consumption, aPAD exceedance is even more dramatic for this commodity, ranging from about 45 percent to over 800 percent. At the higher end (90th percentile) of consumption, the Agency's level of concern is exceeded any time a child consumes squash with PDP detected levels of carbofuran (>200 to >4000 percent of the aPAD).

HED focused on children in making these calculations, because children have the highest estimated dietary exposure to carbofuran; however, it is reasonable to assume that adult exposures from a single treated food item could also exceed HED's level of concern, particularly at the high end of consumption

5.0 OCCUPATIONAL EXPOSURE AND RISK ASSESSMENT

An occupational exposure assessment is required for an active ingredient if (1) certain toxicological criteria are triggered and (2) there is potential exposure to handlers (mixers, loaders, applicators, etc.) during use or to persons entering treated sites after application is complete. For agricultural workers, there is the potential for both short and intermediate term exposure via the dermal and inhalation routes with use of carbofuran.

The HED ORE chapter includes an assessment of occupational exposure to carbofuran (see OPP memo S. Weiss, 8/09/05, D319935, Carbofuran: HED's Occupational and Residential Exposure Chapter of the Reregistration Eligibility Decision Document; Note: this chapter will be updated to reflect current toxicity endpoint selection and MOEs. The following sections of the risk assessment take into consideration current toxicity endpoint selection and MOEs).

Carbofuran can be applied with aerial equipment, chemigation systems, groundboom sprayers, airblast sprayers, and tractor-drawn granular spreaders, and handheld equipment.

Application rates vary from 0.25 to 10 pounds active ingredient per acre depending upon the application scenario. Many of registered uses of carbofuran involve applications to the soil only and do not result in treatment of plant foliage. Application of sprays to foliage may occur for alfalfa, small grains (wheat, barely, oats), corn (field, pop, sweet), ornamentals, potatoes, soybeans, sugarcane, sunflowers, sorghum, and sugar beets. Crops/use-sites and rates included in the ORE assessment are based on the 9/22/04 Food/Feed Use Patterns Summary and Non-Food/Non-Feed Use Patterns Summary provided by BEAD.

Ornamentals: BEAD's 9/22/04 use summary lists foliar application to ornamental and/or shade trees, herbaceous plants, nonflowering plants, woody shrubs and vines at a rate of 10 lb ai per acre. This use does not appear on Section 3 labels. The SLN label from CA830058 lists a rate 10 lb ai/acre applied to soil for field grown ornamentals but does not mention foliar uses. HED assumed that carbofuran is not intended for foliar application to ornamental and/or shade trees, herbaceous plants, nonflowering plants, woody shrubs and vines. In FMC's 7/28/2005 error correction submission, it was also reported that foliar applications to ornamentals do not occur.

Artichokes: BEAD's 9/22/04 use summary lists foliar application to artichokes at a rate of 1 lb ai per acre. This use does not appear on Section 3 labels. The SLN label from CA860037 lists a rate 1 lb ai/acre with a ground sprayer but does not mention foliar uses. HED assumed that carbofuran is not intended for foliar application to artichokes.

Cotton: The label for EPA 279-2876 lists an application of 1.0 lb ai per acre in-furrow at planting. HED assumed carbofuran is no longer registered for foliar applications to cotton.

Estimated occupational exposures represent central to high-end values. Average daily exposures were estimated based on maximum label rates with average values for handler unit exposures, foliage residues, foliage postapplication contact rates, exposure duration, area treated, and other exposure factor inputs.

5.1 Handler

A chemical can produce different effects based on how long a person is exposed, how frequently exposures occur, and the level of exposure. HED classifies exposures up to 30 days as short-term and exposures greater than 30 days up to six months as intermediate-term. HED generally completes both short- and intermediate-term assessments for occupational scenarios in essentially all cases, because these kinds of exposures are likely and acceptable use/usage data are not available to justify deleting intermediate-term scenarios. Based on use data and label instructions, HED believes that occupational handler exposures to carbofuran may occur over a single day or up to weeks at a time for many use-patterns and that intermittent exposures over several weeks also may occur. Some applicators may apply carbofuran over a period of weeks, because they are custom or commercial applicators who are completing a number of applications for a number of different clients. Handler exposures of more than 90 days per

season are not expected to occur for carbofuran. *Only short-term exposures were assessed as ChE inhibition does not increase with continued exposure to carbofuran and because of the rapid reversibility of ChE inhibition.*

Occupational handler exposure assessments are completed by HED using different levels of risk mitigation. Typically, HED uses a tiered approach. The lowest tier is designated as the baseline exposure scenario (i.e., long-sleeve shirt, long pants, shoes, socks, and no respirator). If risks are of concern at baseline attire, then increasing levels of personal protective equipment or PPE (e.g., gloves, double-layer body protection, and respirators) are evaluated. If risks remain a concern with maximum PPE, then engineering controls (e.g., enclosed cabs or cockpits, water-soluble packaging, and closed mixing/loading systems) are evaluated.

No carbofuran-specific data were available for handler exposure. Surrogate exposure data from PHED were used for all handler exposure estimates. Assumptions regarding the area treated per day (e.g. acres per day) for each handler was based on ExpoSac SOP 9.1 "Standard Values for Daily Acres Treated in Agriculture" (7/5/2000).

The following scenarios represent the major exposure scenarios that are expected to occur for registered uses of carbofuran:

Mixer/Loader
- Mixing/loading Liquids For Aerial Application
- Mixing/loading Liquids For Chemigation Application
- Mixing/loading Liquids For Groundboom Application
- Loading Granulars For Tractor-drawn Spreaders Application

Applicator
- Aerial Application
- Sprays For Groundboom Application
- Applying Granulars With Tractor-drawn Spreaders

Flagger
- Flagging For Aerial Application

Mixer/loader/applicator
- Mixing/loading/applying Liquids For Low Pressure Handwand Application
- Mixing/loading/applying Liquids For Backpack Sprayer Application
- Mixing/loading/applying Liquids For High-pressure Handwand Application

Other
- Spreading Granulars By Hand Or With Handheld Equipment

- Mixing/loading Liquids And Using Dip Tank

Estimated total MOEs are a short- term risk concern (i.e MOEs less than 100) at the maximum mitigation level (engineering controls) for all handler scenarios except mixing/loading granulars for tractor-drawn spreader application (rice, cucurbits, spinach) and flagging for spray application (corn, sugarcane) (Table 14). Additionally, total MOEs for mixing/loading/ applying liquids for backpack sprayer were greater than 100 with baseline protection. Total MOEs for mixing/loading/ applying liquids for low-pressure handwand application were greater than 100 with PPE2 protection (single layer protection, gloves, PF5 respirator).

Table 14. Summary of Handler Scenarios Total (Dermal and Inhalation) MOEs with Engineering Controls (Maximum MOEs)

Exposure Scenario	Crop	Application Rate	Daily Area Treated	Total MOEs
MIXER/LOADER				
Mixing/Loading Liquids for Aerial application	Alfalfa, Corn (field and pop), Cotton	1 lb ai per acre	1200 Acres per day	0.96
	Potatoes	2 lb ai per acre	350 Acres per day	1.7
	Sorghum	0.50 lb ai per acre	1200 Acres per day	2.0
	Small grains (wheat, barley, oat), Soybeans	0.25 lb ai per acre	1200 Acres per day	3.9
	Ag Fallow/Idle land	0.19 lb ai per acre	350 Acres per day	18
	Corn (sweet), Sunflowers	0.50 lb ai per acre	350 Acres per day	6.8
	Sugarcane	0.75 lb ai per acre	350 Acres per day	4.4
Mixing/Loading Liquids for Chemigation application	Grapes	6 lb ai per acre	350 Acres per day	0.56
Mixing/Loading Liquids for Groundboom application	Grapes	10 lb ai per acre	80 Acres per day	1.5
	Ornamentals	10 lb ai per acre	40 Acres per day	2.9
	Coffee (seedbeds)	6.90 lb ai per acre	80 Acres per day	2.1
	Tobacco	6 lb ai per acre	80 Acres per day	2.4
	Peppers	3 lb ai per acre	80 Acres per day	4.8
	Sugar Beets	2 lb ai per acre	200 Acres per day	3.0

Table 14. Summary of Handler Scenarios Total (Dermal and Inhalation) MOEs with Engineering Controls (Maximum MOEs)				
Exposure Scenario	Crop	Application Rate	Daily Area Treated	Total MOEs
	Sunflowers	1.40 lb ai per acre	80 Acres per day	10
	Alfalfa, Corn (field and pop), Cotton	1 lb ai per acre	200 Acres per day	6.0
	Potatoes	3 lb ai per acre	80 Acres per day	4.8
	Sugarcane	0.75 lb ai per acre	80 Acres per day	20
	Sorghum	0.50 lb ai per acre	200 Acres per day	12
	Corn (sweet)	1 lb ai per acre	80 Acres per day	15
	Artichoke	1 lb ai per acre	80 Acres per day	15
	Small grains (wheat, barley, oat), Soybeans	0.25 lb ai per acre	200 Acres per day	23
Mixing/Loading Granulars for Tractor-drawn Spreaders application	Rice, cucurbits, spinach	0.50 lb ai per acre	80 Acres per day	**400**
APPLICATOR				
Aerial application	Alfalfa, Corn (field and pop), Cotton	1 lb ai per acre	1200 Acres per day	1.6
	Potatoes	2 lb ai per acre	350 Acres per day	2.7
	Sorghum	0.50 lb ai per acre	1200 Acres per day	3.2
	Small grains (wheat, barley, oat), Soybeans	0.25 lb ai per acre	1200 Acres per day	6.4
	Corn (sweet), Sunflowers	0.50 lb ai per acre	350 Acres per day	11
	Ag Fallow/Idle land	0.19 lb ai per acre	350 Acres per day	29
	Sugarcane	0.75 lb ai per acre	350 Acres per day	7.2
Groundboom application	Grapes	10 lb ai per acre	80 Acres per day	2.6
	Ornamentals	10 lb ai per acre	40 Acres per day	5.2
	Coffee (seed beds)	6.90 lb ai per acre	80 Acres per day	3.2
	Tobacco	6 lb ai per acre	80 Acres per day	4.4
	Peppers	3 lb ai per acre	80 Acres per day	8.4

Table 14. Summary of Handler Scenarios Total (Dermal and Inhalation) MOEs with Engineering Controls (Maximum MOEs)				
Exposure Scenario	Crop	Application Rate	Daily Area Treated	Total MOEs
	Sugar Beets	2 lb ai per acre	200 Acres per day	5.2
	Sunflowers	1.40 lb ai per acre	80 Acres per day	18
	Alfalfa, Corn (field and pop), Cotton	1 lb ai per acre	200 Acres per day	10
	Potatoes	3 lb ai per acre	80 Acres per day	8.4
	Sugarcane	0.75 lb ai per acre	80 Acres per day	34
	Sorghum	0.50 lb ai per acre	200 Acres per day	20
	Corn (sweet)	1 lb ai per acre	80 Acres per day	26
	Small grains (wheat, barley, oat), Soybeans	0.25 lb ai per acre	200 Acres per day	40
	Artichoke	1 lb ai per acre	80 Acres per day	26
Applying Granulars for Tractor-drawn Spreaders application	Rice, cucurbits, spinach	0.50 lb ai per acre	80 Acres per day	52
FLAGGER				
Flagging for Spray application	Potatoes	2 lb ai per acre	350 Acres per day	48
	Sorghum	2 lb ai per acre	1200 Acres per day	14
	Small grains (wheat, barley, oat), Soybeans	2 lb ai per acre	1200 Acres per day	14
	Corn	0.50 lb ai per acre	350 Acres per day	**200**
	Sugarcane	0.75 lb ai per acre	350 Acres per day	**130**
MIXER/LOADER/APPLICATOR				
Mixing/Loading/ Applying Liquids for Low-Pressure HandWand application	Misc Crops/Sites	0.00063 lb ai per gallon	1000 Gallons per day	No data
Mixing/Loading/ Applying Liquids for Backpack sprayer	Misc Crops/Sites	0.00063 lb ai per gallon	1000 Gallons per day	No data
Mixing/Loading/ Applying Liquids for High-Pressure HandWand	Misc Crops/Sites	0.00063 lb ai per gallon	1000 Gallons per day	No data

*Maximum rates for sprays applied to foliage may differ than from soil applications. Maximum rates in handler and postapplication assessment may not be the same.

Table 15. Summary of Short-term Handler Scenarios Total (Dermal and Inhalation) MOEs that are >100 with PPE6 (Double layer protection, gloves, PF10 respirator)

Exposure Scenario	Crop	Application Rate	Daily Area Treated	Total MOEs
Mixing/Loading/ Applying Liquids for Low-Pressure HandWand application	Misc Crops/Sites	0.00063 lb ai per gallon	1000 Gallons per day	**1100**
Mixing/Loading/ Applying Liquids for Backpack sprayer	Misc Crops/Sites	0.00063 lb ai per gallon	1000 Gallons per day	**280**

Table 16. Summary of Short-term Handler Scenarios Total (Dermal and Inhalation) MOEs that are >100 with PPE2 (single layer protection, gloves, PF5 respirator)

Exposure Scenario	Crop	Application Rate	Daily Area Treated	Total MOEs
Mixing/Loading/ Applying Liquids for Low-Pressure HandWand application	Misc Crops/Sites	0.00063 lb ai per gallon	1000 Gallons per day	**880**
Mixing/Loading/ Applying Liquids for Backpack sprayer	Misc Crops/Sites	0.00063 lb ai per gallon	1000 Gallons per day	**180**

Table 17. Summary of Short-termHandler Scenarios Total (Dermal and Inhalation) MOEs that are >100 at Baseline

Exposure Scenario	Crop	Application Rate	Daily Area Treated	Total MOEs
Mixing/Loading/ Applying Liquids for Backpack sprayer	Misc Crops/Sites	0.00063 lb ai per gallon	1000 Gallons per day	**160**

HED has received two proprietary studies for applications of granulars to banana plants. One study involves backpack application with aldicarb (MRID 451672-01) and in the other, handlers applied fipronil with a spoon (MRID 452507-01). PHED contains unit exposures for granular "hand" application using gloves. These studies and the PHED data are of limited value since workers were wearing gloves (i.e., no baseline unit exposures) which may not reflect typical application methods.

5.2 Postapplication

HED uses the term "postapplication" to describe exposures to individuals that occur as a result of being in an environment that has been previously treated with a pesticide (also referred to as reentry exposure). HED believes that there are distinct job functions or tasks related to the kinds of activities that occur in previously treated areas. Job requirements (e.g., the kinds of jobs to cultivate a crop), the nature of the crop or target that was treated, and how the chemical residues degrade in the environment can cause exposure levels to differ over time. Each factor has been considered in this assessment. A series of assumptions and exposure factors served as the basis for completing the occupational postapplication worker risk assessments (e.g. exposure duration, residue on plant foliage, foliage contact rates, body weight, etc.).

Many of registered uses of carbofuran involve applications to the soil only and do not result in treatment of plant foliage. Multiple application of sprays to foliage may occur for alfalfa, small grains (wheat, barely, oats), corn (field, pop, sweet), potatoes, soybeans, sugarcane, sunflowers, and sugar beets. Harvesting for all these crops are expected to be fully mechanized.

Short-term exposures may occur for several crops requiring reentry by crop advisors. It also may occur for field workers involved in irrigation activities, early season hoeing and thinning, and de-tasseling corn grown for seed. [Based on the registered use pattern, intermediate-term exposures are not expected for postapplication activities.]

A 14 day reentry restriction is currently on carbofuran labeling for foliar application to corn, sunflowers, and sorghum. All other crops have a 48 hour REI on product label based on the acute toxicity of carbofuran per EPA's Worker Protection Standard.

Drench applications made to container grown nursery stock my result dermal exposure to workers performing postapplication reentry tasks and for workers handling treated soil while moving containers. HED has no exposure data to estimate these exposures.

DFR studies for carbofuran are available for cotton, corn, and potatoes**.** Since no DFR data were available for alfalfa, soybeans, sugar beets, small grains, sunflowers, sorghum, or sugarcane, the DFR data from potatoes and cotton were used a surrogate. Dermal transfer coefficients were taken from HED's revised policy entitled *Policy 003.1 Science Advisory Council For Exposure Policy Regarding Agricultural Transfer Coefficients* (August 7, 2000).

Most crops with postapplication activities failed to reach MOEs of 100 within the currently prescribed label REIs (see Table 18). Only sunflower and sorghum had postapplication MOEs of 100 within the label REI of 14 days (MOEs reached in 13 days).

- **Soybeans and Small grains (wheat, barley, oats):** The MOEs for scouting and irrigation tasks reach 100 on day 12. The REI listed on BEAD's 9/22/04 Use Summary report is 48 hours.
- **Alfalfa and Sugar Beets:** MOEs of 100 were not reached within 14 days (duration of relevant study). Using available data, it is not possible to calculate the number of days until MOE of 100 is reached. The REI listed on BEAD's 9/22/04 Use Summary report is 48 hours.
- **Sweet Corn**: The MOEs for high end contact activities such as de-tasseling did not reach 100 within 32 days (duration of study) using the California DFR data scaled to 0.5 lb ai per acre. Using available data, it is not possible to calculate the number of days until MOE of 100 is reached. The REI listed on BEAD's 9/22/04 Use Summary report is 14 days.
- **Field and Pop Corn:** The MOEs for medium end contact activities such as scouting, weeding, and irrigation did not reach 100 within 32 days (duration of study) using the California DFR. Using available data, it is not possible to calculate the number of days until MOE of 100 is reached. The REI listed on BEAD's 9/22/04 Use Summary report is 14 days.
- **Sugar Cane and Potato:** The MOEs for medium end contact activities were not reached within 14 days (duration of relevant study) using the potato DFR data. Using available data, it is not possible to calculate the number of days until MOE of 100 is reached. The REI listed on BEAD's 9/22/04 Use Summary report is 48 hours.
- **Sunflower and Sorghum:** The MOEs for medium end contact activities reached 100 at 13 days. The REI listed on BEAD's 9/22/04 Use Summary report is 14 days.

Table 18. Crop Groupings: Selected Transfer Coefficients, Treated Crops, Rates, MOEs, Current REIs

Transfer Coefficient Group	Crop	Max Foliar Rate (lb ai/acre)	DFR Data Used	Transfer Coefficient (cm2/hr)			# of days until MOE reaches 100			REI on current product label
				Low	Med	High	Low	Med	High	
Field/row crops, low/medium	Soybeans	0.25	Cotton	100	1500		6	12		48 hrs
	Small Grains	0.25	Cotton	100	1500		6	12		48 hrs
	Alfalfa	1	Potatoes	100	1500		4	>14*		48 hrs
	Sugar Beets	2	Potatoes	100	1500		8	>14*		48 hrs
Field/row crops, tall	Corn (field and pop)	1	Corn (MN site)	100	1000		7	10		14 days for foliar applications
			Corn (CA site)	100	1000		25	>32*		14 days for foliar applications
	Corn (sweet)	0.5	Corn (MN site)	100	1000	17000	2	10	>11*	14 days for foliar applications
			Corn (CA site)	100	1000	17000	18	32	>32*	14 days for foliar applications
	Sunflowers	0.5	Potatoes	100	1000		0	13		14 days for foliar applications
	Sorghum	0.5	Potatoes	100	1000		0	13		14 days for foliar applications
Sugarcane	Sugarcane	0.75	Potatoes	100	1000	2000	2	>14*		48 hrs
Vegetable, root	Potatoes	1	Potatoes	300	1500		4	>14*		48 hrs

Crop groupings and transfer coefficients from Science Advisory Council for Exposure: Policy Memo #003.1 'Agricultural Transfer Coefficients', August 17, 2000.

* Those values reported as greater than (>) a number of days until MOE reaches 100 require extrapolation outside the parameters of the days tested for each respective study used to determine DFR data.

5.3 Residential Exposure

Non-occupational exposures are not assessed in this document as there are currently no registered residential or other non-occupational uses for carbofuran. Carbofuran is a restricted use pesticide and is only available for retail sale to and use by certified applicators (or persons under their direct supervision) and only for those uses covered by the certified applicator's certification. This is based upon information obtained from registered carbofuran labels, information supplied by the registrant, and usage reviews conducted by the Biological Economic Assessment Division (BEAD).

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for carbofuran. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

5.3.1 Smoker Assessment

No carbofuran products are intended for sale to homeowners or for use by professional applicators in residential environments. Therefore, no residential exposure risk assessment has been performed. However, an inhalation risk assessment for adult smokers has been completed since carbofuran is registered for use on tobacco.

HED assumed that the average U.S. adult smoker (defined as a person ≥18 years of age who smokes ≥ 100 cigarettes per year) smokes 15 cigarettes per day (Pierce, J. P., et al. 1989. *Tobacco Use in 1986 - Methods and Basic Tabulations from Adult Use of Tobacco Survey*. U.S. Dept. of Health and Human Services Publication Number OM90-2004. Office on Smoking and Health, Rockville, Maryland). Based on the pyrolysis study submitted by the registrant, parent carbofuran residues were found in mainstream cigarette smoke at 3.2 ppm (MRID 40250301). No other metabolites of concern were identified in the smoke. This residue level is based on analysis obtained from a standard smoking machine [1 puff (35 mL) per minute] using cigarettes made from tobacco that had been grown in soil treated with ^{14}C-carbofuran at 6 lb ai/A (1x maximum label rate). In assessing smoker exposure, HED has further assumed that 100% of the pesticide residue inhaled is absorbed (i.e., that none of the residue is exhaled along

with the smoke). These assumptions result in an overestimate of likely actual exposure. With the assumptions regarding residue levels and smoking frequency, and assuming an average body weight of 70 kg, HED estimates that adult exposure to carbofuran through smoking will not exceed 0.00068 mg/kg/day for males [3.2 µg/g cigarette × 1 g/cigarette × 15 cigarettes/day × 1 mg/1000µg ÷ 70 kg body weight = 0.00068 mg/kg/day] and, assuming 60 kg body weight, will not exceed 0.00080 mg/kg/day for females.

The short-term inhalation BMDL10 is 0.01 mg/kg/day and is based on red blood cell cholinesterase inhibition in adult male rats (oral study; inhalation absorption rate = 100%). HED has not examined intermediate- or long-term exposure to carbofuran via tobacco due to the severity and quantity of health effects associated with the long-term use of tobacco products. Additionally, short-term exposure estimates may be considered protective of longer term exposures because of the rapid reversibility of cholinesterase inhibition from carbofuran exposure. Based on the short-term inhalation BMDL10, the short-term MOE for carbofuran exposure from the use of tobacco is estimated to be 12. This conservative risk estimate is above HED's level of concern for inhalation exposure to carbofuran (less than the short-term inhalation MOE of 100).

5.4 Incident Reports

A 1997 HED incident review stated that, overall, carbofuran was judged second among 28 pesticides on measures of hazard derived from California and Poison Control Center data (Blondell, Spann, D238109, 8/20/97). Most of the risk from this product is due to use by pesticide handlers, especially mixer/loaders who handle the concentrated material. Less often, groups of people have been poisoned from spray drift or from exposure to field residue. A recent case in California illustrates the dermal toxicity from field residues when encountered two hours after application. Such residues are capable of causing moderate to relatively serious effects which require medical treatment.

Detailed descriptions of incidents reported to the California Pesticide Illness Surveillance Program from 1982 through 2002 identified a total of 88 cases in which carbofuran was either used alone or in combination with other chemicals but was judged to be responsible for the health effects. The majority of the illnesses were of a systemic type. The majority of incidents occur among handlers who mix, load, and apply carbofuran in agricultural fields.

The following data bases have been consulted to update the poisoning incident data on the active ingredient carbofuran. (J. Blondell, Review of Carbofuran Incident Reports, D306793, 2/9/05):

1) OPP Incident Data System (IDS) to 2003.

The August 20, 1997 review of carbofuran incidents reported 139 incidents due to carbofuran from June 1992 through 1996 (Blondell, Spann, D238109, 8/20/97). Since that

time, there have been 42 new reports through 2003. Common among these reports is evidence that carbofuran is a prevalent cause of eye problems which was reported in about one-quarter of all the cases. Some of the cases involved single workers or groups of workers reentering a field shortly after application and being exposed to carbofuran residues. Fifty percent of these cases involved exposure to the applicator during spray operations. Although data were often limited, most cases involved failure to wear proper protective equipment or occurred when workers were cleaning or repairing spray equipment. There were three reports of deaths all due to ingestion where homicide was suspected. One case treated in an ICU for two days alleged muscle weakness that persisted for at least one month after poisoning due to inappropriate exposure to granules.

2) Poison Control Centers, 1993 through 2001.

Results for the years 1993 through 2001 are presented below for occupational and non-occupational reports involving adults and older children and for children under age six. Cases involving exposures to multiple products or unrelated outcome are excluded.

Number of carbofuran exposures reported to the Toxic Exposure Surveillance System (AAPCC), number with determined outcome, number seen in a health care facility for occupational and non-occupational cases (adults and children six years and older) and for children under six years of age only, 1993-2001:

Subgroup	Exposures	Outcome determined	Seen in Health Care Facility
Occupational: adults and older children	221	188	149
Non-occupational: adults and older children	241	184	144
Children under age six	36	31	19

Of the 88 reports of moderate or major medical outcome from 1993 through 1998, the most common symptoms reported included gastrointestinal (61 reports, primarily nausea, vomiting and diarrhea), neurological (48 reports, primarily muscle weakness, dizziness, drowsiness, tremor, and headache), miscellaneous symptoms (35 reports of diaphoresis or excessive sweating and 7 reports of other types of excessive secretions), ocular effects (33 reports, primarily miosis, blurred vision, eye irritation/pain, and tearing), and cardiovascular effects (26 reports, primarily bradycardia and hypertension). Of the 88 reports of moderate or major medical outcome, 14 (16%) were due to accidental ingestion. A similar pattern was observed for the 30 reports of moderate or major medical outcome cases reported from 1999 through 2001.

From 1993 through 2001 there were 46 reports of diaphoresis, 23 reports of miosis, 21 reports of bradycardia, 20 reports of muscle weakness, and 12 reports of tremor. These symptoms are all specific to cholinergic poisoning and most resulted from dermal and inhalation exposure rather than oral exposure.

3) California Department of Pesticide Regulation, 1982-2002.

Uniform classification and collection procedures permit analyzing California data for evidence of trends. A comparison of the ratios (poisoning per 1,000 applications) and number of poisonings for the 1982-89 period with 1990-1995 indicate that both the number of cases reported and the ratio of poisoning per 1,000 applications appear to have gone down markedly in the second period. Some of this change is due to changes in the way applications were reported starting in 1990. In that year all applications had to be reported not just those that were restricted or applied by a commercial applicator. It is not possible to determine whether all of these increases are an artifact of changes in reporting requirements and how much may be a real increase. In any event, it is evident that increase reporting of applications is unlikely to explain all of the decrease in poisoning ratios.

Eighty percent of the exposures to carbofuran resulted in systemic effects according to the data from 1982 through 1993. Eye effects accounted for 13% of the effects reported. Handlers were also involved in the majority of cases reported in California from 1982 through 1993. Mixer/loaders were commonly poisoned than applicators, however, this has likely changed in more recent years with the use of closed mixing/loading systems for application.

From 1995 through 2002 there were 42 cases of carbofuran poisoning reported in California, more than the total number reported from 1982 through 1994 (34 cases). All of these cases were systemic with the exception of 3 eye injuries. The majority of these cases occurred as a result of a single reentry case in 1998. A crew of 35 field workers became ill while weeding a cotton field sprayed with carbofuran two hours earlier and were taken to a medical clinic complaining of symptoms. The most common symptoms in ten or more workers were headache (34 cases), nausea (34), vomiting (29), dizziness (29), lacrimation (tearing 25), photophobia (25), pupils constricted or non-reactive (22), muscle weakness (18), abdominal pain/upset stomach (17), salivation (14), diaphoresis (sweating 12), unusual weakness (12), and eye irritation/pain (10). Other notable symptoms specific to cholinergic poisoning included bradycardia (8 cases) and urinary frequency/urgency (6 cases). This particular incident did include exposure to abamectin and mepiquat chloride, however, carbofuran was deemed the primary cause of symptoms.

4) National Pesticide Telecommunications Network (NPTN), 1984-1991.

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, carbofuran was ranked 37th with 103 incidents in humans reported and 23 incidents in animals (mostly pets).

5) National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR) performs standardized surveillance in seven states from 1998 through 2002.

States included in this reporting system are Arizona, California, Florida, Louisiana, Michigan, New York, Oregon, Texas, and Washington. Nineteen reports due to carbofuran alone were reported out of 4,221 reports. Eleven of the cases occurred in Texas. The pattern of incidents is similar to those reported for California.

6) Scientific Literature

Reentry into treated field is a relatively rare cause of carbofuran poisoning, but can occur.

In California, on July 31, 1998, the California Department of Health Services (CDHS) investigated an incident in Fresno County involving 34 farm workers. CDHS investigated this incident by reviewing medical records of the 34 workers and interviewing 29. The findings indicated that the workers became ill after early reentry into a cotton field that had been sprayed with carbofuran (Centers for Disease Control 1999). Workers entered the field two hours after an aerial application (instead of the required 48 hour restricted reentry interval) of carbofuran, abamectin, and mepiquat chloride. The 34 workers weeded for approximately four hours and then most workers reported nausea (97%), headache (94%), eye irritation (85%), muscle weakness (82%), tearing (68%), vomiting (79%), and salivation (56%). All workers received hospital treatment for their symptoms. Urinary metabolites of carbofuran were detected in urine of 58% of 31 samples taken up to 11 days following the exposure. Foliage levels on the day of exposure measured up to 0.77 ug/cm^2, levels consistent with application that morning. The authors concluded the carbofuran exposure was the probable cause of the illnesses reported.

6.0 AGGREGATE RISK ASSESSMENT

In accordance with FQPA, HED must consider and aggregate (add) pesticide exposures and risks resulting from food, drinking water, and residential exposures. Since there is no potential for exposures to carbofuran in residential settings, aggregate exposure and risk assessments include only dietary food and water sources of exposure and, for carbofuran, are limited to short-term (acute) durations.

6.1 Acute Aggregate Risk

Acute dietary exposure and risk from food alone was above HED's level of concern (i.e., >100% aPAD). For the most highly exposed subpopulation (children, 1-2 yrs) the acute dietary (food only) risk estimate is 490% of the aPAD. Since estimated acute exposures exceed the aPAD for food alone, exposure from drinking water was not aggregated with food in the dietary assessment. However, HED is concerned about any additional exposure (to all subpopulations) through drinking water.

EFED provided Estimated Drinking Water Concentrations (EDWCs) for surface and ground water. Using the PRZM/EXAMS model, the acute EDWCs in surface water range from **0.11ppb** (low application to CA alfalfa) to **75 ppb** (maximum label application to TX sorghum) for nine crop/location scenarios. EDWCs for ground water, based on prospective ground water monitoring data, range from **1.4 ppb** (low application to alfalfa) to **110 ppb** (maximum application to grapes) (see Section 4.3, Table 9 and Table 10 for all values).

Assuming there is no acute dietary food exposure to carbofuran, and *all* of the allowable exposure occurred through water sources (i.e., assuming the aPAD of 0.00006 mg/kg/day is completely allotted to exposure to residues in water), the DWLOC (Drinking Water Level of Concern) for the general US population would be **2.1 ppb** and for infants and children the DWLOC would be **0.6 ppb**. These values are based on daily water consumption estimates of 2 liters for adults and 1 liter for infants and children. DWLOCs based on consumption of a single 8 ounce serving of water would be **2.6 ppb** for infants and children and **18** ppb for adults. Therefore, even if all of the allowable dietary exposure (i.e, entire aPAD, or "risk cup") occurred through drinking water, HED would have concerns for acute exposure to carbofuran, particularly for individuals (both adults and children) who may derive their water from watersheds that are highly cropped and where carbofuran applications may be made up to the maximum label rates (representative scenarios include TX sorghum, IL corn, MS cotton, NC tobacco, ID potato, CA and PA alfalfa, CA grape, and ME potato). Exposure to individuals (adults) whose drinking water comes from sources where crop/location scenarios result in lower EDWCs (scenarios with lower applications including ME potato, CA grape and CA alfalfa) may not be of concern, if the entire risk cup were available for water exposures (for infants and children, of the nine representative crop/location scenarios, only low applications to CA grape would result in EDWCs that are below the DWLOCs; again, this assumes 100% of the risk cup would be available for water).

Additional DWLOCs were calculated for comparison to the EDWCs (see Section 4.3, Table 9 and Table 10 for all values). All calculations assumed that a portion of the acute dietary "risk cup" were available for water exposures (100, 75, 50, or 25%):

Population subgroup	DWLOC (100% risk cup available)	DWLOC (75% risk cup available)	DWLOC (50% risk cup available)	DWLOC (25% risk cup available)
US Population	2.1 ppb[1]	1 .3 ppb	1.0 ppb	0.52 ppb
Infants/children	0.6 ppb[1]	0.37 ppb	0.3 ppb	0.15 ppb

[1]These values are based on daily water consumption estimates of 2 liters for adults and 1 liter for children. DWLOCs based on consumption of a single 8 oz. serving of water are 2.6 ppb for infants and children and 18 ppb for adults.

7.0 CUMULATIVE RISK ASSESSMENT

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Carbofuran is a member of the N-methyl carbamate class of pesticides. This class also includes carbaryl, aldicarb, methomyl and oxamyl among others. The N-methyl carbamates, as a group, have been determined to share a common mechanism of toxicity (July 2001 memo from Office Director Marcia Mulkey). The preliminary cumulative risk assessment for the N-methyl carbamate (NMC) Cumulative Assessment Group, which includes carbofuran was released in July 2005. The preliminary cumulative risk assessment was reviewed by the FIFRA SAP in August 2005. The revised CRA is currently being developed and will be released during 2006. The results of this NMC cumulative assessment as well as the single chemical carbofuran assessment presented here will be considered during the carbofuran reregistration process in which decisions regarding establishing, modifying, or revoking carbofuran tolerances will be made.

8.0 DATA NEEDS

Data gaps exist for the following studies:

Product chemistry: Certain storage stability data are still required. See Product and Residue Chemistry Chapter (Memorandum from D. Drew, 1/13/05, D306796) for details.

Residue chemistry: Numerous datagaps exist. Please refer to the Product and Residue Chemistry chapter for details (D. Drew, 1/13/05, D306796).

Toxicology:

A 28-day inhalation study in rats is required. The protocol for this study should also be submitted to OPP for review prior to initiating this study. This study will require preliminary work to determine the optimum time following removal from inhalation exposure and blood sampling in order to assure maximum inhibition of cholinesterase.

The registrant should submit additional comparative cholinesterase data which measures RBC and brain ChE inhibition in pups and adults. This comparative ChE study should also include a range-finding study and well-conducted time course study such that the definitive study is performed at the time of peak effect for ChE inhibition.

Occupational Handlers:

HED has insufficient data to estimate exposure for the following handler scenarios:

-Slurry dip treatment of pine seedlings:

FMC has indicated that the USDA/APHIS is currently interacting with various stakeholders with regard to a plant dip exposure study and that the Agricultural Handlers Exposure Task Force (AHETF), of which FMC is a member, has agreed to support USDA's efforts. The registrant should indicate when the study will be available. HED may review the study for suitability for use in handler exposure assessments.

-Applying granulars to pine seedlings:

At this time, HED is not requiring specific handler data for applying granulars to pine progeny test seedlings. Any data received for applying granulars to bananas and plantains will be reviewed for suitability for assessing exposures for applying granulars to pine seedlings.

-Applying granulars to bananas and plantains:

FMC has indicated that the USDA/APHIS is currently interacting with various stakeholders to potentially investigate bananas and plantains granular exposure studies as they are a unique use pattern. The registrant should indicate when the study will be available. HED may review the study for suitability for use in handler exposure assessments.

Occupational Postapplication Activities:

Drench applications made to container grown nursery stock my result dermal exposure to workers performing postapplication reentry tasks and for workers handling treated soil while moving containers (OPPTS Guideline: 875.2400, Dermal exposure). HED has no exposure data to estimate these exposures.

9.0 REFERENCES

Revised HED Product Chemistry and Residue Chemistry Chapter of the RED (D. Drew, 1/13/05, D306796)

HED's Occupational and Residential Exposure Chapter of the Reregistration Eligibility Decision Document (S.Weiss, 8/09/05, D319935)

Revised Carbofuran Acute Probabilistic Dietary Exposure Assessment for the Reregistration Eligibility Decision (Phase IV)(S. Stanton, 3/7/06, D327358); and Carbofuran: Revised Acute Probabilistic Dietary Exposure Assessment to Support Risk Mitigation for the Reregistration Eligibility Decision (Phase VI) (S.Stanton, 7/20/06, D330841)

Carbofuran. Reregistration Case No. 0101. Outcome of the 7/28/97 meeting of the HED Metabolism Committee (D. Miller, 10/30/97, No DP Barcode)

Estimated Drinking Water Concentrations(email communication D.Young to D.Drew, 3/8/06)

Benchmark dose analysis of cholinesterase inhibition data in neonatal and adult rats (MRID no. 46688914) following exposure to *carbofuran* (A.Lowit, 1/19/06, D325342, TXR no. 0054034)

FIFRA SAP. (2002). Methods Used to Conduct a Preliminary Cumulative Risk Assessment for Organophosphate Pesticides. Report from the FIFRA Scientific Advisory Panel Meeting of February 5-7, 2002 (Report dated March 19, 2002). FIFRA Scientific Advisory Panel, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency. Washington, DC. SAP Report 2002-01.

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USEPA 2005 Preliminary N-Methyl Carbamate Cumulative Risk Assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency. Washington, DC. http://www.epa.gov/scipoly/sap/index.htm#sept

APPENDIX 1: Tolerance Reassessment Summary for Carbofuran

Commodity	Current Tolerance, ppm	Tolerance Reassessment, ppm	Comment/ *[Correct Commodity Definition]*
Tolerances Listed Under 40 CFR §180.254 (a)			
Alfalfa , fresh	10 (5)	5	*[Alfalfa, forage]*
Alfalfa, hay	40 (20)	12	
Banana	0.1	0.1	
Barley, grain	0.2 (0.1)	0.1	
Barley, straw	5.0 (1.0)	1	
Beet, sugar	0.1	0.1	*[Beet, sugar, roots]*
Beet, sugar, tops	2 (1)	0.2	
Coffee bean	0.1	2	*[Coffee, green bean]*
Corn, forage	25 (5)	8	*[Corn, field, forage]* *[Corn, sweet, forage]*
Corn, fresh (including sweet corn) (K+CWHR)	1.0 (0.2)	0.2	*[Corn, sweet, kernal plus cob with husks removed]*
Corn, grain (including popcorn)	0.2 (0.1)	0.1	*[Corn, field, grain]* *[Corn, pop, grain]*
Corn, stover	25 (5)	8	*[Corn, field, stover]* *[Corn, sweet,stover]* *[Corn, pop, stover]*
Cotton, undelinted seed	1.0 (0.2)	0.2	
Cranberry	0.5 (0.3)	0.3	Voluntary cancellation on cranberries has been requested.Tolerance maintained for import purposes.
Cucumber	0.4 (0.2)	0.6	Revoke individual tolerances and establish a crop group tolerance for *Cucurbit Vegetables Group* 9
Melons	0.4 (0.2)		
Pumpkin	0.8 (0.6)		
Squash	0.8 (0.6)		

Commodity	Current Tolerance, ppm	Tolerance Reassessment, ppm	Comment/ *[Correct Commodity Definition]*
Grape	0.4 (0.2)	0.2	Revocation to have been effective 1997. [Registrant submitted request for 24(c) (CA wine grapes) in 1998]
Grape, raisin	2.0 (1.0)	1.0	Revocation to have been effective 1997. [Registrant submitted request for 24(c) (CA wine grapes) in 1998]
Milk	0.1 (0.02)	0.1	
Oat, grain	0.2 (0.1)	0.1	
Oat, straw	5.0 (1.0)	1	
Pepper	1 (0.2)	0.05	*[pepper, bell and pepper, nonbell]*
Potato	2 (1)	0.5	
Raisins, waste	6.0 (3.0)	Revoke	*[grape, raisin waste]* No longer considered a significant livestock feed item.
Rice, grain	0.2	0.2	No Section 3 registrations. Tolerance maintained for import purposes.
Rice, straw	1 (0.2)	0.2	No Section 3 registrations. Tolerance maintained for import purposes.
Sorghum, fodder	3 (0.5)	2	*[Sorghum, grain, stover]*
Sorghum, forage	3 (0.5)	2	*[Sorghum, grain, forage]*
Sorghum, grain	0.1	0.1	*[Sorghum, grain, grain]*
Soybean	1.0 (0.2)	0.2	*[Soybean, seed]*
Soybean, forage	35.0 (20.0)	20	
Soybean, hay	35.0 (20.0)	20	
Strawberry	0.5 (0.2)	0.2	Revocation to have been effective 5/97. Tolerance maintained for import purposes.
Sugarcane, cane	0.1	0.2	

Commodity	Current Tolerance, ppm	Tolerance Reassessment, ppm	Comment/ *[Correct Commodity Definition]*
Sunflower, seed	1.0 (0.5)	0.5	
Wheat, grain	0.2 (0.1)	0.1	
Wheat, straw	5.0 (1.0)	1	
Tolerances Listed Under 40 CFR §180.254 (c)			
Artichoke, globe	0.4 (0.2)	0.2	
Canola	1.0 (0.2)	Revoke	*[Canola, seed]* Time limited tolerance expired 2/22/98.
Tolerances to be Proposed			
Barley, hay	--	TBD	Field trial data are required.
Cotton, gin byproducts	--	2.0	
Oat, hay	--	TBD	Field trial data are required.
Oat, forage	--	TBD	Field trial data are required.
Wheat, forage	--	TBD	Field trial data are required.
Wheat, hay	--	TBD	Field trial data are required.
Grain, aspirated fractions	--	TBD	Field trial data are required.

(Number in parentheses reflects the ppm level that residues of carbamates may not exceed.)