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DATE: September 22, 2008

SUBJECT: OEHHA'S COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT AND THE DRAFT EXPOSURE ASSESSMENT DOCUMENT FOR ACEPHATE

Enclosed please find comments from the Office of Environmental Health Hazard Assessment (OEHHA) on the draft Department of Pesticide Regulation (DPR) risk characterization document (RCD) and exposure assessment document (EAD) for the pesticide active ingredient, acephate. The two draft documents were sent to OEHHA for scientific review on June 2, 2008.

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OEHHA has reviewed the risk assessment prepared by DPR under the general authority of the Health and Safety Code, Section 59004, and also under the Food and Agricultural Code, 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.

If you have any questions regarding OEHHA's comments on the draft RCD for acephate, please contact Dr. Lubow Jowa at (916) 327-7327 (primary reviewer). For questions regarding OEHHA's comments on the draft EAD for acephate, please contact Dr. Jolanta Bankowska at (510) 622-3162 (primary reviewer). You may also contact Dr. David Ting at (510) 622-3226, or Dr. Anna M. Fan at (510) 622-3165 for any other inquiries.

Enclosure

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Office of Environmental Health Hazard Assessment's Comments on the Draft Risk Characterization Document (RCD) for Acephate

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, 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.

Acephate is an organophosphate 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 exposure to acephate. This draft risk characterization document (RCD) evaluates occupational, dietary, and combined occupational and dietary exposure for acute, subchronic, and chronic durations. Acephate is not heavily used in California, and its use is declining. A leading factor in the decreased use, which is an important consideration for the general population exposure, is the suspension of home and garden uses. DPR previously prepared a RCD on methamidophos, a principal degradate of acephate, which OEHHA also reviewed.

General comments on the draft RCD:

1) OEHHA agrees with DPR's choices of critical studies and toxicological endpoints for determining the critical no-observed-effect levels (NOELs). DPR's determination of the critical values for acute and chronic worker and dietary exposure differs from those of the U.S. Environmental Protection Agency (U.S. EPA) by a small margin (except for acute worker and seasonal worker scenarios). For chronic worker and dietary exposures, DPR uses depression of dog brain cholinesterase with the use of an uncertainty factor of three to derive a NOEL from the Lowest Observed Effect Level (LOEL). DPR ordinarily would use a factor of (up to) ten to estimate a NOEL from the effect of depression of brain cholinesterase. They used a factor of three in this case because the benchmark dose modeling result indicates the 95% lower confidence limit on the 10% response level determined by the benchmark dose modeling ($BMDL_{10}$) (point of departure) is only about 3-fold lower than the LOEL. We support this dose estimation.

2) We also support the use of depression of cholinesterase in the acute human dosing study as the basis for deriving a NOEL for acute worker and acute dietary exposure. Although there are many studies showing depression of all types of cholinesterases with acephate in experimental animals, DPR chose to go with an experimental human study in which groups of ten individuals were dosed at 0.35, 0.7, 1, or 1.25 mg/kg/day. Significant inhibition of red blood cell (RBC) cholinesterase was only observed at 1.25 mg/kg/day, but not lower. The use of the NOEL of 1 mg/kg-day based upon the human data reduces the uncertainty of extrapolating from animal effects to human.

3) OEHHA is not fully supportive of DPR's approach on the carcinogenicity assessment. We have not evaluated the carcinogenicity of acephate for any OEHHA program, so we have no formal position on the carcinogenicity of acephate at this time. However, the U.S. EPA positions on these issues in the available documents can be compared with those of the DPR. We have reviewed U.S. EPA's

discussion on the carcinogenicity of acephate in IRIS (U.S. EPA, 1993), the Federal Register (1996), and an undated U.S. EPA review (1982?), and make the following observations:

a) The U.S. EPA concluded from the female mouse study that the increase in liver tumors at the highest dose is treatment related, and considered the study to be suggestive of possible carcinogenicity (U.S. EPA, 1993). It is noteworthy that liver tumors found in 12/15 of the high-dose females were hepatocellular carcinomas, and no treatment-related effects on clinical toxicity or survival were observed. The U.S. EPA (1993) computed a cancer potency factor, based on the liver tumor incidence data from this study. However, DPR does not consider these tumors to be treatment related, concluding that the high dose was excessive, based on reduced body weight and observations of liver toxicity, consisting of increases in hyperplastic nodules, hypertrophy, intracellular inclusion bodies, mononuclear cell foci, and karyomegaly in both males and females.

OEHHA questions DPR's conclusion that the maximum tolerated dose (MTD) may have been exceeded in the high-dose groups, thus rendering the statistically significant increase in liver tumors observed in the female mice of limited relevance for risk assessment purposes. First, liver toxicity, as indicated by the non-neoplastic liver changes (i.e., increases in hyperplastic nodules, hypertrophy, intracellular inclusion bodies, mononuclear cell foci, and karyomegaly), was observed in both males and females. DPR suggests that these changes resulted in the liver tumors in the high-dose females, yet there appears to be no satisfactory mechanism to explain the absence of liver tumors in the high-dose males. Second, while the decrease in body weight of mice in the high-dose group is significant, 29 percent in females and 24 percent in males, it is unclear why the decrease in body weight would only cause liver tumors in females, but not in the males. Third, one can argue that the depression in body weight, at least in part, could be attributed to a decrease in food consumption (22 percent in females and 18 percent in males) in the high-dose groups. This makes the decrease in body weight less useful as an indicator of toxicity than when a decrease in body weight is observed together with a normal or higher rate of food consumption.

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The basis for DPR's conclusion that the MTD may have been exceeded is not consistent with U.S. EPA guidance (U.S. EPA, 2005). The U.S. EPA Guidelines for Carcinogenic Risk Assessment state that an "adequate high dose would generally be one that produces some toxic effects without unduly affecting mortality from effects other than cancer or producing significant adverse effects on the nutrition and health of the test animals." The guidelines further state that the high dose would generally be considered inadequate if neither toxicity nor change in weight gain is observed" (U.S. EPA, 2005). Thus, decreased weight gain is one indicator of adequate dosing. U.S. EPA Guidelines state that significantly increased mortality (from effects other than cancer) is usually an indication that an adequate high dose has been exceeded (U.S. EPA, 2005), but this is not the case in this mouse study as there are no clinical signs of toxicity or lethality at the high dose. U.S. EPA Guidelines also state that a significant reduction in body weight gain (e.g. greater than 10%) *may* also be associated with an excessive high dose (U.S. EPA, 2005). But, clearly, decreased body weight is not by itself an indication of an excessive high dose (U. S. EPA, 2005). As noted before in the U.S. EPA (1993) review of this study, they were very concerned that there were no other substantial signs of toxicity, apart from body weight loss, whereupon to dismiss this study's results as indicative of possible carcinogenicity.

b) DPR dismisses the significant increase in adrenal tumors in male rats as indicative of carcinogenicity based on the lack of a dose-response relationship and the likelihood that the MTD was exceeded. OEHHA agrees that there is no apparent dose-response. The authors of the study attributed the statistically higher incidence of adrenal tumors in the males to the unusually low incidence of adrenal tumors in the controls. DPR states that this explanation is debatable since some of the provided historical control data showed lower tumor levels than those reported in this study.

In reviewing the tumor data of the male rats, U.S. EPA (1993) found the incidence of pheochromocytomas (medullary adrenal tumors) in [all dosed groups] was within the range of historical incidences and other published results for that rat strain. Due to the high variability of pheochromocytomas in rats, U.S. EPA has been reluctant to use them as an endpoint for carcinogenicity assessment. Also, U.S. EPA noted that there was no increase in malignancy in the lesions or decrease of latency period in the treated males. After obtaining an independent review of the slides, U.S. EPA concluded that the increase in adrenal tumors was not treatment-related.

OEHHA questions DPR on its determination concerning the significance of the exceedance of the MTD and the increased adrenal tumor in male rats. A significant decrease in body weight (18 percent) with an increase in food consumption can be used as an indication of toxicity in the high-dosed males. But there were only a transient decrease in body weight and food consumption in the mid-dose males and its tumor rate was about the same as that of the high-dose males. DPR needs to strengthen its argument to defend this point.

U.S. EPA has updated some of its conclusions on these two cancer studies, prepared in support of the Interim Reregistration Eligibility Document (U.S. EPA, 2006a) and the Organophosphate Pesticides Cumulative Risk Assessment (2006b). We have obtained recently the additional documentation from U.S. EPA in the form of a DVD of the docket for many old pesticide risk assessments. We have delivered a copy to DPR (to the library) for your reference. The DVD provides the acephate human risk assessment (U.S. EPA, 1999), which explains that although U.S. EPA still considers acephate a Group C carcinogen, it

no longer recommends using the slope factor from the mouse study in risk assessment as stated in the IRIS (U.S. EPA, 1993).

In summary, OEHHA does not agree that the liver tumors observed in female mice can be dismissed, based entirely on MTD considerations. The increased incidence of malignant and benign liver tumors observed in the high-dose female mice suggests possible carcinogenicity of acephate. The rat adrenal tumors should also be reevaluated in light of the work already conducted by the U.S. EPA. Hence, we encourage DPR to obtain and review the U.S. EPA work in this area and reevaluate and/or provide additional support for its determination of carcinogenicity on acephate.

4) In OEHHA's review of the draft methamidophos RCD (DPR, 2003), we noted that the document did not include exposure to methamidophos residues as a result of acephate applications (methamidophos is a major degradate of acephate). At that time, OEHHA noted that U.S. EPA's risk assessment for methamidophos (U.S. EPA, 2000) evaluated dietary exposures with and without acephate contributions. Significant exposures to methamidophos in children were noted with combined contributions. Therefore, OEHHA recommended that DPR complete an exposure assessment for acephate in order to assess cumulative risks from exposure to methamidophos. DPR states in this draft acephate RCD (p. 76), that upon completion of the RCDs for acephate and methamidophos, it will consider the risks from cumulative and aggregate exposure under the Food Quality Protection Act (FQPA) of 1996. DPR notes that to do so would be especially relevant because certain high consumption foods such as potatoes and tomatoes do not have tolerance levels for acephate. The lack of tolerance levels is the result of acephate being applied directly to foliage and not to the fruit or root of the plant, i.e., potatoes and tomatoes. While acephate does not migrate, these commodities can still be affected from migration of residues from acephate's major metabolite, methamidophos. This is why we agree with DPR and continue to support and encourage the completion of the combined risk assessment.

5) As to FQPA considerations, OEHHA agrees with DPR that toxicity data indicates young and immature animals are not more sensitive to acephate than adults and it is acceptable to use a factor of one for the FQPA adjustment. In what DPR describes as definitive developmental neurotoxicity study, all measured parameters (including cholinesterase inhibition) showed no increased sensitivity of the offspring relative to the parent. U.S. EPA (2006a,b,c) has done the same in its evaluation. DPR notes that when other organophosphates (OPs) are considered this may have to change. We recommend that DPR specifically state here that when other OPs are considered together with acephate, their own FQPA factors (such as the factor of two for methamidophos) should be included.

6) OEHHA agrees with the DPR conclusion that occupational risks present a concern, as the estimated margin of exposure (MOE) values are less than ten. We agree that mitigation measures are needed to reduce the risk to farm workers.

Specific comments on the draft RCD:

1) In Table 18, the grouping of lowest-observed-effect levels (LOELs) with NOELs, distinguished by a slash between them, might be confusing to a non-technical reader. A further separation or delineation between these values would be helpful. In addition, we recommend that real values and estimated values should be distinguished in the table, perhaps by the use of parentheses or brackets

with explanatory footnotes. In addition, the NOEL/LOEL of the human study should be explained as a combined analysis for both sexes or a NOEL/LOEL should be designated for each sex.

2) Table 29, typographical error in the title.

3) The U.S. EPA reference on p. 84 should be in the "U.S. EPA" subtitle later in the list.

4) On p. 45, please specify how often vital signs and EKG were monitored. It seems doubtful that they would have been done at the same time as the blood draws.

5) Please update the web sites in the reference list, as the U.S. EPA ones have changed.

6) Please reference IRED, RED and cumulative risk documents in the reference section.

References

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Office of Environmental Health Hazard Assessment's Comments on the draft Exposure Assessment Document (EAD) for Acephate

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, 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.

Overall, OEHHA supports the approaches, choices of studies and procedures used in the draft EAD. Our comments presented below are focused on issues of concern and do not discuss matters on which we are in agreement.

General comments on the draft EAD:

1) Exposure scenarios described and evaluated in this EAD include eighteen occupational handler exposure scenarios and nine residential exposure scenarios. DPR identified and evaluated more exposure scenarios than United States Environmental Protection Agency (U.S. EPA) described in its Reregistration Eligibility Decision (RED) document for acephate. (U.S. EPA, 2001a). In the U.S. EPA document sixteen handler exposure and seven residential exposure scenarios were assessed. In 2002 U.S. EPA cancelled acephate uses in homes and gardens. However, in California some of these products are still being used; therefore, exposures were estimated in the EAD based on products registered in California.

2) The metabolism and environmental fate of acephate play an important role in assessing human health risk. Overall this insecticide is not persistent in the environment. The EAD for acephate refers to its degradation and/or metabolism when appropriate. However, it would be helpful to include a summary of the environmental fate information underlying the breakdown of this chemical in soil and groundwater, in surface water and in vegetation. According to the Proposed Acceptability for Continuing Registration (mpra_publications@bc-gc.ca) the half-life of acephate for hydrolysis in water was 60 days at pH 5-7; biotransformation was, however, a more important route of transformation, with a half-life of less than seven days. Acephate is stable to photo transformation in both water and soil. It would be useful to include this information in the EAD.

3) Overall we agree with the choices of approaches used by DPR for acephate exposure risk assessment. These approaches seem to be more health protective than those chosen by U.S. EPA. Again it would be valuable and informative to compare and summarize these choices indicating differences in assessment values obtained by DPR and U.S. EPA.

4) It is not clear whether aggregate exposure assessments for dermal, inhalation and dietary exposures were performed for all groups of field workers exposed to acephate and/or methamidophos during seasonal, annual and life-time exposures. Combined occupational and dietary exposures were discussed in the risk characterization document (RCD) but not in the EAD. We suggest including some information and/or referrals to the RCD when appropriate.

5) We understand that in the near future DPR plans to redo the human risk assessment for acephate and take into consideration human exposure assessments to methamidophos and later on exposure assessments to other cholinesterase inhibiting pesticides. Different sub-groups of the general population could be impacted differently by cholinesterase inhibiting pesticides, separately or in combination. OEHHA suggests that efforts should be made to identify sensitive sub-groups, such as elderly people.

Specific comments on the draft EAD:

1. Many abbreviations are used in the EAD for acephate. It would be useful to have the list of abbreviations and their definitions included at the beginning of the document.

2. First paragraph on page 13 refers to 61 acephate products registered in California and classified in different toxicity categories. It would be useful to provide the list of these products indicating their names, acephate content and toxicity category.

3. On page 18, explanations given under Table 4 (c and d) refer to the assumed “minimal exposures”. It would be beneficial to define “minimal exposures” providing numerical values.