Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Linda S. Adams
Secretary of Environmental Protection

Arnold Schwarzenegger
Governor

MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, California 95812-4015

Sue Edmiston, Chief
Worker Health and Safety Branch
Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, California 95812-4015

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor
Oakland, California 94612

DATE: January 20, 2010

SUBJECT: COMMENTS ON THE DRAFT ADDENDUM TO THE 2004 RISK CHARACTERIZATION DOCUMENT FOR METHYL PARATHION DIETARY AND AMBIENT AIR EXPOSURES

Attached please find a copy of the Office of Environmental Health Hazard Assessment's (OEHHA) comments for the active ingredient methyl parathion. These comments were prepared in response to the Department of Pesticide Regulation's (DPR) two draft documents: "Methyl Parathion, Risk Characterization Document, Occupational, Ambient Air and Aggregate Exposures," dated June 5, 2009, and "Estimation of Exposure of Persons in California to the Pesticide Products that contain Methyl Parathion," dated May 28, 2009.

OEHHA reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code, Section 59004, and 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. Pursuant to the FAC Sections 14022 and 14023, OEHHA provides consultation and technical assistance to DPR on the evaluation of health effects of candidate toxic air contaminants (TAC) and prepares health-based findings.

Thank you for providing the draft documents for our review. If you have any questions regarding OEHHA's comments, please contact Dr. David Ting or Dr. Anna Fan at (510) 622-3200.

Attachment

cc: Allan Hirsch
Chief Deputy Director
Office of Environmental Health Hazard Assessment

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
Office of Environmental Health Hazard Assessment

David Ting, Ph.D., Chief
Pesticide and Food Toxicology Section
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

Charles Salocks, Ph.D., Chief
Pesticide Epidemiology Section
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

David Chan, Ph.D.
Staff Toxicologist
School Site Risk Assessment Guidance Section
Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment

Dan Qiao, Ph.D.
Staff Toxicologist
School Site Risk Assessment Guidance Section
Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment

ATTACHMENT

COMMENTS ON THE DRAFT ADDENDUM TO THE 2004 RISK CHARACTERIZATION DOCUMENT FOR METHYL PARATHION DIETARY AND AMBIENT AIR EXPOSURES

BACKGROUND INFORMATION

OEHHA previously reviewed DPR's 1999 evaluation of methyl parathion as a Toxic Air Contaminant and 2004 Risk Characterization Document (RCD). At the request of DPR, OEHHA reviewed the 2009 addendum to the 2004 RCD for dietary and ambient air exposures. The addendum consists of an updated air exposure assessment, occupational exposure assessments, and an updated RCD that characterizes the risk from air, occupational, and aggregate exposures. Estimates from the 2004 dietary exposure assessment have been included in the aggregate assessment. In assessing aggregate exposure for the general population, DPR considered air and dietary exposures. In evaluating aggregate exposure for workers, DPR included air, dietary, and occupational exposures.

According to DPR's evaluation, all acute margins of exposure (MOEs) for application site air exposure (based on the highest air concentration measured) were less than the DPR health protective benchmark of 100. Most of the acute (based on the 95th percentile exposure estimates) and seasonal (based on the average exposure estimates) MOEs for occupational exposures were less than 100. Almost all acute MOEs for dietary exposures were less than 100 at the $\geq$95th percentile for various age subgroups. MOEs for acute and seasonal aggregate exposures show similar results.

As part of our review of the addendum, we also revisited the DPR 1999 and 2004 documents for background and context. Our comments below, however, focus primarily on issues identified from the addendum.

COMMENTS

Exposure pathway model

A conceptual model that provides an overview of the exposure pathways considered by DPR is lacking. DPR indicated that methyl parathion is registered for use on alfalfa, almonds, barley, beans, cabbage, canola, corn, cotton, hops, oats, onions, pecans, potatoes, rice, rye, sugar beets, sunflowers, walnuts, and wheat. Based on these

registered uses, DPR should outline pertinent exposure pathways, and discuss which pathways are deemed complete for purpose of this exposure assessment.

Water ingestion pathway

DPR did not discuss exposures from the water ingestion pathway in either the 2009 updated exposure assessment or the 2009 updated RCD. Since a conceptual exposure model was not presented, it is difficult to ascertain the reasons for not including the water ingestion pathway. Trend data presented by DPR show that very little methyl parathion has been applied to rice between 2002 and 2006. If trend data was a basis for not including the water ingestion pathway in the exposure assessment, it seems such a rationale lacks validity so long as methyl parathion is registered for use on rice.

DPR in its 2004 RCD briefly mentioned that the lack of monitoring data precluded a drinking water exposure assessment. However, methyl parathion was detected in the Colusa Water Basin where it was applied in the rice-growing region of Colusa County (Central Valley Regional Water Quality Control Board, 1989 and Department of Fish and Game, 1990 cited in California Department of Food and Agriculture, 1991). In its risk assessment to support the re-registration eligibility decision for methyl parathion, U.S. EPA (2006) discussed surface and ground water levels of methyl parathion in estimating drinking water exposures. U.S. EPA also cited the Colusa studies and noted that spray drift from aerial applications led to as much as 15 percent deposition into water bodies adjacent to rice fields. Methyl parathion was detected up to 6 parts per billion (ppb) in the Colusa Water Basin; however, with imposition of irrigation and application controls, that level was reduced to 0.12 ppb. U.S. EPA deemed the water exposure pathway to be complete and used available data to estimate drinking water exposures. OEHHA recommends that DPR include the water ingestion pathway as a part of its exposure assessment.

Paraoxon in drinking water

U.S. EPA noted that methyl parathion could be oxidized to paraoxon during water treatment (U.S. EPA, 2009). This is of concern because methyl paraoxon is more toxic than the parent compound. DPR has established a toxicity equivalence factor of 10 based on a comparison of acute toxicity between methyl parathion and methyl paraoxon in rats. U.S. EPA will consider how this methyl parathion issue should be addressed in its drinking water assessment. OEHHA suggests that DPR also consider and discuss this issue as part of its exposure assessment and risk characterization.

Exposure concentration estimation

DPR used average exposure estimates in computing chronic exposures. The average rather than 95 percent upper confidence limit (UCL) of the average was used because DPR feels that assuming long-term exposure with a "high-end" concentration is not

reasonable. U.S. EPA in issuing its guidance indicated that because of the uncertainty associated with any point estimate of exposure concentration, the 95 percent UCL of the average should be used (U.S. EPA, 1989). OEHHA agrees that using the maximum concentration would be unreasonable for chronic exposure; however, using the 95 percent UCL of the average to account for the uncertainty associated with this point estimate is desirable and appropriate. Accordingly, OEHHA recommends that DPR also estimate chronic exposures based on the 95 percent UCL to delineate the uncertainty boundary of the average.

Biomonitoring data in estimating aggregate exposure to workers

DPR recognized that use of biomonitoring data may underestimate occupational exposure to methyl parathion. The metabolite, p-nitrophenol in urine, was used as a basis to estimate methyl parathion exposure. This metabolite can be detected in urine up to 84 hours after exposure, but the approach used by DPR only accounted for excretion of p-nitrophenol for the first 24 hours. DPR should elaborate whether an adjustment factor could be used to correct the underestimation.

Seasonal dietary exposure

The dietary exposure data of the U.S. population for the spring season was used to assess the seasonal dietary exposure for adult females, adult males, and workers. Considering methyl parathion is mainly used during the summer (from May to August), a justification is needed on the use of dietary exposure data for the spring season.

Safety factor for children

As recognized in the 2009 addendum and the 2004 RCD, increased pre- and post-natal sensitivities were observed from animal studies. These include:

- age-related difference in the detoxification of methyl parathion in rats
- age-related difference in lethal doses (LD_{50}s) and cholinesterase inhibition in rats following acute methyl parathion exposure
- age-related difference in cholinesterase inhibition following acute and repeated exposure in a developmental neurotoxicity study in rats

In OEHHA's 2003 comments on DPR's draft RCD for the active ingredient methyl parathion dated September 15, 2003, OEHHA recommended an additional uncertainty factor of 10 to protect children and infants based on the increased sensitivities to neurotoxic effects of the chemical observed in young animals (OEHHA, 2003). DPR, however, in its response to OEHHA's comments, indicated that an additional uncertainty factor for children and infants is not necessary based on the following reasons (DPR, 2004):

- the No Observed Effect Level (NOEL) for subchronic exposure was derived from immature rats
- the critical acute NOEL of 0.025 mg/kg-day is lower than the acute NOEL of 0.11 mg/kg-day derived from the pups in a recently available developmental neurotoxicity study (see Table 1)

Table 1. Summary of studies and endpoints considered by DPR for the risk characterization of methyl parathion

Route	Species & Age	Duration	Endpoint	Study	NOEL or LOEL (mg/kg-day)
Acute Oral	rat, 7-8 weeks old	single dose	plasma, RBC, and brain ChE; neuropathy	Minnema, 1994	0.025 (NOEL)
	rat, PND11	single dose	plasma, RBC, and brain ChE	Beyrouty, 2002	0.11 (NOEL)
Subchronic Oral	rat, GD6-20, LD1-10, & PND11-21 (direct dosing of the pups)	developmental neurotoxicity study (36 days)	plasma, RBC, and brain ChE	Beyrouty, 2002	0.03 (NOEL)
Subchronic Dermal	rat, 47-54 days of age	4 weeks	brain ChE, behavioral effects	Beyrouty, 2001	0.3 (LOEL)
Chronic Oral	mouse	104 weeks	brain ChE	Eiben, 1991	0.2 (LOEL)

The endpoints used by DPR were cholinesterase inhibition and neuropathy, no endocrine disruption endpoints were considered. As acknowledged in the 2004 RCD, methyl parathion has been indicated to possess endocrine disruption potential. Considering the widespread effects of endocrine disruptors, and increased susceptibility

to endocrine disruption in young versus adult animals, OEHHA recommends an additional safety factor be applied in establishing a methyl parathion health criterion for acute and subchronic exposures for protection of children and infants[1]. Such a health criterion will facilitate the risk characterization of those MOEs applicable to children in the 2009 addendum.

OEHHA also noted that U.S. EPA (2006) applied a ten-fold Food Quality Protection Act (FQPA) safety factor in its assessment to support the re-registration eligibility decision for methyl parathion. The ten-fold factor was later removed by U.S. EPA when it re-analyzed the data in response to public comments (U.S. EPA, 2005 and 2009). U.S. EPA presented a conclusion similar to that reached by DPR that the NOEL used is based on the most sensitive endpoint and will protect all endpoints identified in the developmental neurotoxicity study. U.S. EPA further assessed whether this NOEL would be protective of endocrine effects identified in the open literature. This involved one study that pertains to the inhibition of ovarian compensatory hypertrophy by methyl parathion and another to the hypoinsulinemia and hyperglycemia induced by methyl parathion. U.S. EPA concluded that the chosen NOEL would also adequately protect these endocrine endpoints. OEHHA noted that adult animals were used in these two studies. As such, this "most sensitive" NOEL may be adequate to protect endocrine disruption effect in adults; but the analysis does not demonstrate the adequacy of this NOEL in protecting endocrine disruption effects in children and infants. On that basis, OEHHA also recommends DPR consider an additional safety factor for protection of children and infants.

Cumulative risks

U.S. EPA has completed its cumulative risk assessment for organophosphates. It would be helpful if DPR were to include a discussion about methyl parathion in the context of the cumulative toxicity of organophosphate compounds.

Reference

California Department of Food and Agriculture. 1991. Protocol to Sample Methyl Parathion and Methyl Paraoxon in Paddy Water of Commercial Rice Fields.

[1] The 2009 addendum focuses on estimating air and occupational exposures. Based on the May through August use pattern of methyl parathion, DPR assumes these exposures are only of acute or subchronic duration. Chronic exposure assessment is not a subject in the 2009 addendum. Because OEHHA's current task is to review the 2009 addendum, we have restricted our recommendation of safety factor for children to establishing a methyl parathion health criterion for acute and subchronic exposures.

DPR. 2009. Final Draft of Exposure Assessment Document on Methyl Parathion--Estimation of Exposure of Persons in California to the Pesticide Products that Contain Methyl Parathion.

DPR. 2009. Draft Methyl Parathion Risk Characterization Document; Occupational, Ambient Air and Aggregate Exposures; Addendum to the 2004 Risk Characterization Document for Methyl Parathion Dietary and Ambient Air Exposures.

DPR. 2004. Risk Characterization Document for Methyl Parathion Dietary and Ambient Air Exposures.

DPR, 2004. Response to OEHHA Comments to the Methyl Parathion RCD.

DPR. 1999. Evaluation of Methyl Parathion as a Toxic Air Contaminant.
Feldmann, R. J., and Maibach, H. I. 1974. Percutaneous penetration of some pesticides and herbicides in man. *Toxicol. Appl. Pharmacol* 28: 126-132.

OEHHA, 2003. Comments on DPR's Draft Risk Characterization Document for the Active Ingredient Methyl Parathion.

U.S. EPA. 2009. Methyl Parathion Summary Document, Registration Review: Initial Docket (EPA-HQ-OPP-2009-0332).

U.S. EPA. 2006. Re-registration Eligibility Decision for Methyl Parathion.

U.S. EPA. 2005. The Health Effects Division's Response to Public Comments on EPA's Interim Reregistration Eligibility Decision Document for Methyl Parathion (OPP Docket# OPP-2003-0237). DP Barcode D308015.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund Volume 1: Human Health Evaluation Manual (EPA/540/1-89/002).