

# Office of Environmental Health Hazard Assessment

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## MEMORANDUM

**TO:** Gary T. Patterson, Ph.D., Chief  
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**FROM:** Anna M. Fan, Ph.D., Chief  
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**DATE:** July 7, 2005

**SUBJECT:** COMMENTS AND RECOMMENDATIONS REGARDING THE DRAFT RISK CHARACTERIZATION AND EXPOSURE ASSESMENT DOCUMENTS FOR THE ACTIVE INGREDIENT CARBOFURAN

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Thank you for the opportunity to review the draft risk characterization (RCD) and exposure assessment (EAD) documents for carbofuran, both dated March 1, 2005, prepared by the Department of Pesticide Regulation (DPR). The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code (HSC), Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

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In addition, pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides review, consultation and comments to DPR on the evaluation of the health effects of candidate toxic air contaminants (TAC) included in the TAC documents. As part of its statutory responsibility, OEHHA also prepares findings on the health effects of the candidate toxic air contaminants. This documentation is to be included as part of the DPR report.

This draft RCD (in conjunction with the accompanying EAD) evaluates occupational, dietary and airborne (ambient and application site) exposures to carbofuran. Because exposures of the general public to carbofuran in ambient and application site air were evaluated in this RCD package, OEHHA considers this active ingredient a candidate TAC. Overall, we find both documents thorough and clearly written. Generally, we find the assumptions, considerations and conclusions contained in these documents appropriate, scientifically defensible and sufficiently supported. OEHHA does have a major concern, however, regarding the setting of the seasonal and chronic regulatory levels one order-of-magnitude higher than the critical acute LED<sub>05</sub>. This concern and other suggestions and recommendations are outlined below. We hope that you find our comments and recommendations supportive and useful.

Carbofuran is a broad spectrum, systemic insecticide, acaricide and nematicide that is effective versus a large number of pests in many crops. It is a carbamate and a potent cholinesterase inhibitor, an effect responsible for its usefulness a pesticide and its acute toxicity to humans and other non-target species. Due to a number of unintentional bird-kill incidents in the late 1980s and early 1990s, granular formulations of carbofuran are banned in California. Currently there is only one product (Furdan 4F, a 44% liquid concentrate) registered for use in California.

Our comments on the draft RCD (and EAD where applicable) are as follows:

1. Acute oral, dermal and inhalation exposures to carbofuran are evaluated in the draft RCD using the results from a developmental toxicity range finding study in rats (WARF, 1978). From this study, a maternal lowest-observed-adverse effect level (LOAEL) of 0.1 mg/kg is identified based on chewing behavior observed at this and higher (0.3 and 1.0 mg/kg gavage doses) doses. No reproductive or developmental effects were observed in the study. The chewing behavior observed in the study exhibited a dose-related increase in incidence was considered an acute response to treatment. Benchmark dose (BMD) analysis of the dataset derived an LED<sub>05</sub> (lower bound on the 5% BMD response) of 0.01 mg/kg that was used to evaluate risk in the RCD.

The use of chewing behavior with a LED<sub>05</sub> of 0.01 mg/kg as a critical endpoint and regulatory value is supported by the results of the Jayatunga et al. (1998) study from which a LED<sub>05</sub> of 0.01 mg/kg based on decreased locomotor activity and head-dip



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behavior at all doses tested was also derived using BMD (observed LOAEL of 0.2 mg/kg). Additional

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justification and support for using the LED<sub>05</sub> of 0.01 mg/kg from the WARF (1978) study is provided by the results of a human oral exposure study (FMC, 1976) showing cholinergic signs of dry mouth, salivation, diaphoresis, abdominal pain, drowsiness, nausea, and vomiting at a dose level of 0.25 mg/kg – a dose only 2.5 times greater than the LOAEL of 0.1 mg/kg in the critical rat study. It is noted in the RCD that the critical endpoint of chewing behavior is not unprecedented, in that this behavior is a critical acute determinant in several risk assessments (acephate, fenthion, azinphosmethyl, and mepiviphos) and is a critical subchronic determinant in one case (dichlorvos), albeit in these examples chewing behavior was accompanied by other cholinergic signs at the same dose. A case is made (in the RCD) that this chewing behavior is an *adverse* effect that is potentially central nervous system in origin. Indeed, on page 125 of the RCD, the following statement is found: “Yet the distinct possibility of central nervous system involvement, with the attendant possibility that other centrally coordinated, but difficult-to-document, processes such as learning or perception were also affected, suggested the possibility that the effect was more severe.” Based on the evidence provided in the RCD, OEHHA agrees with the identification of 0.01 mg/kg as the acute regulatory value for carbofuran.

Seasonal (oral, inhalation and dermal) and chronic (oral) exposures to carbofuran are evaluated in the RCD based on a NOAEL of 0.1 mg/kg-day identified in the rat oral (gavage) reproduction study by Pant et al. (1995). The NOAEL was based upon the observation of testicular toxicity and body weight gain suppression at the next higher dose of 0.2 mg/kg-day. Although exposures in the Pant et al. (1995) were for 60-days, this NOAEL was also used for the evaluation of human chronic exposure as a health protective measure. The lowest chronic NOAEL was 0.3 mg/kg-day from a 1-year feeding study in dogs (Toxigenics, 1983) that was based on the observation of testicular degeneration and convulsions at the next higher dose of 0.6 mg/kg-day. Because testicular toxicity was observed in both the subchronic and chronic studies, the health-protective decision was made to use the subchronic NOAEL to evaluate both subchronic and chronic human exposures. While OEHHA agrees with the NOAEL identification in either study, we have concerns regarding the use of a subchronic or chronic regulatory value that exceeds the acute regulatory value.

The critical acute regulatory endpoint of chewing behavior identified in a rat developmental study is considered in the RCD as adverse, and is an effect that suggests the possibility of other significant central effects such as an impact upon “learning or perception.” Because of the adverse nature of this effect and the fact that it is a true sign rather than a clinical measurement (e.g. cholinesterase inhibition), OEHHA believes that the seasonal/chronic NOAEL of 0.1 mg/kg-day is not appropriately health protective. Accordingly, OEHHA recommends that the acute regulatory value of 0.01 mg/kg be used



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to evaluate seasonal and chronic exposures to carbofuran in addition to acute exposures.  
We are also concerned that

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the seasonal/chronic regulatory value of 0.1 mg/kg-day as proposed in the RCD is not appropriately protective against known effects in humans as it is only 2.5-fold less than a dose rate which resulted in profound signs and symptoms of cholinergic toxicity of dry mouth, salivation, diaphoresis, abdominal pain, drowsiness, nausea, and vomiting in a human study. Adoption of the acute regulatory value of 0.01 mg/kg for all exposure durations will protect against these known human effects as well.

2. A default dermal absorption factor of 50% is used in the RCD/EAD for estimating internal dose from dermal exposure to carbofuran. A study by Shah et al. (1987), revealed dermal absorption in rats at 72 hours post-application to be 83% at the lowest dose (28 nmol/cm<sup>2</sup>) tested. The same authors (Shah et al., 1981) showed dermal penetration by cabofuran to be faster and more extensive in mice (97.5% dermal absorption at 8 hours). Several reasons for not using this data were presented in the EAD: (1) data was not reported on a wet-weight basis, (2) acetone was used as the vehicle, (3) treated skin was not washed after exposure period, (4) doses were too high (with the exception of the lowest dose in the rat study), (5) treated areas not sufficiently large, and (6) treated skin was covered with perforated blister in the rat study. We find these reasons insufficient to dismiss the data from animal studies, particularly considering that a number of these “reasons” would tend to underestimate absorption rather than overestimate the amount of carbofuran absorbed. Indeed, we find this data more compelling than a “review of data from several chemicals,” which was used to derive the default value of 50%. Accordingly, OEHHA proposes that a dermal absorption rate of 83% be used in estimating absorbed carbofuran doses. We also note that a dermal absorption value of 83.4% was apparently applied in an earlier version of the EAD (see page 23 of the RCD where it refers to a dermal absorption value of 83.4% being used to calculate human absorption).
3. A default human inhalation absorption factor of 100% is apparently used in the RCD, as stated on page 94 (and page 9 of the EAD). A default pulmonary absorption in rats of 50% is apparently also assumed in the document (See page 89). It is not clear why two different values are assumed for inhalation absorption. OEHHA suggests that this discrepancy be addressed.
4. OEHHA is concerned that seasonal and chronic airborne exposures for the maximally exposed individual is not evaluated in the RCD/TAC. Individuals residing in rural areas near orchards and other crops to which carbofuran is applied may experience repeated exposures to the relatively high airborne concentrations of this active ingredient following repeated applications. Such exposures may occur several times over the course of a growing season as well as over the course of many growing seasons. Therefore, we



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recommend that seasonal and chronic exposures and risks be estimated for this hypothetical receptor.

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5. Bystander exposure is estimated using the 24-hour time weighted average (TWA) of the measured air concentrations. We are concerned that this is not sufficiently health-protective. Accordingly, OEHHA recommends that application site exposures be estimated using the highest sub-24-hour air concentration to protect against acute toxicity from short-term spikes in air concentrations.
6. Chronic occupational exposure to carbofuran was not evaluated in the RCD. OEHHA believes it plausible that seasonal exposure could occur over the course of several growing seasons to the same group of workers. We therefore recommend that chronic occupational exposure to carbofuran be evaluated in the RCD. This is a particular concern considering the potentially irreversible testicular toxicity associated with long-term exposure to carbofuran.
7. Occupational exposure to carbofuran was estimated in the RCD/EAD employing three different methodologies, depending upon the exposure type. Handler exposure was estimated using the Pesticide Handler Exposure Database (PHED); exposures for dip/slurry applicators were estimated using dermal absorption equations from U.S. EPA's Risk Assessment Guidance for Superfund (RAGS) and inhalation exposure estimates using U.S. EPA's SWIMODEL program; and exposures of fieldworkers were estimated using dislodgeable foliar residue values and transfer co-efficients. Uncertainties associated with the use of these methods to estimate worker exposures are described in detail in both the RCD and EAD. OEHHA is concerned that no validation of these estimates were performed. Indeed, in the one available handler study (Hussain et al. 1990), many of the measured handler exposures were higher than the mean PHED values used in the assessment. OEHHA recommends that the worker exposures estimated in the RCD be validated before the RCD becomes finalized.
8. Seasonal exposure of drip irrigation mixer/loaders is assumed in the RCD/EAD to occur over the course of two months/year, while chronic exposure to the same individuals is assumed to occur over three months annually. This apparent discrepancy is not discussed in the document(s). OEHHA suggests correcting this apparent inconsistency.
9. MOEs for acute and seasonal occupational exposures to carbofuran were significantly less than 100 for most exposure scenarios and routes of exposure. In fact, for combined dermal and inhalation exposures, most occupational MOEs were less than one, suggesting a significant potential health impact to agricultural workers exposed to carbofuran. Accordingly, because of high potential worker risks, OEHHA recommends that DPR expedite the development of a strategy for mitigation of worker exposure.

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10. Estimates of acute and seasonal exposure to carbofuran in ambient air resulted in MOEs greater than 100, suggesting that carbofuran exposure to the general public via the ambient air is not of toxicological concern. Even applying the suggested regulatory value of 0.01 mg/kg to seasonal exposures, MOEs would still be greater than 100. We note that some of the MOEs for infants are less than 1,000, which is the regulatory benchmark for triggering the listing of carbofuran as a TAC. Acute MOEs for bystanders were less than 100, suggesting the potential for negative human health impacts from application site exposure of the general public to carbofuran. Accordingly, OEHHA recommends that DPR expedite the development of measures to mitigate these exposures.
11. Acute dietary MOEs for essentially all sub-populations evaluated in the RCD were less than 100 and many were less than 10. Tolerance assessment supported this analysis in that MOEs for nearly all commodities were less than 100. Considering these results, OEHHA recommends that DPR engage U.S. EPA in discussions aimed at reviewing the current federal tolerance to carbofuran on all products.

Again, thank you for the opportunity to review this document and we hope that you find our comments useful. Should you have any questions regarding OEHHA's review of this RCD, please contact Dr. David Rice at (916) 324-1277 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or me at (510) 622-3165.

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