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DATE: January 30, 2006

SUBJECT: COMMENTS AND RECOMMENDATIONS REGARDING THE FINAL DRAFT RISK CHARACTERIZATION (REVISION 1) AND EXPOSURE ASSESSMENT DOCUMENTS FOR THE ACTIVE INGREDIENT METHIDATHION

Thank you for the opportunity to review the final draft risk characterization (RCD - dated December 8, 2005) and final exposure assessment (EAD – dated December 7, 2005) documents 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 risk 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 final draft combines the prior RCD for methidathion, which evaluated dietary and drinking water exposures with the draft addendum to the RCD that evaluated occupational exposures and exposure of the general public to methidathion from application site and ambient air. OEHHA has provided comments on these two documents as well as earlier versions of the EAD in a number of previous memoranda (submitted in December 1999, May 2003 and February 2004). Overall, we find the current documents thorough, well written and the conclusions, for the most part, sufficiently and appropriately supported by the data. Accordingly, we have relatively few comments or suggestions at this time. The first two comments have been offered before and relate to our concerns regarding the uncertainty factor (3) used to convert a Lowest Observed Adverse Effect Level (LOAEL) to a No Observed Adverse Effect Level (NOAEL) for evaluating acute exposures and the lack of annual exposure evaluation for bystanders. The third comment concerns the EAD, where we request additional discussion regarding changes in the exposure estimates for individuals exposed to ambient air. Our final comment concerns the oncogenicity evaluation and is included in this memorandum as a result of a review of the RCD by our Air Toxicology and Epidemiology Branch (ATEB). We hope that you find these additional comments supportive and useful.

Please also be advised that we are finalizing our draft findings and intend to submit them for inclusion into the RCD under the FAC authority noted above. We intend to submit these findings no later than February 24, 2006.

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 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 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. 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.

3. Mean and 95^{th} percentile upper-bound air concentrations of 0.086 and 0.486 mg/m^3, respectively (SD of 0.156), were calculated in the previous "Final Draft" EAD (dated July 23, 2003) from air monitoring data collected in Tulare County in 1991. The mean was used to calculate seasonal and annual exposure and the 95^{th} percentile value was used to evaluate acute exposures of the general public to methidathion in ambient air.

Using the same data set, mean and 95th percentile upper-bound air concentrations of 0.069 and 0.186 mg/m^3, respectively (SD of 0.156), were calculated in the current "Final Draft" EAD dated December 7, 2005. Clearly, (and confirmed by information supplied by Sheryl Beauvais of DPR) the data were treated differently in the two drafts. No mention of these differences is found in the EAD. Because there is such a large discrepancy in the exposure estimates between the two versions of the EAD, we recommend that a discussion be added to the document detailing the differences between the calculations.

4. It is stated in the RCD "While the genotoxicity data for methidathion suggests that it does not act directly on DNA, it was not conclusive based on the few positive tests." The RCD also states that the "genotoxicity data for methidathion was predominantly negative" and that "the gene conversion/ forward mutation assay is a good screen for mutagenic activity, but its usefulness is limited when extrapolating the results to higher organisms. The biological significance of a positive sister chromatid exchange assay is also unclear since it represents an exchange of identical information." OEHHA believes that the data indicates that methidathion is genotoxic, albeit not in bacterial cells.

   Although methidathion was generally negative in bacterial gene mutation and DNA damage assays, and in mammalian unscheduled DNA synthesis (UDS – indicative of DNA damage) and host-mediated mouse lymphoma gene mutation assays, it was positive in a yeast gene mutation and gene recombination assay, and provided mixed results in mammalian chromosomal damage assays.

   The bacterial gene mutation assay results were negative, but these systems cannot detect chromosomal damage. The yeast gene mutation and gene recombination assay results were positive for both gene mutations and gene recombination (indicative of chromosomal damage), in a species (*Saccharomyces cerevisiae*) which is a eukaryotic species, and therefore more closely models mammalian cells than the bacteria used in the *Salmonella* and *E. coli* mutation assays. Methidathion was negative in primary rat hepatocyte UDS assays, a single host-mediated mouse lymphoma assay and a single mouse dominant lethal (*in vivo* chromosomal damage) assay. However, these assays tend to be relatively insensitive, and the UDS assay cannot detect chromosomal damage. Of the more sensitive mammalian chromosomal damage assays, methidathion was negative in the *in vivo* mouse micronucleus assay, but induced SCEs in Chinese hamster V79 cells, and in Chinese hamsters *in vivo*. It should also be noted that the SCE assay is considered to be a sensitive and accurate short-term test for induced mammalian chromosomal instability.

OEHHA believes that the data indicates that methidathion may cause gene mutations in eukaryotic cells, and does cause chromosomal damage in mammalian cells, and has therefore shown evidence of genotoxicity. We suggest that the oncogenicity/weight of evidence discussion be changed accordingly.

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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References

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