# 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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Office of Environmental Health Hazard Assessment

for Anna Fan

**DATE:** January 29, 2009

**SUBJECT:** COMMENTS ON THE DRAFT CARBARYL DIETARY RISK CHARACTERIZATION DOCUMENT

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Enclosed please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) comments on the draft carbaryl risk characterization document (RCD) prepared by the Department of Pesticide Regulation (DPR).

OEHHA reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code, 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 pesticides.

Should you have any questions regarding OEHHA's comments on the RCD, please contact Dr. David Ting at (510) 622-3226, or Dr. Anna M. Fan at (510) 622-3165.

Enclosure

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## Office of Environmental Health Hazard Assessment's Comments on the draft Carbaryl Dietary Risk Characterization Document (1-napthyl methylcarbamate)

The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by the Department of Pesticide Regulation (DPR) under the general authority of the Health and Safety Code, 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 pesticides.

Carbaryl is a broad spectrum carbamate insecticide used for the control of a broad spectrum of pests on lettuce, cotton, celery, and beans. DPR initiated this risk assessment because of the need to assess health risks associated with dietary exposure to carbaryl. Thus this draft dietary risk characterization document (RCD) evaluates dietary exposure for acute, subchronic, and chronic durations. Carbaryl is used in many products (57 registered uses) and has more than 100 federally established food tolerances.

### General comments on the draft dietary RCD:

Carbaryl is a known inhibitor of cholinesterase activity and a potential carcinogen. Cholinesterase inhibition is used to determine acute and seasonal chronic health risks for the adult and child populations. For the evaluation of acute exposures, DPR identified a critical No Observed Effect Level (NOEL) of 1 mg/kg based on weight gain deficits, cholinergic signs, and brain and red blood cell (RBC) inhibition observed at 10 mg/kg from a neurodevelopmental study. For the evaluation of seasonal chronic exposures, DPR determined an $LED_{10}$ (the lower 95% confidence limit on the 10 percent cholinesterase inhibition dose level) of 0.5 mg/kg-day based on the inhibition of brain cholinesterase activity in an one-year dog study. For the evaluation of cancer risks, DPR concluded that carbaryl induced a number of different tumors in rat and mouse bioassays and estimated a cancer potency factor of $1.0 \times 10^{-3}$ mg/kg/day based on the combined hemangiomas and hemangiosarcomas incidence data in male mice. OEHHA agrees with DPR's choices of studies and toxicological endpoints as the basis for all carbaryl risk assessments with one exception, the acute exposure value.

### Acute and chronic oral hazard identification values

For determining acute oral toxicity risk of carbaryl, DPR used a developmental neurotoxicity study reported by Robinson and Broxup (1997). In this study, pregnant Sprague-Dawley rats were given carbaryl at 0, 0.1, 1 or 10 mg/kg/day. At the highest dose, 10 mg/kg/day, signs of body weight gain deficits, cholinergic signs (as detected by the functional observational battery (FOB), and brain and RBC cholinesterase inhibition were observed in the dams, but not in the pups. Mean motor counts were also elevated in $F_1$ females on day 13 at the highest dose; however, this was not statistically significant. The dams, exposed between gestation day 6 and *post partum* day 10 inclusive, showed

signs of cholinesterase inhibition within a few days, which is why this endpoint is suitable for acute risk assessment. At the second highest dose, 1.0 mg/kg, no significant changes were seen with cholinesterase inhibition, but one FOB parameter (change in gait) was significantly depressed at one time point for the dams. DPR believes that the effects at the 1.0 mg/kg level are so minimal that this dose can be considered as the NOEL. OEHHA is not sure about this point, as there seems to be an overall propensity for the responses of the second highest dose to be greater than those of the control or low dose groups. We recommend that DPR perform benchmark dose extrapolation with several time points for this and other endpoints such as pinpoint pupils or cholinesterase measures, and then decide on the appropriate $LED_{10}$ for acute risk assessment.

For its acute oral risk toxicity value for carbaryl, U.S. EPA employed the Moser (2007) study. This study was designed to determine if immature animals are more sensitive than adults are to the toxic effects of carbaryl. The study reported the effects of a single gavage dosing of carbaryl on cholinesterase activity (brain and RBC) and motor activity in adult (92 days) and young (postnatal [PND] days 11 and 17) male Long-Evans hooded rats. The doses used were 0 (corn oil vehicle), 3, 7.5, 15 or 30 mg/kg body weight. Cholinesterase activity assays of various tissue samples were performed 40 minutes after dosing, with special care taken to minimize carbaryl dissociation from the enzyme during the radiometric procedure. Neither deaths nor severe toxicity was noted during the examination period of this study (40 minutes). All PND 11 rat groups' brain cholinesterase activities were lower than the PND 17 and the adult rats. With carbaryl dosing, significant depression of brain cholinesterase activity was observed at 3 mg/kg and higher for the PND 11 group, and at 7.5 and higher in the PND 17 and adult rat groups. U.S. EPA (2007a and b) applied benchmark dose modeling to the toxicity data of PND 11 and determined an acute oral $LED_{10}$ value of 1.1 mg/kg. U.S. EPA used this value as the point of departure for its regulatory risk assessment to estimate health risk from acute oral exposure to carbaryl.

For its chronic oral risk assessment of carbaryl, DPR used the cholinesterase inhibition data of a one-year dog dietary study. Following 52 weeks of exposure, there was a 20% inhibition (statistically significant) in females at 3.7 mg/kg/day compared to controls and a 14% inhibition (not statistically significant) in males at 3.4 mg/kg/day. Although no clinical signs or histopathological changes were evident even at the high dose of 34 mg/kg/day, the significant depression of brain cholinesterase observed suggests that subtle neurological effects are possible, and those cannot be ruled out. DPR used the benchmark dose approach to evaluate the Week 52 female brain cholinesterase data and determined a $LED_{10}$ value of 0.5 mg/kg/day ($ED_{10}$ = 1.7 mg/kg/day).

In its human health risk assessment on carbaryl, U.S. EPA (2007a and b) decided not to develop a chronic toxicity value based on cholinesterase inhibition. In the Reregistration Eligibility Decision (RED) document, U.S. EPA gave the reasons, "Because of the rapid recovery of cholinesterase inhibition, chronic and long-term assessments were not conducted..." and "Recent data for carbaryl and the other N-methyl carbamates show that cholinesterase inhibition is reversible, with recovery in less than 24 hours." It is important to note that in the development of the RED for carbaryl, U.S. EPA (2007b) had

considered a chronic value for carbaryl based on the same study that DPR used, but dismissed it for the reason stated above.

It is also possible that the U.S. EPA decided not to use the results of the dog study because there is pharmacological evidence that dogs might have a "slower metabolism" than humans regarding carbaryl. However, we found no statements to that effect in any documents provided in the carbaryl docket maintained by the U.S. EPA. Cholinesterase activity inhibition has been used as an endpoint for chronic risk assessment of other pesticides and so we believe that DPR took the prudent approach in considering chronic toxicity of carbaryl in its assessment.

## Carcinogenic Risk Evaluation

Carbaryl has been associated with induction of tumors in chronic studies conducted in rats and mice. In a mouse study (Hamada, 1993a), an increased number of certain tumors were found in all dosed groups versus controls for both male and females. In this study, 80 CD-1 mice of both sexes were administered technical Carbaryl (99.3% purity) in the diet at concentrations of 0, 100, 1000 or 8000 ppm for 104 weeks (males: 0, 14.73, 145.99 or 1248.93 mg/kg/day, females: 0, 18.11, 180.86 or 1440.62 mg/kg/day, respectively). Survival rates of both sexes were unaffected by treatment.

U.S. EPA (2007b) in the supporting documentation for the RED discusses the chronic mouse study:

> The study demonstrated that Carbaryl is carcinogenic in mice at doses of 100 ppm (14.73 mg/kg/day) and higher in males and 8000 ppm (1440.62 mg/kg/day) in females. There was an increased incidence of vascular neoplasms (hemangiomas and hemangiosarcomas) in all treated males and in the 8000 ppm group females at the terminal and unscheduled necropsies but not at week 53. Considering all animals, there was an increased incidence of adenomas, multiple adenomas and carcinomas of the kidney in the 8000 ppm group males. The incidence of hepatic neoplasms (adenomas, carcinomas and one hepatoblastoma) was increased in the 8000 ppm group females. The HED CPRC [1994 assessment] concluded that the 8000 ppm dose was excessive based on the significantly decreased body weight gain in males (33%) and females (19%) during week 13, a significant decrease in RBC and brain cholinesterase activity, clinical signs of toxicity and histopathological changes in the bladder, kidneys and spleen in both sexes.

U.S. EPA's Cancer Assessment Review Committee (CARC) (cited in U.S. EPA, 2007c) classified carbaryl as *likely* to be carcinogenic in humans based on an increased incidence of hemangiosarcomas in male mice.

The complete CARC report (U.S. EPA, 2002) explained U.S. EPA's determination. The Agency re-evaluated the slides of the mouse study and as a result concluded that there was an increasing trend toward kidney tubule cell adenomas or carcinomas, and combined adenomas and carcinomas. Similar findings were made for liver and spleen hemangiomas and hemangiosarcomas. The incidences of hemangiosarcomas also

exceeded the level of historical controls. The CARC conclusion was that incidences of vascular tumors in male mice occurred at doses which were adequate and not excessive. In the females these occurrences were at excessive doses, but were supportive of vascular tumor findings in male mice.

Like U.S. EPA (2007b), DPR views the increased incidence of vascular tumors found in the liver and spleen as indicative of potential carcinogenicity, while acknowledging that the maximum tolerated dose could have been exceeded at the high dose. Increased tumors rates were found in the low- and mid-dose mice without the indication of substantial clinical toxicity. Furthermore, DPR acknowledged that there was potential genotoxicity based on few tests so genotoxicity could not be excluded as a possible component in carbaryl-induced cancers in mice. For this reason and also for reasons of appropriate curve-fitting, the multistage model was employed to determine a cancer slope factor of $1.0 \times 10^{-3}$ $(mg/kg/day)^{-1}$. U.S. EPA's (2007b and c) potency estimate was similar, but not identical to DPR's value. DPR should consider the re-evaluated histopathology data from U.S. EPA (2002) and may wish to recompute its own slope factor for the mouse tumors. However, it is unlikely that the results will be different from the current DPR slope factor.

In a combined carcinogenicity/chronic toxicity study (Hamada, 1993b), 90 Sprague-Dawley rats/sex/group were administered carbaryl in the diet at dosages of 0, 250, 1500 or 7500 ppm for 104 weeks (males: 0, 10.0, 60.2 and 349.5 mg/kg/day; females: 0, 12.6, 78.6 and 484.6 mg/kg/day). An additional 10 animals/sex/dose were administered the same doses and were sacrificed after 53 weeks. Another 10 animals/sex from the control and high dose group animals were sacrificed at week 57 after switching the diet of the high dose animals to control feed for weeks 53-57 of the study. While animals at the high dose expressed significant increases in certain tumors as described below, interestingly, the survival rate was increased over controls because the incidence of other tumors found in controls decreased substantially in the carbaryl dosed groups. For females, the high dose group actually outlived the controls by two-fold. Moreover, the survival rate of controls was only 33 percent for females which is rather low for animals for this type of study. OEHHA requests that DPR check the survival data for historical controls for this strain of rats to verify if the study mortality rates are reasonable.

U.S. EPA (2007b, p90) discusses the rat data as follows:

> The study demonstrated that Carbaryl is carcinogenic in male and female rats at 7500 ppm. There was an increased incidence of liver adenomas in females. In the bladder, there was an increased incidence of benign transitional cell papilloma and transitional cell carcinomas in males and females. One transitional cell carcinoma was also observed in the kidney of a male rat. In the thyroid, the incidence of benign follicular cell adenomas was increased in males; one follicular cell carcinoma was also seen in a male.
> The HED CPRC [1994] evaluated the toxicity data on Carbaryl and considered 7500 ppm to be an excessive dose based on the following findings: 1) changes in body weight gain during week 13 for males and females by 40% and 52%,

respectively, as compared to controls; 2) decreased food efficiency; 3) alterations in hematology and clinical chemistry; and 4) decreases in plasma, RBC and brain cholinesterase at weeks 53 and 105.

U.S. EPA's CARC (U.S. EPA, 2002) also had the histopathology data reevaluated for this study just as they had for mouse study. They concluded that carbaryl induced a statistically significant increase in urinary bladder tumors in male and female rats, thyroid tumors in males and liver tumors in female rats. However, these tumors were induced at an excessive dose and therefore, not relevant for human cancer risk assessment. Nevertheless, they noted an incidence of transitional cell hyperplasia of the bladder, a preneoplastic stage at week 53 necropsy which they felt might be indicative of potential carcinogenicity. The CARC (U.S. EPA, 2002) stated that had the mid-dose been higher (obviously, they were considering a dose lower than the current study's high dose), tumors might have developed. They believed that the maximum tolerated dose (MTD) was not achieved at the mid-dose.

DPR's view is that carbaryl is carcinogenic to rats based on the results of the rat study, but unlike U.S. EPA they compute a potency value based on the liver tumors only (p 118-9):

> However, hepatocellular adenomas did rise in mid dose females (the incidence at ascending doses in "at risk" females was 1/64, 0/70, 3/69 and 7/68*; *$p<0.05$). While the mid dose "effect" was neither statistically significant nor overly convincing, use of these data might contribute to a quantitative risk analysis. It should be recognized, however, that even at the mid dose it was plausible that the MTD was exceeded, based on the 12% body weight decrement observed at that dose. In addition, the mid dose female incidence rate was similar to that in mid dose males, where there was no evidence of a dose-response relation (1/66, 1/67, 3/69, 1/67 at ascending doses). This raised the possibility that the mid dose incidence in females was itself unrelated to carbaryl exposure. Nonetheless, for comparative purposes, the liver adenoma data were subjected to benchmark dose analysis similar to that of the mouse hemangiosarcoma /hemangioma data above....

Based on the data presented in the draft, we agree with DPR that the mid-dose hepatocellular adenoma rates are "neither significant nor convincing." However, we know the U.S. EPA (2002) had revised the liver histopathology data of the rat study. U.S. EPA (2002) concluded that there appeared to be a trend toward increasing tumors with dose for several bladder tumors and liver adenomas. The mid-dose occurrence of the hepatocellular adenomas was within the range of historical controls. It may be useful for DPR to review the new data set and determine if it is necessary to change its evaluation. Still, the mouse tumor data is better, and we recommend that the cancer risk be computed from it.

We agree with DPR's determination that carbaryl is a potential human carcinogen and that the mouse tumor data is more appropriate than the rat tumor data for dose-response evaluation. We also support the manner in which the cancer potency factor of $1 \times 10^{-3}$ $(mg/kg/day)^{-1}$ was derived.

According to DPR, carbaryl should be viewed as potentially genotoxic; we agree with this determination. Based on the studies available, there is no evidence that carbaryl is a mutagen. There is a possibility of carbaryl being clastogenic from *in vitro* studies, but not from *in vivo* studies.

## Neurodevelopmental toxicity and the Food Quality Protection Act (FQPA) factor

U.S. EPA and DPR have the same position on using FQPA factors for their risk assessments on carbaryl. Both DPR and U.S. EPA used cholinesterase inhibition data for determining acute oral toxicity. Both applied a FQPA factor of one because the critical effect was either based on the responses of young rats (U.S. EPA, 2007b) or upon adults from a developmental study (DPR). Hence, there is no need to have a FQPA factor greater than one. OEHHA supports DPR's decision of applying a FQPA factor of one.

We also support DPR's effort to investigate and discuss the nature of possible developmental effects from carbaryl suggested by other studies, particularly in the dog, although U.S. EPA apparently dismisses that possibility entirely. We encourage DPR to continue to monitor developments in this area, and use the new information in risk assessment when appropriate.

## Dietary risks based on tolerances

OEHHA supports DPR's concern that under certain shorter-term exposure conditions, the Margins of Exposure (MOEs) for children of age 1-2 are below 100. This includes some common commodities (e.g., grapes and raisins, apples and apple juice) at the tolerance levels. We like to point out that MOEs for these commodities are also very low (near 100) for the older children and 19 population subgroups with high consumption rates (upper 95$^{th}$ percentile). We agree with DPR that the tolerances of these commodities need to be lowered (all of them are 10 ppm) to be more health protective.

From the RED for carbaryl (2007a), U.S. EPA determined that carbaryl residues on strawberries are the most significant source of dietary exposure to children age 1-2. Carbaryl residues on strawberries were also identified as the main contributor to dietary risk to young children in the 2003 dietary assessment.

DPR stated that a chronic exposure assessment which assumes residue levels set at the respective tolerance levels was not warranted as it is highly improbable that a single or multiple commodities containing pesticide levels at the tolerance would be consumed on a long-term basis. OEHHA would agree with this.

DPR also suggested that inflated estimates of carbaryl intake through cactus fruit and olive consumption might have exaggerated the overall exposure. DPR acknowledged estimating cactus fruit and olive consumption was difficult for children. We have no specific recommendations to give DPR regarding this issue.

We support the discussion of the toxicity of the metabolites of carbaryl, particularly 1-naphthol, the principal metabolite of carbaryl. The toxicity of 1-naphthol was not included in the acute and chronic assessments because it is not expected to be a cholinesterase inhibitor, which was the critical toxicity endpoint for the assessments. 1-Napthol has not been tested for carcinogenicity, therefore we cannot determine if it is a carcinogen. In a complete set of genotoxicity assays required under FIFRA, 1-naphthol was found to be predominantly negative. It was positive in one *Rec* assay, and in two Ames assays (out of nine). We support DPR's decision of not including 1-napthol in the carbaryl risk assessment; however, we recommend DPR to monitor developments in the toxicity testing of 1-naphthol.

We suggest removing FIFRA designations, such as "supplemental," "acceptable," and "unreviewed," to study summaries cited in this document. These designations may be meaningful for pesticide regulation purposes, but may confuse those readers who are not familiar with the terminology and meaning attached to the designations. Another approach is to define these designations and explain what they meant and how they are used in pesticide regulation. DPR should clarify that FIFRA designation of a study is not the sole criterion for judging the quality of the study and its usefulness for risk assessment.

## Specific comments on the draft RCD:

1) Table formats and contents could be better constructed. Table IIIa and b, species should be identified in the titles.

2) Cholinesterase data should be presented consistently in all tables where it is found. See p 68, Table III-8, column heading, Plasma ChE units should be in the overall row for the first part of the table or used as a footnote for the first entry where this occurs. Otherwise, it looks like Plasma ChE is the general title for the column of time of sampling (weeks of the experiment). The format for the next two ChE types, RBC and brain, is better because there is no intervening break between the two dose categories. Instead of just listing the units for cholinesterase in the subtitle, it would helpful to include also the percent inhibition of ChE rather than having it footnoted. In Table III, 6b, the category of time is in the right column but the footnotes for the levels belong in the next column.

   Suggestion: Since there are several tables with cholinesterase inhibition data, instead of calling it "cholinesterase data," it might be clearer to call it "Cholinesterase activity of.....in μmol/ml and/or percent inhibition."

   Please double check the column designations on Table III-3, where $LED_{10}$ and $ED_{10}$ values are shown. The labels seem to be reversed as $LED_{10}$ values are higher than the $ED_{10}$ ones, which seems to contradict what is in the text as well as defy logic.

3) Table III-9. Units of mg/kg/day are repeated in the heading and in the individual entries. Suggestion: Leave mg/kg/day in the heading and delete the units in the table and put parentheses around ppm, i.e., (10 ppm).

   Table III-6a. The units of body or food consumption in grams should be stated in the title and not in the foot note.

4) In the discussion of the Collins et al. 1971 gerbil study, we do not accept that the data may not be relevant because no actual body weight or food consumption data are provided. If the exposed animals were experiencing toxicity from carbaryl or experiencing aversion to dosing, then the weight gain is likely to be less than expected. Nevertheless, the body weight of an animal at the end of the study is expected to be higher than that at the beginning of the study. Using the initial body weight in the dose calculation (mg/kg-day) would over-estimate the dose and the LOAEL/NOAEL. .

   We recommend putting the data on page 92 in a table; there seems no point of having it in a footnote.

   We are also curious about the unsummarized data on rats from the parallel study conducted by Collins. In spite of DPR's reservations, it would be helpful to include some summary of these data. Were no dose-related changes really observed regardless of the author's interpretation? Perhaps a review of these data is warranted at least for DPR's records.

5) We liked having the definition of medical terms provided in the document.

6) There is no statement outlining the statutory authority under which this Dietary Exposure Risk Assessment is conducted.

7) p. 3 2nd para. Rats decarbamylate carbaryl. Humans apparently do too, but humans "excreted only a third of dose in the urine in 24 hours, suggesting that the fate of a significant fraction of the dose was unknown." On the surface, failure to excrete something in 24 hours alone is not a reason to conclude that something else happened to the dose. Can the author provide additional information here?

8) p. 94 Gerbil data, footnote. We are confused by this statement: "Use of these values was based on the unproven assumption that they were unaffected by the carbaryl intake." Define which "values," and rewrite sentence.

9) Rewrite and simplify: p.4 "The brain cholinesterase data, which evidenced a statistically significant decrease of 20% in females at 3.7 mg/kg/day compared to the controls (there was a non-statistically significant decrease of 14% in males at 3.4 mg/kg/day; however, it was the male data that was used to determine the LOEL), after 52 weeks of exposure."

10) Rewrite and simplify p. 51. "The high incidence of sciatic nerve degeneration in all groups did not obscure the apparent high dose increase [of what?] among animals sustaining unscheduled deaths. The essentially total appearance of this parameter...." Does it mean every animal in the high dose group had this condition?

11) We recommend that DPR use the standardized designation of BMDL for $LED_{10}$. We recognize that these terms are identical in meaning, but consistency would be desirable. DPR used BMDL in its recent acephate RCD which we reviewed and in this document, the terms used in Appendix III. Benchmark dose extrapolation-data presentations have BMDL designations as well.

12) There is an error in Table III-15a. The value for slight hypotonic gait on gd 15 at the 10 mg/kg dose level is not statistically significant. The Fisher exact test value is 0.3.

Typographical errors:

1) p. 127, 4th paragraph: sunflower seeds…
2) p. 64 4th paragraph. ….D-limonene exposure resulted…..
3) p. 110. Sensitization……."sensitization"
4) p. 167. Moser (2007) not 2008 in table

## References


Hamada, N.H. (Hazleton Laboratories America). (1993a) Oncogenicity study with carbaryl technical in CD-1 mice. Project ID #656-138; DPR Vol. #169-267, Rec. #123769.

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Robinson, K. and B. Broxup (ClinTrials BioResearch Ltd.) (1997). A developmental neurotoxicity study of orally administered carbaryl, technical grade, in the rat. Lab. Project #97391. DPR Vol. #169-384, Rec. #166126.

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