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DATE: February 20, 2004

SUBJECT: COMMENTS AND RECOMMENDATIONS REGARDING THE DRAFT ADDENDUM TO THE RISK CHARACTERIZATION AND EXPOSURE ASSESMENT DOCUMENTS FOR THE ACTIVE INGREDIENT METHIDATHION

Thank you for the opportunity to review the revised draft addendum to the risk characterization document (RCD - addendum dated October 3, 2003) and final exposure assessment (EAD – dated July 22, 2003) for methidathion 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.

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 addendum adds to the previous draft addendum (dated November 6, 2002), which itself amended the original RCD for methidathion dated August 17, 1999. OEHHA submitted comments on the original RCD and on the first addendum via memoranda submitted in December 1999 and May 2003, respectively. The original RCD (current version is dated June, 2001) evaluated dietary and drinking water exposures, whereas the first draft of the addendum addressed occupational exposures to methidathion. The current revisions of the addendum and the exposure assessment add ambient and application site air exposures and risk assessments to the overall evaluation of methidathion. We assume that these revisions essentially complete the RCD/Toxic Air Contaminant (TAC) evaluation for this active ingredient. Our first three comments are limited to the ambient and application site air exposures/risk assessments, although the first one is a restatement of a previously stated concern as it applies to all acute exposures to methidathion, including inhalation. Our last two comments pertain to the RCD itself, and they are included in this memorandum as a result of a review of the entire RCD and RCD addendum package by our Air Toxicology and Epidemiology Section (ATES). We hope that you find these additional comments supportive and useful.

Because ambient exposures to methidathion in ambient and application site air were evaluated in this RCD package, OEHHA considers this active ingredient a candidate TAC. The identification of methidathion as a candidate TAC necessitated the additional review by ATES, and, under the FAC authority noted above, we are preparing findings on the health effects of this chemical. We will submit these findings by February 27, 2004.

Our comments and recommendations on the draft RCD addendum for methidathion are provided below.

1. Acute exposures to methidathion are evaluated in the draft addendum using the results from an acute neurotoxicity study in rats (Chang and Richter, 1994). From this study, a lowest-observed-adverse effect level (LOAEL) of 1 mg/kg is identified. The LOAEL is based on reduced cholinesterase (ChE) activity in the cerebral cortex of male rats (59 percent of controls) at the lowest dose tested. A no-observed-adverse-effect level (NOAEL) of 0.3 mg/kg is calculated in the draft addendum by dividing the LOAEL by a factor of three. According to the draft addendum, "A smaller uncertainty was used to estimate the NOEL because the severity of the endpoint was mild given that no significant blood ChE inhibition was seen, only one region of the brain in one sex was affected and neurological signs were not observed in the functional observational battery in either sex until 8 mg/kg." We note that at dose levels of 8 and 16 mg/kg, statistically significant neurological signs were observed in males and that neurological signs were also reported for female rats at 1 and 4 mg/kg. The signs in female rats, although biologically significant, were not statistically different than controls. Furthermore, in the neurotoxicity section of the toxicology profile in the RCD it is stated "In the acute and subchronic neurotoxicity studies in rats, signs of neurotoxicity were observed in the functional observational battery, including changes in autonomic signs, CNS signs, sensorimotor effects, impaired neuromuscular functions and reduced body temperature. A reduction in maze activity was also observed. A reduction in ChE activity in four different regions of the brain (cerebellum, cerebral cortex with hippocampus, and striatum) and the spinal cord were seen." It should also be noted that statistically significant inhibition of ChE activity in three regions of the brain and reductions in serum ChE activity were reported at 4, 8, and 16 mg/kg.

   While we agree with the selection of the study and the endpoint to use for the acute occupational exposure risk assessment, we have concerns about the uncertainty factor selection. Typically, uncertainty factors of less than ten are applied to estimate a NOAEL from a LOAEL when the severity level of the toxic effect(s) is considered to be mild. However, we do not consider a level of 41 percent inhibition of ChE activity in cerebral cortex to be a "mild" effect. Considering inhibition of cerebral cholinesterase a "mild" effect is inconsistent with the discussion above and the comment on page 5 of the draft addendum: "In general, DPR considers brain ChE inhibition to be indicative of overt toxicity since it is one of the primary functional target sites and more subtle central neurological signs, such as memory and learning losses, may not be easily detected in animals unless they are specifically tested for these effects." Therefore, we recommend an uncertainty factor of 10 be applied and that an estimated NOAEL of 0.1 mg/kg be used to calculate margins of exposure (MOEs) for acute methidathion exposures.

2. A default inhalation absorption factor of 50% is applied in the draft addendum and in the final exposure assessment. The selection of this absorption percentage is justified in the RCD and EAD by the following: "No inhalation absorption studies are available. In the absence of these data, DPR uses a default absorption value of 50%, based on experimentally determined inhalation absorption values of many different chemicals at environmentally relevant concentrations (Raabe, 1988; Ross et al., 2001). OEHHA is concerned that a generic approach based on "values from many different chemicals" may underestimate actual inhalation absorption of methidathion. In the absence of a chemical-specific value, we recommend assuming 100% inhalation absorption for this chemical. We note that U.S. EPA assumed 100% absorption of methidathion by the inhalation route in their recent Interim Reregistration Eligibility Decision for Methidathion (U.S. EPA, 2002).

3. OEHHA is concerned that seasonal and chronic 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 methidathion 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 recommend that seasonal and chronic exposures and risks be estimated for this hypothetical receptor.

4. As mentioned in our previous memorandum (May 2003), we agree with the selection of Chang and Walberg, 1991 as the study for evaluating chronic exposures to methamidophos. The critical NOAEL of 0.15 mg/kg/day identified from this study is based on elevated liver enzymes in the serum and histological lesions in the liver at the next highest dose level of 1.33 mg/kg/day. We note that the Johnston, 1967 study, did not determine a NOAEL, but identified a LOAEL lower than Chang and Walberg, 1991 (0.2 mg/kg/day – based on brain cholinesterase inhibition). Several reasons, including high mortality, insufficient hematological and clinical chemistry analysis, and incomplete histopathology and individual data, were listed as major deficiencies of this study. OEHHA suggests expanding the description of these deficiencies into a discussion of the rationale for not selecting this study to evaluate chronic exposures and adding to the discussion the uncertainties surrounding the dose determination (no feed analysis, food consumption not measured, etc.). We also suggest pointing out that the results of the study by Yau *et al*., 1985 supercede those from the Johnston, 1967 study since the former study did not suffer from these deficiencies and established a LOAEL and NOAEL (1.77 and 0.17 mg/kg/day, respectively) for the same endpoint (inhibition of brain cholinesterase). OEHHA feels that these additions will clarify the rationale for the selection of Chang and Walberg, 1991 as the critical chronic study.

5. In the RCD discussion of positive methidathion genotoxicity data it is stated that: "… The biological significance of a positive sister chromatid exchange (SCE) assay is also unclear since it represents an exchange of identical information." We feel that the SCE data should not be downplayed as SCE assays are considered to be useful short-term tests for induced chromosomal instability. We suggest changing the text accordingly.

   The genotoxicity study section of the RCD would also benefit from the inclusion of a study by Kevekordes *et al*. (1996), which demonstrated that methidathion induced a significant increase in SCEs in human lymphocytes *in vitro* in the absence but not presence of metabolic activation.

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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