Re-evaluation Decision RVD2010-16

Carbofuran

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario
K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

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Re-evaluation Decision for Carbofuran

After a re-evaluation of the insecticide carbofuran, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is requiring phase-out of carbofuran products in Canada.

An evaluation of available scientific information found that, under the current conditions of use, carbofuran products pose an unacceptable risk to human health and the environment, and therefore do not meet Health Canada's current standards for human health and environmental protection. As a result, all uses of carbofuran will be phased out. This includes registered uses on canola, mustard, sunflower, corn (sweet, field and silage), sugar beet, green pepper, potato, raspberry and strawberry. The PMRA did not receive indications from stakeholders suggesting the need for a transition strategy as part of the phase-out time lines. Therefore the time lines will be determined as per normal practice.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies, and any other relevant information available.

The regulatory approach regarding the re-evaluation of carbofuran was first proposed in the consultation document[1] Proposed Re-evaluation Decision PRVD2009-11, *Carbofuran*. This Re-evaluation Decision[2] describes this stage of the PMRA's regulatory process concerning the re-evaluation of carbofuran and summarizes the Agency's decision and the reasons for it. Appendix I summarizes comments and information received during the consultation process and the PMRA's response to these comments. This decision is consistent with the proposed re-evaluation decision stated in Proposed Re-evaluation Decision PRVD2009-11, *Carbofuran*. To comply with this decision, registrants of products containing carbofuran will be informed of the specific requirements affecting their product registration(s) and of the regulatory options available to them.

For more details on the information presented in this Re-evaluation Decision, please refer to the Science Evaluation in the related Proposed Re-evaluation Decision PRVD2009-11, *Carbofuran*.

1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act.*

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration.[3] The Act also requires that products have value[4] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at www.healthcanada.gc.ca/pmra.

Carbofuran is one of the carbamate pesticides re-evaluated as outlined in the Re-evaluation Note REV2002-06, *Re-evaluation of Selected Carbamate Pesticides*. The PMRA has considered all currently available information regarding health and environmental risk, including reviews from the United States Environmental Protection Agency (USEPA), as a source of information for conducting Canadian re-evaluation assessments.

Regulatory Status in Organisation for Economic Cooperation and Development Countries

Based on the available information, carbofuran is not authorised for use in the European Union. The commission made a decision on June 13, 2007 concerning the non-inclusion of carbofuran in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing carbofuran.

The United States Environmental Protection Agency (USEPA) reviewed the safety and benefits of all uses of carbofuran and concluded that ecological and human health risks were of concern.

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3 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

4 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

On May 15, 2009, the USEPA issued a final rule[5] and has since revoked all of the existing carbofuran tolerances, referred to as maximum residue limits in Canada, on crops effective December 31, 2009. The notice also indicated that USEPA will move to cancel all remaining uses of carbofuran in the future.

What is Carbofuran?

Carbofuran is a systemic, carbamate insecticide (Resistance Management Mode of Action group 1A), used to control a broad range of insect pests on certain field, vegetable and fruit crops. It is applied using conventional ground equipment to canola, mustard, sunflower, corn (sweet, field and silage), sugar beet, green pepper, potato, raspberry, strawberry and can also be applied by aerial equipment to corn (field, silage and sweet), canola and mustard. It may be applied by farmers, farm workers and professional applicators.

Health Considerations

Can Approved Uses of Carbofuran Affect Human Health?

Risks of concern to human health have been identified for both occupational and dietary carbofuran exposure.

Potential exposure to carbofuran may occur through diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Carbofuran was found to be highly toxic via the oral route of exposure but was of low dermal toxicity in rats. Acute inhalation studies were not available. Carbofuran was a minimal eye irritant and was not a dermal sensitizer.

Acute overexposure to carbofuran can inhibit cholinesterase, an enzyme necessary for normal functioning of the nervous system. This can produce a variety of symptoms in animals and humans including ataxia, salivation, lacrimation, tremors and breathing difficulties. With carbofuran, cholinesterase inhibition can occur rather rapidly with exposure (within minutes) but rapidly recovers along with the cessation of any of the aforementioned cholinergic symptoms.

There was no evidence that carbofuran was carcinogenic or teratogenic. An assessment of mutagenic potential in a variety of in vitro and in vivo genotoxicity studies showed that carbofuran has weak mutagenic properties in bacterial and mammalian cells. A cancer risk assessment was not required. The nervous system was the main target of toxicity in rats, rabbits

[5] Federal Register (Volume 74, Number 93) Rules and Regulations.

and dogs. At higher dose levels, the male reproductive system of rats, rabbits and dogs also appear to be targeted by carbofuran. When carbofuran was given to pregnant animals, effects on the developing fetus were observed at doses that were greater than those that were toxic to the mother, indicating that the fetus is not more sensitive to carbofuran than the adult animal.

Residues in Food and Water

Dietary risks from food are of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Acute dietary exposure to carbofuran as a percentage of the acute reference dose ranges from 141% for adults aged 50+ years old to 733% for children aged 1 to 2 years old, and is 339% for the general population. The acute dietary exposure to carbofuran is higher than the acute reference dose for all population subgroups; therefore, it is of concern.

Chronic dietary exposure to carbofuran as a percentage of the acceptable daily intake ranges from 19% for adults aged 50+ years old to 76% for children aged 1 to 2 years old, and is 30% for the general population. The chronic dietary exposure to carbofuran is less than the acceptable daily intake for all population subgroups; therefore, it is not of concern.

An aggregate risk assessment combining exposure from food and drinking water was conducted using either estimated environmental concentrations (EECs) from the modelling assessment or EECs from monitoring data. The dietary risks from food and drinking water are of concern whether EECs from modelling or monitoring data are used.

The *Food and Drugs Act* prohibits the sale of food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for food purposes through the evaluation of scientific data under the *Pest Control Products Act.* Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. MRLs for carbofuran are currently established for carrots, onions, peppers, potatoes, rutabagas, turnips and strawberries. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. However, changes to this general MRL may be implemented in the future, as indicated in Information Note: Progress on Minimizing Reliance on the 0.1 Parts per Million as a General Maximum Residue Limit for Food Pesticide Residue, December 2009.

To protect the Canadian food supply and to mitigate dietary risks of concern, all MRLs for carbofuran must be amended or revoked. Notwithstanding the general MRL of 0.1 ppm, the intent of this action to amend or revoke these MRLs is to prevent residues of carbofuran in or on foods. As noted above, changes to regulation B.15.002(1) may be implemented in the future.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern.

There are currently no residential uses of carbofuran. Given that homeowners would not be applying the product, a risk assessment for this scenario was not conducted.

Occupational Risks from Handling Carbofuran

Both mixer/loader/applicator and post-application risks are of concern.

Risk estimates associated with certain mixing, loading and applying activities are of concern to the PMRA. Based on the precautions and directions for use on the existing carbofuran product labels, postapplication risks to workers performing activities, such as thinning, pruning and harvesting of most crops, did not meet current standards and are also of concern.

Environmental Considerations

What Happens When Carbofuran Is Introduced into the Environment?

Carbofuran poses a potential risk to terrestrial and aquatic organisms.

When carbofuran is released into the environment some of it can be found in soil and surface water. Carbofuran is highly mobile in soils and can therefore leach into groundwater and enter surface water in runoff. Carbofuran breaks down into several transformation products through hydrolysis, phototransformation and moderate biotransformation at rates that depend on environmental conditions. Hydrolysis is faster in water with a pH > 6 (basic conditions), with a half-life ranging from a few hours to 28 days. Carbofuran is stable to hydrolysis in acidic water (pH < 7). Phototransformation is fast in water, with a half-life of 6 days. Carbofuran is persistent in acidic soils (half life of 321 days) and moderately persistent in soils with a pH > 7 (half-life 149 days). Carbofuran is not expected to volatilize significantly and has a low potential for bioaccumulation in biota.

Carbofuran poses a risk to terrestrial and aquatic organisms. Birds and small wild mammals are at risk in and around the site of application due to the consumption of contaminated food items. These risks were determined to be of concern and cannot be mitigated.

Thirty three environmental incident reports from the United States and Canada were considered during the review of carbofuran, and indicated that exposure to carbofuran under the currently registered use pattern resulted in avian, small wild mammal and bee mortality.

Value Considerations

What Is the Value of Carbofuran?

For the control of some pests in agriculture, carbofuran is the only insecticide available, or there are few viable registered alternative products to carbofuran.

Carbofuran is absorbed by the host plant, providing a systemic mode of action in addition to contact action. It is effective in two ways:

- as a contact insecticide, killing target insects upon direct contact; and
- as an insecticide that works as a stomach poison, killing target insects upon ingestion of treated plants.

Being a systemic insecticide, carbofuran is absorbed and transported throughout the plant, imparting protection to the entire plant. Systemic insecticides are effective against insects with piercing-sucking mouthparts, such as leafhoppers, spittlebugs and tarnished plant bug, as the systemic insecticide moves within the vascular tissues and into plant cells where these pests feed.

As a systemic insecticide that acts upon ingestion, carbofuran is effective for the control of pests that otherwise could not be targeted by contact insecticides or non-systemic insecticides that act as a stomach poison, such as chewing insects, once they enter the host plants. For example, European corn borer larvae bore into the midrib of the leaf and migrate into the stalk of the plant or husk of the ear (corn), or feed inside the stems and fruit (pepper).

For canola, mustard, raspberry, strawberry and sugar beet, there are no registered (or viable) alternative active ingredients to carbofuran for the control of certain pests.

Measures to Minimize Risk

Based on the evaluation of available scientific information, the risks associated with carbofuran do not meet Health Canada's current standards for human health and environmental protection. Therefore, all products containing carbofuran will be phased out.

Next Steps

The PMRA has determined that carbofuran will be phased out. The PMRA did not receive indications from stakeholders suggesting the need for a transition strategy as part of the phase-out time lines. Therefore the time lines will be determined as per normal practice.

Other Information

The summaries of assessments found in the PRVD2009-11 serve as evaluation reports. Lists of references considered by the Agency in support of the registration decision are found in this Re-evaluation Decision. The relevant test data on which the decision is based are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service.

Any person may file a notice of objection regarding this decision on carbofuran within 60 days of the date of publication of this Re-evaluation Decision. For more information regarding the basis for objection (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

Appendix I Comments and Responses

One general comment was received from the public in support of the PMRA's proposal to phase out carbofuran. In addition, provincial representatives noted some important uses for carbofuran, for which alternatives are being developed.

The PMRA received written comments from FMC Corporation on May 21 and October 7, 2009, relating to the Proposed Re-evaluation Decision PRVD2009-11, *Carbofuran*.

Comments Pertaining to the Health Assessments

The health assessment-related comments from FMC have been summarized, and the corresponding responses are presented below.

1. Comment Relating to the Reference List, *PRVD2009-11 Page 6:*

It is unclear from the references and Appendix III which information was used in the human health risk assessment. Please provide a complete list with appropriate references for all registrant-submitted studies and all other information considered.

PMRA Response:

The reference list from the PRVD2009-11 only includes toxicology studies which were determined to be of sufficient quality and relevance to the risk assessment of carbofuran. Additional toxicology studies which were reviewed but were not considered adequate or relevant to the hazard characterization or dose-response analysis of carbofuran were not included in the reference list. The PMRA has updated the previous reference list with the recently reviewed registrant-submitted and published studies.

2. Comment Relating to the Use of Data Evaluation Reports (DERs), *PRVD2009-11 Page 6:*

It is unclear whether the US EPA summary decision documents or the study-specific DERs were used. Please clarify which documents were used.

PMRA Response:

The only study-specific DERs that were available to the PMRA were for studies found to be unacceptable. Therefore, these study-specific DERs were not included in the reference list presented in the PRVD2009-11.

Since the publication of the PRVD2009-11, two additional US EPA DERs became available and were considered in the updated risk assessment of carbofuran. One of these documents, PMRA #1848775, was a USEPA review of the Acute Range-Finding Study in PND11 rats (MRID 47143703), the Time-Course Study in Adult and PND11 Rats (MRID 47143704) and the Cholinesterase Depression Study in PND11 and Adult Rats (MRID 47143705). As well, PMRA #1848744 was a US EPA review of the 21-day Dermal Toxicity Study in Rats (MRID 47143702) and the 7-day Dermal Toxicity Study in Rats (MRID 47143701). Full references for these studies have been included in the updated reference list.

3. Comment Relating to New Interim and New Completed Toxicology Studies, *PRVD2009-11 Page 6:*

The following FMC-generated toxicology studies were submitted to PMRA but are not referenced in the PRVD2009-11:

- Acute Oral ChE Inhibition study in Day 11 & Adult Rats (Interim Report)
- Acute Oral Time Course of ChE Depression in Day 11 & Adult Rats (Interim Report)
- 21-Day Dermal Toxicity in SD Rats (Interim Report)
- 7-Day Dermal Toxicity in SD Rats (US EPA MRID 47143701)

The interim reports are now complete, and have been submitted to the US EPA. The following studies will be submitted to PMRA:

- Acute Oral Dose Range Finding (USEPA MRID 47143703) and ChE Inhibition Studies (USEPA MRID 47143705) in Day 11 & Adult Rats
- Acute Oral Time Course of ChE Depression in Day 11 & Adult Rats (USEPA MRID 47143704)
- 21-Day Dermal Toxicity in SD Rats (USEPA MRID 47143702)

PMRA Response:

These acute oral comparative cholinesterase inhibition and short-term dermal toxicity studies (and the corresponding interim reports) conducted with rats were recently reviewed by the PMRA and as noted in the response to question 1, have been included in the updated reference list. Both sets of studies were considered acceptable for risk assessment purposes by the PMRA. Results and conclusions from these studies are presented below.

Although results were presented for the level of erythrocyte cholinesterase inhibition in the set of oral studies, these data were not used for risk assessment purposes for either PND11 pups or adult rats. The PMRA had little confidence in the results for erythrocyte cholinesterase activity across all dose groups in pups and adults since several measurements failed to meet the acceptance criteria for reproducibility established by the study laboratory, and the results were highly variable. Due to the inability to accurately measure and reproduce the erythrocyte cholinesterase data in these studies, the PMRA did not determine a NOAEL for erythrocyte cholinesterase inhibition in both genders of the PND11 pups and adult rats.

In contrast to the erythrocyte cholinesterase results, the measurements for brain cholinesterase activity were considered acceptable by the PMRA. Dose-dependent and biologically significant reductions in brain cholinesterase activity were noted in both PND11 pups and adult male rats at all doses. Female adult rats also experienced biologically significant decreases in brain cholinesterase activity in comparison to controls but only at the two highest dose levels.

Based on brain cholinesterase inhibition, a LOAEL of 0.03 mg/kg bw was set for PND11 pups and male adults. A corresponding NOAEL was not established. The NOAEL in female adult rats was 0.03 mg/kg bw based on brain cholinesterase inhibition noted at the LOAEL of 0.1 mg/kg bw. These effect levels were in agreement with those set by the USEPA. In an effort to further refine the endpoints relating to brain cholinesterase activity, a benchmark dose (BMD) analysis was performed. The results from the BMD

analysis determined that the effect on brain cholinesterase activity in pups was more pronounced than in adult males. The $BMDL_{10}$ for adult males was 0.015 mg/kg bw whereas the $BMDL_{10}$ for pups (both genders combined) was 0.011 mg/kg bw. The $BMDL_{10}$ value of 0.011 mg/kg bw was used for risk assessment purposes as it was based on the more sensitive subpopulation.

In the dermal toxicity studies, brain cholinesterase activity decreased in a dose-dependent and biologically significant manner in both male and female rats starting from the second highest dose level of 50 mg/kg bw/day. Erythrocyte cholinesterase activity was not significantly affected at any dose level in either gender. In these dermal toxicity studies, the NOAEL was determined to be 25 mg/kg bw/day based on reductions in brain cholinesterase activity level at the LOAEL of 50 mg/kg bw/day in both genders of rats.

4. Comment Relating to the Critical Study for Derivation of the Acute Reference Dose (ARfD), *PRVD2009-11 Page 21:*

Please provide the full reference for the critical study for derivation of the ARD.

PMRA Response:

The previously set Acute Reference Dose (ARfD) of 0.0002 mg/kg bw (LOAEL = 0.05 mg/kg bw, UF = 300) was based on two published acute oral cholinesterase activity studies in the rat. The full references for these studies were presented on page 124 of the PRVD2009-11 as follows:

- Ferguson, P.W., ***et al.*** (1984). Carbofuran metabolism and toxicity in the rat. *Fundamental and Applied Toxicology,* 4:14-21. (PMRA # 1421578).
- Cambon, C., *et al*. (1979). Effect of the insecticidal carbamate derivatives (carbofuran, pirimicarb, aldicarb) on the activity of acetylcholinesterase in tissues from pregnant rats and fetuses. *Toxicology and Applied Pharmacology,* 49: 203-208. (PMRA# 1421577).

The previously set ARfD has been revisited in light of the recently reviewed acute oral cholinesterase inhibition studies. From the new cholinesterase inhibition studies, a $BMDL_{10}$ of 0.011 mg/kg bw was established based on 10% brain cholinesterase inhibition in PND11 pups. Standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation were applied. With respect to the *Pest Control Products Act* (PCPA) factor, all of the required studies relevant to assessing risks to infants and children were available. This included reproductive toxicity, developmental toxicity, developmental neurotoxicity and acute comparative cholinesterase studies. There was uncertainty about whether erythrocyte cholinesterase inhibition was a more sensitive endpoint than brain cholinesterase inhibition; however, there was no clear difference between these endpoints noted throughout the carbofuran database. These acute comparative cholinesterase studies examined the most sensitive population and the most sensitive indicator of toxicity (cholinesterase inhibition). Accordingly, the PCPA factor was reduced to 1-fold resulting in a composite assessment factor of 100. Applying the composite assessment factor of 100 to the $BMDL_{10}$ value of 0.011 mg/kg bw resulted in an updated ARfD of 0.00011 mg/kg bw. This reference dose is slightly lower than the previous ARfD established by the PMRA. However, it should be noted that a recently published acute comparative cholinesterase study (Moser *et* al.,

2010)[6] identified a LOAEL of 0.1 mg/kg bw based on brain cholinesterase inhibition in PND11 pups. If this endpoint was used for the ARfD, a 3-fold uncertainty factor would be applied for use of a LOAEL as well as the standard 100-fold uncertainty factors and a PCPA factor of 1-fold. The resultant ARfD of 0.0003 mg/kg bw would be similar to the updated ARfD of 0.0001 mg/kg bw. The $BMDL_{10}$ reported for brain cholinesterase inhibition in the Moser paper was 0.00098 mg/kg bw, a value lower than the current point of departure. The lack of individual animal data however, precluded verification of the $BMDL_{10}$. In addition, the confidence limits for the $BMDL_{10}$ values spanned several orders of magnitude, reflecting considerable uncertainty in that estimate. Consequently, the FMC comparative cholinesterase studies were used for risk assessment. It is possible that the updated reference dose could be further altered (albeit in a more conservative manner) upon full review of the Moser study.

As previously stated in the PRVD2009-11 for the Acceptable Daily Intake (ADI) of carbofuran, the quick-acting and reversible nature of carbamate inhibition was considered as justification to default to the acute effect level which was lower than the subchronic and chronic effect levels. In the case of carbofuran, long-term exposures were considered as multiple daily exposures with each causing transient inhibition of cholinesterase with potential resulting toxicity. As such, the $BMDL_{10}$ of 0.011 mg/kg bw was selected for the ADI derivation based on inhibition of brain cholinesterase activity in pups from the acute comparative cholinesterase studies. Similar to the ARfD, standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation along with a PCPA factor of 1-fold were applied to the $BMDL_{10}$ value of 0.011 mg/kg bw for determining the ADI. The resulting updated ADI of 0.00011 mg/kg bw/day, was slightly lower than the previously established ADI.

Since there were no repeat-dose inhalation studies available for the inhalation risk assessment of carbofuran, it was assumed that absorption via inhalation exposure was equivalent to oral absorption. As such, for short- and intermediate-term exposures, the acute comparative cholinesterase inhibition studies in rats were used for the inhalation risk assessment. The $BMDL_{10}$ of 0.011 mg/kg bw was chosen, based on inhibition of brain cholinesterase activity in pups, along with a target margin of exposure (MOE) of 100. This MOE accounted for standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation.

In light of the recently reviewed dermal toxicity studies, the short- and intermediate-term dermal risk assessment of carbofuran was also revisited. Previously, a 21-day dermal toxicity study conducted with rabbits was used for the dermal risk assessment. The dermal NOAEL of 10 mg/kg bw/day was selected with a target MOE of 100, accounting for standard uncertainty factors (10-fold for intraspecies variability and 10-fold for interspecies extrapolation). The recently reviewed dermal toxicity studies were of the same duration as the previous dermal toxicity study; however, the species examined in the newer studies was rats instead of rabbits. The dermal study in rats was selected over the rabbit study because there was more extensive reporting in comparison to the rabbit study and hence, higher confidence in the rat study. Results of these recently reviewed

[6] Moser *et al*. (2010). Time-Course, Dose-Response and Age Comparative Sensitivity of *N*-Methyl Carbamates in Rats. *Toxicological Sciences*, 114(1): 113-123.

studies identified a NOAEL of 25 mg/kg bw/day based on reductions in brain cholinesterase activity at the next dosage level of 50 mg/kg bw/day in both genders of rats. Standard uncertainty factors (10-fold for intraspecies variability and 10-fold for interspecies extrapolation) were applied. In addition, an uncertainty factor of 3-fold was applied since the dermal study was conducted in adult animals and not in the young, where a sensitivity issue has been established via the oral route of exposure (as observed in the acute comparative cholinesterase inhibition study). The resulting target MOE was 300. This MOE is considered protective of all populations including nursing infants and the unborn children of exposed female workers. Similar to the other reference doses, this reference dose is also slightly lower than the dermal risk assessment values previously set by the PMRA.

5. Comment Relating to Incident Reports, *PRVD2009-11 Page 25:*

The number of possible carbofuran poisoning incidents reported by the USEPA (i.e. >700) is incorrect and misleading. Occupational incidents are few in number and have demonstrated a downward trend. There are only 11 incidents between 1972 and 2006 that clearly result from carbofuran use in accordance with the label.

PMRA Response:
Between 2007 and 2009, there was one PMRA incident report relating to human health that was included in the PRVD2009-11. As of February 16, 2010, no additional incident reports relating to human health were submitted to the PMRA. The number of possible carbofuran poisoning incidents reported in the United States was obtained from a published document. This information reported by the USEPA was considered in a weight-of-evidence approach for our current risk assessment. As such, the information presented for incident reports in the PRVD2009-11 will be retained as is.

6. Comment Relating to Toxicology-Related Data Gaps (i.e. Comparative Cholinesterase Study), *PRVD2009-11 Page 25:*
The FMC-generated interim and completed toxicology studies were submitted to the PMRA to address the data gap (see list in #3).

PMRA Response:
The acute oral cholinesterase inhibition studies were recently reviewed and were considered acceptable for risk assessment purposes by the PMRA. Based on the inclusion of these cholinesterase studies in the current risk assessment of carbofuran, the PMRA reference list has been updated to reflect these changes.

The following data gaps presented in the PRVD2009-11 are still outstanding and include an acute inhalation study, a dermal irritation study and a short-term inhalation study. The requirement for an acceptable comparative cholinesterase inhibition study has been satisfied.

7. Comment Relating to Dietary Risk (Exposure from Food):

The PMRA has stated the dietary risks from food are of concern, however the assessment used as the basis for the preliminary conclusion is not adequately refined to use as the basis for a final regulatory decision. Additional refinements, including percent crop treated, percentages of crop imported and the incorporation of cholinesterase reversibility, are appropriate and will significantly reduce the food exposure estimates. Also, no consideration was given to mitigation measures that may result in acceptable risk even using the overly conservative approach contained in the PRVD2009-11. Those mitigation measures may include the cancellation of certain crop uses, reducing the use rates, or geographically restricting certain uses. As the methodology used by PMRA is similar to the EPA's approach, there are several documents that have been provided to EPA that will provide PMRA with valuable insights to appropriate refinements proposed by the registrant, and in many cases, accepted by the EPA.

PMRA Response:

The dietary risk assessment in the PRVD2009-11 included the following refinements:

- Use of monitoring data from Canadian Food Inspection Agency (CFIA) and United States Department of Agriculture Pesticide Data Program;
- Canadian percent crop treated;
- U.S. percent crop treated;
- Domestic and imported crop data;
- Processing factors.

Mitigation measures involving changes in use pattern (e.g. cancellation of certain crop uses) were not considered, as FMC had indicated to PMRA that they were continuing to support all uses. Regarding cholinesterase reversibility, the USEPA[7] did consider this and concluded that the risk to carbofuran is not substantively overestimated using the current exposure models and the 24-hour approach. This is due to the fact that exposure to carbofuran occurs predominantly through single eating events and not from multiple events that occur throughout the day.

The dietary risk assessment has been updated as follows:

- Use of updated toxicological reference doses;
- Use of the most recent available monitoring data (2004-2008) from CFIA;
- Exclusion of the emergency uses on turnips and rutabagas;
- Incorporation of drinking water residue estimates from modeling and monitoring data;
- Consideration of the U.S. revocation of all tolerances that took effect after December 31, 2009.

[7] U.S. EPA, Carbofuran Acute Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Reregistration Eligibility Decision, April 29, 2009 [EPA-HQ-OPP-2005-0162-0574]

The updated dietary risk assessment is considered to be as refined as possible with the data available to PMRA. Results of the updated dietary risk assessment are as follows:

- Chronic exposure to carbofuran through food-only is 76% of the ADI for the most exposed subpopulation of children 1-2 years of age and is 30% of the ADI for the general population; therefore, it is not of concern. However, acute exposure to carbofuran through food-only is 733% of the ARfD for the most exposed subpopulation of children 1-2 years of age and is 339% of the ARfD for the general population; therefore, it is of concern. The primary acute risk drivers are orange[8] (juice, ~ 22-58%) and field corn (syrup, ~ 12-41%). Regarding residues on citrus crops, carbofuran is not registered for this use. However, carbosulfan, which is registered for this use in many countries, degrades to carbofuran. It is believed that this is the basis of carbofuran residues in/on citrus commodities reported in the CFIA residue monitoring program.

- **Based on modelling estimates** for drinking water, aggregate (i.e. food and drinking water) chronic exposure to carbofuran is 195% of the ADI for the most exposed subpopulation of all infants (less than 1 year of age); therefore, it is of concern. The primary risk driver is water (~ 61-88%). Aggregate acute exposure to carbofuran is >10000% of the ARfD for the most exposed subpopulation of all infants (less than 1 year of age) and is 5229% of the ARfD for the general population; therefore, it is of concern. The primary acute dietary risk driver is water (~ 84-92%).

- **Based on monitoring data** for drinking water, aggregate (i.e. food and drinking water) chronic exposure to carbofuran is 79% of the ADI for the most exposed subpopulation of children of 1-2 years of age and is 32% of the ADI for the general population. Note that monitoring data are not typically used to assess acute exposure because the data does not capture the peak residues, and that the following aggregate acute exposure results are presented for information purposes only. The aggregate acute exposure to carbofuran is 1842% of the ARfD for the most exposed subpopulation of all infants (less than 1 year of age) and is 775% of the ARfD for the general population. The primary acute dietary risk driver is water (~ 51-76%).

The dietary risks from food and drinking water are of concern whether estimated environmental concentrations (EECs) from modelling or monitoring data are used.

[8] Carbosulfan is a pesticide registered for use in some countries (Australia, Cambodia, India, Philippines, Viet Nam, Denmark, Germany, Hungary, United Kingdom, and many African countries). Carbosulfan is used on citrus fruit. The parent compound carbosulfan degrades to carbofuran as a major metabolite. Codex establishes an MRL of 2 ppm in/on citrus for Carbofuran based on the use of Carbosulfan.

8. Comment Relating to Dietary Risk (Exposure from Water):

PMRA did not consider potential exposure from drinking water sources in the PRVD2009-11, as the Agency's current dietary assessment exceeded the level of concern using potential exposures from food only. FMC believes an appropriately refined dietary risk assessment for food exposure will result in acceptable exposures and thus an aggregate assessment considering contributions from food and drinking water will be required.

FMC has submitted numerous drinking water assessments and supporting materials to quantify the potential for carbofuran reaching ground and surface water sources used as drinking water.

PMRA Response:

The dietary risk assessment in the PRVD2009-11 did not include drinking water since exposure to carbofuran through food-only was of concern. Since then, the dietary risk assessment has been updated and includes drinking water residue values from modelling estimates and monitoring data as noted in the response to comment # 7.

The EECs of carbofuran in drinking water derived from water modelling and the available water monitoring data are summarized in the table below.

An aggregate (i.e. food and drinking water) risk assessment was conducted using either EECs from the modelling assessment or EECs from monitoring data. See response to comment #7 for a summary of results.

Concentrations for Carbofuran in Drinking Water Sources Estimated from Models and Monitoring Data*

	Groundwater Concentration (µg/L)		Surface Water Acute Concentration (µg/L)		Surface Water Chronic Concentration (µg/L)	
	Acute	Chronic	Reservoir [4]	Dugout [4]	Reservoir [6]	Dugout [6]
Modelling Assessment	0.69[1]	0.57[2]	**29**	42	**2.5**	5.8
Monitoring Assessment	1.4[3]	0.067[7]	**4.0**[5]		**0.12**[7]	

* Bold numbers were used in the dietary exposure and risk assessment

[1] 90th percentile of daily averages from LEACHM

[2] 90th percentile of yearly average from LEACHM

[3] 95th percentile of the maximum detected concentration from groundwater monitoring studies

[4] 90th percentile of the annual peak concentrations predicted by PRZM-EXAMS

[5] 95th percentile of the maximum detected concentrations from surface water monitoring studies

[6] 90th percentile of the annual average concentrations predicted by PRZM-EXAMS

[7] 95th percentile of the arithmetic means of all the relevant (groundwater or surface water) monitoring studies (includes detects and non-detects)

9. Comment Relating to Occupational Risk:

PMRA has stated that certain mixing, loading and applying activities, as well as some post-application activities, are of concern. FMC believes the engineering controls for the carbofuran products affords mixers, loaders and applicators acceptable protection from potential exposure and the risk assessment inputs and assumptions are overly conservative. Although the overall approach used by the EPA in establishing an assessment of risk from dermal and inhalation exposure differs somewhat from the PMRA's approach, there are several documents that have been provided to EPA that will provide PMRA with valuable insights to appropriate refinements proposed by the registrant with regard to occupational risk.

PMRA Response:

The PMRA's occupational risk assessment presented in the PRVD2009-11 indicated that certain current label uses for carbofuran present risks of concern. The risk assessment was in keeping with current label directions, and the assumptions applied were not overly conservative. It should be noted that no comments were received from Canadian stakeholders to suggest alternative assumptions. The methods and refinements applied in the occupational risk assessment were consistent with the current practices of the PMRA. The calculated Aggregate Risk Indices (ARI) and Restricted-entry Intervals (REIs) were presented in the PRVD2009-11.

Following the comment period for the PRVD2009-11, closed mixing and loading systems along with revised toxicological endpoints were considered in the occupational risk assessment. The recent toxicological re-evaluation of carbofuran indicates an inhalation risk that can be mitigated only when respirators and additional engineering controls (closed mixing and loading) are considered.

According to the revised occupational risk assessment, both mixer/loader/applicator and post-application exposure are of concern for most crops. The mixer/loader/applicator risk assessments yielded Aggregate Risk Indices (ARIs) that were below target (see Table 1.0 for details). In addition, target MOEs were not met for the majority of post-application scenarios when applying the label Restricted-entry Interval (REI) of 2 days. Increased REIs were calculated in order to mitigate post-application exposure. Although most of the revised REIs are considered to be agronomically feasible, some are not.

The risk to mixer/loader/applicators without closed/mixing and loading systems is of particular concern, given that relatively low ARIs were determined (see Table 2.0 for details). No further mitigation measures are available for inhalation risk beyond limiting the amount of active ingredient handled per day. The feasibility of requiring closed systems and reducing the application rates of current end use products is unknown.

Mitigation measures that were considered include closed mixing and loading systems, closed cabs for groundboom equipment, increased personal protective equipment, as well as increased application intervals and restricted entry intervals.

10. Comment relating to "Measures to Minimize Risk":

In the PRVD2009-11, PMRA states that additional mitigation measures are not being proposed at this time. FMC believes that all refinements to the various risk assessments should be incorporated. If following the completion of an appropriately refined risk assessment, risks of concern remain then risk mitigation measures should be considered.

PMRA Response:

The updated dietary risk assessment is considered to be as refined as possible with the data available to PMRA. The dietary risks from food and drinking water are of concern (see response to comment #7).

Table 1.0 M/L/A exposure estimates and MOEs with Maximum PPE and Closed Mixing and Loading[a]

Crop	Form[b]	Application Equipment [c]	Application Rates[d] (kg ai/ha)	Area treated per day[e] (ha)	Daily Exposure (µg/kg/day)		Margins of Exposure		Aggregate Risk Indices[j]
					Dermal[f]	Inhalation[g]	Dermal[h]	Inhalation[i]	
canola (rapeseed)	SU	aerial - M/L	0.132	400	5.84	0.01	4282	1326	6.87
		aerial - A			7.29	0.05	3431	208	1.76
		groundboom (c)		300	6.88	0.04	3634	274	2.23
		groundboom (f)		100	2.29	0.01	10903	822	6.70
sunflower	SU	groundboom (c)	0.132	300	6.88	0.04	3634	274	2.23
		groundboom (f)		100	2.29	0.01	10903	822	6.70
corn (field, silage, sweet)	SU	aerial - M/L	0.528	400	23.35	0.03	1071	331	1.72
		aerial - A			29.15	0.21	858	52	0.44
		groundboom (c)		140	12.84	0.07	1947	147	1.20
		groundboom (f)		80	7.34	0.04	3407	257	2.09
mustard	SU	aerial - M/L	0.132	400	5.84	0.01	4282	1326	6.87
		aerial - A			7.29	0.05	3431	208	1.76
		groundboom (c)		300	6.88	0.04	3634	274	2.23
		groundboom (f)		100	2.29	0.01	10903	822	6.70
green pepper	SU	groundboom (c)	0.528	80	7.34	0.04	3407	257	2.09
		groundboom (f)		30	2.75	0.02	9086	685	5.58
potato	SU	groundboom	0.528	80	7.34	0.04	3407	257	2.09
sugar beet	SU	groundboom (c)	1.123	100	19.51	0.11	1281	97	0.79
		groundboom (f)		30	5.85	0.03	4271	322	2.63
raspberry	SU	groundboom (c)	1.2	80	16.68	0.10	1499	113	0.92
		groundboom (f)		30	6.25	0.04	3998	301	2.46
strawberry	SU	groundboom (c)	1.2	80	16.68	0.10	1499	113	0.92
		groundboom (f)		30	6.25	0.04	3998	301	2.46

[a] Mixer/Loader: A closed mixing and loading system with chemical resistant coveralls over a single layer with chemical resistant gloves and a suitable respirator. Groundboom Applicator: A closed cab with chemical resistant coveralls over a single layer (no gloves). Aerial Applicator: A single layer (long sleeved shirt and long pants), no gloves.

[b, c] SU = Suspension; M/L = Mixer/Loader; A = Applicator; Form = Formulation; groundboom (c) = custom groundboom application; groundboom (f) = farmer groundboom application.

[d] Maximum listed label rate in kilograms of active ingredient per hectare (kg ai/ha).

[e] Based on default assumptions and stakeholder input.

[f] Where dermal exposure µg/kg/day = (unit exposure x area treated x rate)/70 kg bw.

[g] Where inhalation exposure µg/kg/day = (unit exposure x area treated x rate)/70 kg bw; includes a 90% protection factor for respirators used by Mixer/Loaders.

[h] Based on a dermal NOAEL of 25 mg/kg bw/day and a target dermal MOE of 300.

[i] Based on a $BMDL_{10}$ of 0.011 mg/kg bw/day and a target inhalation MOE of 100.

[j] Aggregate Risk Index = 1 / ((1/(Dermal MOE/Target Dermal MOE))+(1/(Inhalation MOE/Target inhalation MOE))). Shaded cells indicate calculated ARIs that do not meet the target of 1.

Table 2.0 M/L/A exposure estimates and MOEs with Maximum PPE and Open Mixing and Loading[a]

Crop	Form[b]	Application Equipment[c]	Application Rates[d] (kg ai/ha)	Area treated per day[e] (ha)	Daily Exposure (µg/kg/day)		Margins of Exposure		Aggregate Risk Indices[j]
					Dermal[f]	Inhalation[g]	Dermal[h]	Inhalation[i]	
canola (rapeseed)	SU	aerial - M/L	0.132	400	21.94	0.12	1139	91	0.74
		aerial - A			7.29	0.05	3431	208	1.76
		groundboom (c)		300	18.96	0.12	1319	88	0.74
		groundboom (f)		100	6.32	0.04	3956	265	2.21
sunflower	SU	groundboom (c)	0.132	300	18.96	0.12	1319	88	0.74
		groundboom (f)		100	6.32	0.04	3956	265	2.21
corn (field, silage, sweet)	SU	aerial - M/L	0.528	400	87.77	0.48	285	23	0.18
		aerial - A			29.15	0.21	858	52	0.44
		groundboom (c)		140	35.39	0.23	706	47	0.39
		groundboom (f)		80	20.22	0.13	1236	83	0.69
mustard	SU	aerial - M/L	0.132	400	21.94	0.12	1139	91	0.74
		aerial - A			7.29	0.05	3431	208	1.76
		groundboom (c)		300	18.96	0.12	1319	88	0.74
		groundboom (f)		100	6.32	0.04	3956	265	2.21
green pepper	SU	groundboom (c)	0.528	80	20.22	0.13	1236	83	0.69
		groundboom (f)		30	7.58	0.05	3297	221	1.84
potato	SU	groundboom	0.528	80	20.22	0.13	1236	83	0.69
sugar beet	SU	groundboom (c)	1.123	100	53.77	0.35	465	31	0.26
		groundboom (f)		30	16.13	0.1	1550	104	0.86
raspberry	SU	groundboom (c)	1.2	80	45.96	0.30	544	36	0.30
		groundboom (f)		30	17.23	0.11	1451	97	0.81
strawberry	SU	groundboom (c)	1.2	80	45.96	0.30	544	36	0.30
		groundboom (f)		30	17.23	0.11	1451	97	0.81

[a] Mixer/Loader: An open mixing and loading system with chemical resistant coveralls over a single layer with chemical resistant gloves and a suitable respirator. Groundboom Applicator: A closed cab with chemical resistant coveralls over a single layer (no gloves). Aerial Applicator: A single layer (long sleeved shirt and long pants), no gloves.

[b, c] SU = Suspension; M/L = Mixer/Loader; A = Applicator; Form = Formulation; groundboom (c) = custom groundboom application; groundboom (f) = farmer groundboom application.

[d] Maximum listed label rate in kilograms of active ingredient per hectare (kg ai/ha).

[e] Based on default assumptions and stakeholder input.

[f] Where dermal exposure µg/kg/day = (unit exposure x area treated x rate)/70 kg bw.

[g] Where inhalation exposure µg/kg/day = (unit exposure x area treated x rate)/70 kg bw; includes a 90% protection factor for respirators used by Mixer/Loaders.

[h] Based on a dermal NOAEL of 25 mg/kg bw/day and a target dermal MOE of 300.

[i] Based on a $BMDL_{10}$ of 0.011 mg/kg bw/day and a target inhalation MOE of 100.

[j] Aggregate Risk Index = 1 / ((1/(Dermal MOE/Target Dermal MOE))+(1/(Inhalation MOE/Target inhalation MOE))). Shaded cells indicate calculated ARIs that do not meet the target of 1.

Comments Pertaining to the Environmental Assessment

1. Comment:

The complete set of ecological toxicity studies provided to the EPA and PMRA should be considered by PMRA.

PMRA Response:

The following FMC-generated ecotoxicology studies were submitted to PMRA for consideration in the ecological risk assessments.

- Determination of the time course of brain cholinesterase (ChE) activity depression and recovery in Northern Bobwhite (*Colinus virginianus*) following scheduled oral dosing with Furadan 4F (USEPA MRID 47107601)
- Assessment of mallard duck (*Anas platyrynchos*) avoidance to feed containing Furadan 4F (USEPA MRID 47128701)
- Assessment of the differential toxicity of carbofuran to mallard ducks when dosed as a single bolus versus the same dose mixed in feed (USEPA MRID 47143706)
- Assessment of the differential toxicity of carbofuran to northern bobwhite quail when dosed as a single bolus versus the same dose mixed in feed (USEPA MRID 47152901)

The USEPA Scientific Advisory Panel (SAP) reviewed these four studies from FMC. The SAP agreed that the results would not alter the risk conclusions of the EPA regarding birds. PMRA attended the SAP and concluded that the results of these studies would not alter the risk conclusions regarding birds.

2. Comment:

As the overall approaches used by the EPA and PMRA are similar in assessing non-target organism risk, there are numerous relevant studies, assessments, presentations and summaries that have been provided to the EPA and will provide PMRA with valuable insights to developing an appropriately refined and adequately conservative non-target organism risk assessment.

PMRA Response:

FMC did not provide any comments to the PMRA that were specific to the Canadian environmental risk assessment. The vast majority of the documents submitted to the EPA in reference to the assessment of risk to non-target organisms are specific to the EPA risk assessment and the Science Advisory Panel (SAP) meeting on carbofuran.

The Canadian risk assessment for aquatic organisms and mammals made use of Canadian specific scenarios and assumptions that differ from those used in the USEPA assessment. As such, PMRA cannot provide responses to comments that do not directly relate to the Canadian risk assessment.

The Canadian assessment of risk to birds did make use of the USEPA avian risk assessment as one line of evidence of the potential risk that carbofuran poses to avian species. However, other lines of evidence were also used in addition to the USEPA risk assessment, including a special review of carbofuran by Environment Canada and Canadian incident reports demonstrating adverse effects in bird species. FMC did not provide any comments specific to the Canadian risk assessment and the multiple lines of evidence used to determine potential risk to birds.

References

Studies Considered in Chemistry Assessment

A. Studies/Information Provided by the Applicant/Registrant

PMRA Document Number: 1625973
Reference: Technical Chemistry File CAF-FMC-16. Carbofuran Processes, Impurities, Extended Scan HPLC Chromatograph Of Bayer Processed Carbofuran, Carbofuran Impurities, Data Numbering Code: 2.99

PMRA Document Number: 1626039
Reference: Technical Chemistry File CAF-FMC-16. Furadan (Carbofuran) Change In Manufacturing Process, Raw Material Specifications, Analytical Test Methods., Data Numbering Code: 2.99

Studies Considered in Health Assessment

A. Studies/Information Provided by the Applicant/Registrant

PMRA Document Number: 1347457
Reference: 2005, A Study On The Potential Toxicity Of Carbofuran To The Male Reproductive System, Data Numbering Code: 4.3.8

PMRA Document Number: 1369077
Reference: 2005, Amended final report and Acute dose- response study of carbofuran technical administered by gavage to adult and postnatal day 11 male and female CD (Sprague Dawley) rats, DACO: 4.8.

PMRA Document Number: 1317568
Reference: 2005, Acute Range-finding Study Of Carbofuran Technical (CAS No. 1563-66-2A) Dministered By Gavage To Postnatal Day 11 Male And Female CD (Sprague-Dawley) Rat Pups, Data Numbering Code: 4.2.1 Confidential Business Information

PMRA Document Number: 1347455
Reference: 2005, Acute Time-course Study Of Carbofuran Technical Administered By Gavage To Adult And Postnatal Day 11 Male And Female CD (Sprague-Dawley) Rats, Data Numbering Code: 4.2.9

PMRA Document Number: 1317567
Reference: 2005, Acute Time-course Study Of Carbofuran Technical Administered By Gavage To Adult And Postnatal Day 11 Male And Female CDO (Sprague-Dawley) Rats, Data Numbering Code: 4.2.1 Confidential Business Information

PMRA Document Number: 1347456
Reference: 2006, Acute Range-finding Study Of Carbofuran Technical Administered By Gavage To Postnatal Day 11 Male And Female CD (Sprague-Dawley) Rat Pups, Data Numbering Code: 4.2.9

PMRA Document Number: 1445914
Reference: 2007, 21-Day dermal toxicity study of Carbofuran technical in Crl:CD(SD) rats, DACO: 4.3.3.

PMRA Document Number: 1573320
Reference: 2007, 7-Day dermal toxicity study of Carbofuran technical in Crl:CD(SD) rats, DACO: 4.3.8.

PMRA Document Number: 1573317
Reference: 2007, Acute oral (gavage) dose range-finding study of cholinesterase depression from Carbofuran technical in Juvenile (day 11) rats, DACO: 4.5.12.

PMRA Document Number: 1445912
Reference: 2007, Acute oral (gavage) time course study of cholinesterase depression from Carbofuran technical in Adult and Juvenile (day 11 postpartum) rats, DACO: 4.5.12.

PMRA Document Number: 1445913
Reference: 2007, Cholinesterase depression in Juvenile (day 11) and Adult rats following acute oral (gavage) dose of Carbofuran technical, DACO: 4.5.12.

B. Additional Information Considered

Published

PMRA Document Number: 1421568
Reference: 1999, Guidelines For Drinking-water Quality, Second Edition, Addendum To Volume 2. Health Criteria And Other Supporting Information, Data Numbering Code: 12.5.4

PMRA Document Number: 1421567
Reference: W.H. Hickox, 2000, Public Health Goal For Carbofuran In Drinking Water, California Environmental Protection Agency, Data Numbering Code: 12.5.4

PMRA Document Number: 1421569
Reference: M.I. Yousef et. al., 1995, Toxic Effects Of Carbofuran And Glyphosate On Semen Characteristics In Rabbits. Journal of Environmental Science and Health. B30 (4) pp. 513-534, Data Numbering Code: 4.8

PMRA Document Number: 1421570
Reference: Y.D.S. Seneviratne et. al., 1992, Effect Of Carbofuran (a Carbomate Insecticide) On Human Sperm Motility In Vitro. Medical Science Research. Volume 20: pp. 361-362, Data Numbering Code: 4.8

PMRA Document Number: 1421571
Reference: H.W. Dorough, 1968, Metabolism Of Furadan (NIA-10242) In Rats And Houseflies. Journal Of Agricultural And Food Chemistry. Volume 16(2): Pg. 319-325, Data Numbering Code: 4.8

PMRA Document Number: 1421574
Reference: Y.N.A. Jayatunga et. al., 1998, Effects Of Mid-term Exposure To Carbofuran On Pregnancy Outcome Of Rats. Medical Science Research. Volume 26: pp. 679-683, Data Numbering Code: 4.8

PMRA Document Number: 1421576
Reference: Y.N.A. Jayatunga et. al., 1998, Hazardous Effects Of Carbofuran On Pregnancy Outcome Of Rats. Medical Science Research. Volume 26, pp. 33-37, Data Numbering Code: 4.8

PMRA Document Number: 1421577
Reference: C. Cambon et. al., 1979, Effect Of The Insecticidal Carbamate Derivatives (Carbofuran, Pirimicarb, Aldicarb) On The Activity Of Acetylcholinesterase In Tissues From Pregnant Rats And Fetuses. Toxicology And Applied Pharmacology. Volume 49: pp. 203-208, Data Numbering Code 4.8

PMRA Document Number: 1421578
Reference: P.W. Ferguson et. al., 1984, Carbofuran Metabolism And Toxicity In The Rat. Fundamental And Applied Toxicology. Volume 4: pp. 14-21, Data Numbering Code: 4.8

PMRA Document Number: 1421579
Reference: C. Thomas et. al., 1979, C. Thomas et. al., Biliary Excretion Of Carbamate Insecticides In The Rat. Pesticide Biochemistry And Physiology. Volume 11: pp. 56-63, Data Numbering Code: 4.8

PMRA Document Number: 1421583
Reference: P.N. Baligar And B.b. Kaliwal, 2003, Temporal Effects Of Carbofuran, A Carbamate Insecticide In The Interruption Of Estrous Cycle And Follicular Toxicity In Female Swiss Albino Mice. Bulletin of Environmental Contamination and Toxicology. Volume 71. pp. 422-428, Data Numbering Code 4.8

PMRA Document Number: 1421584
Reference: L.K.S. Chauhan et. al., 2000, Induction Of Chromosome Aberrations, Micronucleus Formation And Sperm Abnormalities In Mouse Following Carbofuran Exposure. Mutation Research. Volume 465: pp. 123-129, Data Numbering Code: 4.8

PMRA Document Number: 1421585
Reference: P.N. Baligar And B.B. Kaliwal, 2002, Reproductive Toxicity Of Carbofuran To The Female Mice: Effects On Estrous Cycle And Follicles. Industrial Health. Volume 40: pp. 345-352, Data Numbering Code: 4.8

PMRA Document Number: 1421586
Reference: N. Pant et. al., 1997, In Utero And Lactational Exposure Of Carbofuran To Rats: Effect On Testes And Sperm. Human And Experimental Toxicology. Volume 16: pp. 267-272, Data Numbering Code: 4.8

PMRA Document Number: 1421587
Reference: N. Pant et. al., 1995, Effect Of Oral Administration Of Carbofuran On Male Reproductive System Of Rat. Human And Experimental Toxicology. Vol 14. pp. 889-894, Data Numbering Code: 4.8

PMRA Document Number: 1421763
Reference: D. de Saint-Georges-Gridelet et al., Cytogenetic Effects Of Carbofuran In Mammals, 1982, Mutation Research, Volume 97, pp.244-245, Data Numbering Code: 4.8.

PMRA Document Number: 1660268
Reference: California Environmental Protection Agency, Department Of Pesticide Regulation, Medical Toxicology Branch, 2003, Summary Of Toxicology Data: Carbofuran, Data Numbering Code: 12.5.4

PMRA Document Number: 1660269
Reference: Joint Meeting On Pesticide Residues, 1996, Pesticide Residues In Food: Carbofuran, Data Numbering Code: 12.5.4

PMRA Document Number: 1720597
Reference: The Commission Of The European Communities, 2009, The Official Journal Of The European Union, June 16th, 2007, Brussels, Belgium. Docket # C, 2467, Data Numbering Code: 12.5

PMRA Document Number: 1720598
Reference: USEPA, 2008, Carbofuran Cancellation Process, Data Numbering Code: 12.5

PMRA Document Number: 1720599
Reference: World Health Organization, 2002, Data Sheet On Pesticide No. 56, Carbofuran, Data Numbering Code: 12.5

PMRA Document Number: 1720600
Reference: USEPA, 2005, Carbofuran: HEDS Occupational And Residential Exposure Chapter Of The Reregistration Eligibility Decision Document (phase 2), Data Numbering Code: 12.5.5

PMRA Document Number: 1720601
Reference: USEPA, 2007, Reregistration Eligibility Decisions Document For Carbofuran, Data Numbering Code: 12.5

PMRA Document Number: 1720603
Reference: USEPA, 2008, Transmittal Of Meeting Minutes Of The FIFRA Scientific Advisory Panel Meeting Held February 5-8, 2008 On The Agency's Proposed Action Under FIFRA 6(b) Notice Of Intent To Cancel Carbofuran, Data Numbering Code: 12.5

PMRA Document Number: 1935095
Reference: USEPA, Carbofuran Acute Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Reregistration Eligibility Decision, April 29, 2009, Data Numbering Code: 12.5.7

PMRA Document Number: 1720604
Reference: California Environmental Protection Agency, 1999, Health And Safety Report: Exposure And Illness Following Early Re-entry Into A Carbofuran-treated Field, Data Numbering Code: 12.5.5

PMRA Document Number: 1734581
Reference: Joint FAO/WHO Meetings On Pesticide Residues (JMPR), 1997, Pesticide Residues In Food - Report 1997, Data Numbering Code: 12.5.7

PMRA Document Number: 1734582
Reference: Joint FAO/WHO Meetings On Pesticide Residues (JMPR), 1997, Pesticide Residues In Food - Evaluation 1997 - Carbofuran (096), Data Numbering Code: 12.5.7

PMRA Document Number: 1734583
Reference: Joint FAO/WHO Meetings On Pesticide Residues (JMPR), 2002, Pesticide Residues In Food - Report 2002, Data Numbering Code: 12.5.7

PMRA Document Number: 1734584
Reference: Joint FAO/WHO Meetings On Pesticide Residues (JMPR), 2002, Pesticide Residues In Food - Evaluation 2002 - Carbofuran (096), Data Numbering Code: 12.5.7

PMRA Document Number: 1734585
Reference: USEPA, 2005, Revised Carbofuran Acute Probabilistic And Chronic Dietary Exposure Assessments For The Reregistration Eligibility Decision. 2005, Data Numbering Code: 12.5.7

PMRA Document Number: 1734586
Reference: USEPA, 2008, 40 CFR Part 180 Carbofuran; Proposed Tolerance Revocations; Proposed Rule. Federal Register, Volume 73, No. 148, 2008, Data Numbering Code: 12.5.7

PMRA Document Number: 1734587
Reference: USEPA, 2004, Aldicarb, Atrazine, Cacodylic Acid, Carbofuran, et. al.; Tolerance Actions. Rules And Regulations. Federal Register, Volume 69. N0 28, 2004, Data Numbering Code: 12.5.7

PMRA Document Number: 1735826
Reference: USEPA, 2006, Carbofuran L.R.E.D. Facts, Data Numbering Code: 12.5

PMRA Document Number: 1735907
Reference: USEPA, 2001, Carbofuran: Revised Updated HED Occupational And Residential Exposure Chapter Of The Reregistration Eligibility Decision Document, Data Numbering Code: 12.5

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