# Office of Environmental Health Hazard Assessment

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**DATE:** May 23, 2003

**SUBJECT:** COMMENTS AND RECOMMENDATIONS REGARDING THE DRAFT ADDENDUM TO THE RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT METHIDATHION

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Thank you for the opportunity to review the draft addendum to the risk characterization document (RCD) for methidathion prepared by the Department of Pesticide Regulation (DPR) and dated November 6, 2002. The Office of Environmental Health Hazard Assessment (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 pesticide active ingredients.

The draft addendum amends the original RCD for methidathion dated August 17, 1999, for which OEHHA submitted comments in December 1999. The original RCD evaluated dietary and drinking water exposures whereas the addendum addresses occupational exposures to methidathion. At present, it is not clear whether the addendum completes the methidathion RCD or whether subsequent addenda will be prepared since certain sources of exposure to this

chemical (such as exposure through ambient air) and exposure to more vulnerable subpopulations such as residents located in the vicinity of agricultural fields are not addressed in either document. Our comments and recommendations on the draft addendum RCD are provided below.

## 1. Selection of Toxicology Studies and Non-Cancer Endpoints

*Acute Toxicity*

Acute occupational exposure to methidathion is evaluated in the draft addendum by using 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. The reduced brain ChE activity observed in rats exhibited a dose-response, albeit at the lowest dose the effect was only observed in male rats. At a dose level of 8 and 16 mg/kg, statisctically significant neurological signs were also observed. Neurological signs were also reported for female rats at 1 and 4 mg/kg, but although biologically significant, statistical analysis indicated these effects were not statistically different than controls. 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." However, in the neurotoxicity section from the toxicology profile for the original RCD addressing dietary and drinking water exposures (date June 2001), 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 selected to calculate a NOAEL from a LOAEL. In developing reference exposure levels, OEHHA has applied uncertainty factors of less than ten 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. This determination is supported in the draft addendum, where it is stated on page 5, "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 neurogical signs, such as memory and learning losses, may not be easily detected in animals unless they are specifically tested for these effects." These tests do not appear to have been performed according to the summary table (Table 7) from the June 2001 RCD. Therefore, we recommend that the addendum use a NOAEL of 0.1 mg/kg, to calculate margins of exposure (MOEs) from acute methidathion exposure. Alternatively a range of NOAELs (from 0.1 to 0.3 mg/kg) might be used.

*Subchronic Toxicity*

Seasonal occupational exposure to methidathion is evaluated based on a 90-day neurotoxicity study in rats (Chow and Turnier, 1995). From this study, a NOAEL of 0.2 mg/kg-day is identified based on reduced ChE activity in the cerebral cortex of male rats (74 percent) and in the striatum (63 percent of controls) and hippocampus (76 percent of controls) of female rats at the next highest dose level of 0.6 mg/kg-day. We agree with the selection of study and the endpoint used to calculate MOEs for seasonal occupational exposure to methidathion.

*Chronic Toxicity*

The dog study conducted by Chang and Walberg (1991) is selected in the draft addendum to evaluate chronic dietary exposure to workers in various occupational scenarios. 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 agree with the selection of study and the endpoint used to calculate MOEs for chronic dietary exposure to methidathion.

**2. Carcinogenicity**

The U.S. Environmental Protection Agency (U.S. EPA) and DPR adopt different approaches to evaluating the carcinogenicity data for methidathion. The two approaches are summarized below.

U.S. EPA currently classifies methidathion as a possible human carcinogen (Group C carcinogen) based on liver tumors in male mice. No quantitative cancer risk assessment for methidathion is available from U.S. EPA. U.S. EPA's rationale for not quantifying cancer risk is as follows: 1) the evidence is limited (common tumor type in only one tissue site in one sex of one species), 2) there is no evidence of oncogenicity in two chronic rat studies, 3) the majority of genotoxicity data for methidathion are negative, and 4) an association between the incidence of hepatotoxicity and liver tumors cannot be excluded.

DPR includes a quantitative assessment for cancer risk. The support for taking this approach, as summarized from the draft addendum RCD is as follows: 1) the mode of action of methidathion carcinogenicity is uncertain, 2) direct DNA interaction cannot be excluded because of the availability of positive genotoxicity tests, and 3) although the association between the hepatotoxicity and liver tumors might be explained by secondary DNA effects from a possible increase in cell proliferation, there are currently no mechanistic studies to support this hypothesis. The multistage-Weibull time-to-tumor model (MULTI-WEIB) is used to estimate the carcinogenic potency of methidathion based on the combined incidence of hepatocellular adenomas and carcinomas in male mice (Goldenthal, 1986).

We support the approach and methods used by DPR in its draft addendum RCD to assess the carcinogenic potency for methidathion.

3. Comparison of Approaches

In response to OEHHA's recommendation made in 1999, the draft addendum includes a comparison of the approaches used by U.S. EPA in preparing the re-registration eligibility document for methidathion (Travaglini, 1999) and the draft RCD. This is helpful, thank you.

We have one outstanding concern with regard to the inhalation absorption factor used to calculate inhalation exposures to methidathion. U.S. EPA uses an inhalation absorption factor of 100 percent whereas the draft RCD uses 50 percent. There is no explanation provided in the draft addendum for the different assumptions used by the two agencies. We recommend that the draft addendum include an explanation for the different approaches with appropriate references to the literature. Alternatively, a range of values for estimating risk might be presented, using 50 and 100 percent absorption rates.

**4. Mitigation**

MOEs for acute, seasonal and chronic occupational exposure to methidathion were less than 100 for all exposure scenarios, except mixer/loader/applicators using low-pressure handwands. The MOEs were less than ten for most exposure scenarios and less than one for some scenarios (e.g., aerial handlers and airblast applicators). Cancer risks range from $10^{-1}$ to $10^{-4}$.

In general, RCDs do not include management options for reducing risks. However, for methidathion, the occupational risks are extremely high and therefore it would be appropriate to develop a strategy, separately from the RCD process, to reduce risks to workers. We would be happy to discuss options for mitigation and the development of worker health regulations if necessary.

Thank you again for the opportunity to comment and provide recommendations on the draft addendum to the RCD for methidathion. If you have any questions about our comments or recommendations please contact Dr. Michael DiBartolomeis or me at (510) 622-3200.

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