CENTER FOR OCCUPATIONAL AND ENVIRONMENTAL HEALTH

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April 25, 2007

Ms. Mary-Ann Warmerdam
Director
Department of Pesticide Regulation
1001 I Street
P.O. Box 4015
Sacramento, CA 95812-4015

Dear Ms. Warmerdam:

With this letter I am pleased to transmit to you the Scientific Review Panel on Toxic Air Contaminants' Findings on methidathion. The findings were based on the Panel's review of the Department of Pesticide Regulation's draft report titled "Methidathion (Supracide®) Risk Characterization Document" (revised November 2006).

The Panel reviewed the draft report as well as the scientific data on which the report is based, the scientific procedures and methods used to support the data, and the conclusions and assessments on which the report is based, as required by state law. The Panel also reviewed comments received and responses to those comments, as well as comments and findings from the Office of Environmental Health Hazard Assessment. In approving the report, it is the Panel's conclusion that the report, with the revisions requested by the Panel, is based on sound scientific knowledge.

The Panel recommends that you take the necessary regulatory steps to list methidathion as a toxic air contaminant. Upon review of the toxicity of methidathion, the available information supports the finding of its being listed as a Toxic Air Contaminant based on it cholinergic effects, evidence of chronic toxicity and carcinogenicity.

An important issue was raised during the consideration of methidathion that related to the issue of multiple exposures to organophosphate pesticides. The Panel agreed with DPR that the health risks of for methidathion were probably underestimated since they do not take into consideration cumulative exposure from other organophosphates. This is an issue of great significance since members of the public may be exposed to multiple pesticides in farming areas and their vicinities. It would be useful to hold a workshop at some stage to discuss multiple chemical exposures. Other issues of concern that were discussed include the lack of data on the toxicity of the oxygen analog of methidathion and the potential toxicity of methidathion metabolites.

Let me also take this opportunity to thank the Department of Pesticide Regulation staff for their efforts in completing this report. The Panel appreciates the time and work that were put into the report as well as responding to further questions from the Panel.

Lastly, we ask that the Panel's findings and this letter be made a part of the final report.

Sincerely,

John R. Froines, Ph.D.
Chairman
Scientific Review Panel

cc: Scientific Review Panel members

Joan E. Denton, Ph.D., Director
Office of Environmental Health Hazard Assessment

Robert F. Sawyer, Ph.D., Chairman
Air Resources Board

Jim Behrmann
Liaison, Scientific Review Panel

Enclosure

Findings of the Scientific Review Panel on the Proposed Identification of Methidathion as a Toxic Air Contaminant as adopted at the Panel's January 11, 2007 Meeting

The Scientific Review Panel on Toxic Air Contaminants (Panel) reviewed the draft report, *"Methidathion (Supracide®) Risk Characterization Document"* (dated June 2006 and revised November 2006), prepared by the Department of Pesticide Regulation (DPR). The Panel reviewed and discussed the reports in its meetings held June 26, 2006 and January 11, 2007, along with findings prepared by the Office of Environmental Health Hazard Assessment (OEHHA) dated November 17, 2006.

A public review draft was released in August 2005 for public comment and review, and copies were also shared with the Air Resources Board and OEHHA. In early 2006 two lead members of the Panel (Dr. Roger Atkinson and Dr. Charles Plopper) reviewed the revised report and the full Panel was sent the June 2006 version of the report on June 5, 2006. The report was revised in response to comments from the Panel and a revised version (November 2006) was sent to the Panel on October 31, 2006. Based on its discussion at the June 26, 2006 and January 11, 2007 meetings, the Panel's review of the draft reports and information and comments submitted through the public comment process, the Panel makes the following findings pursuant to Food and Agricultural Code section 14023:

(1) Methidathion is a non-systemic, organophosphate insecticide/acaricide used to control sucking and chewing insects, such as scale, moths, and aphids, on a wide variety of crops. Methidathion Is applied by aerial or calibrated power-operated ground equipment at rates varying from 0.25 to 5.0 pounds active ingredient per acre. There are two registered products approved for use in California, Supracide® 2E and Supracide®25W.

(2) Methidathion use in California peaked in 1994 when approximately 370,000 pounds were applied and has been declining since 1998. In 2004 (the most recent year with use data), 61,204 pounds of methidathion were used. Artichokes are the primary crop for methidathion. Currently, the counties with the highest use rates are in the San Joaquin Valley. During the past five years, there were winter and summer use peaks.

(3) Methidathion is moderately water-soluble and has the potential to run off into surface water depending on use conditions and environmental factors. Methidathion has been detected in California surface water as a result of rain runoff from wintertime dormant spray applications. The reported aqueous photolysis half-life of methidathion is 8.2 days. Methidathion has a low likelihood of leaching to ground water due to its relatively short soil half-life (1.5 – 8 days); methidathion has not been detected in California ground water. Microbial degradation appears to be the dominant route for methidathion breakdown.

(4) In the atmosphere in the gas phase, methidathion is expected to undergo rapid atmospheric reaction to form the corresponding oxon, methidaoxon which is physiologically active. This conversion of methidathion to methidaoxon may also occur on surfaces. Methidaoxon was observed along with methidathion at a number of sampling sites in California. Little is known about the atmospheric fate of methidathion. Atmospheric hydroxyl radicals are thought to be the most reactive with methidathion in air with estimated lifetimes of 0.8 hours to two days. Given the complexity of the degradation of methidathion further work on the atmospheric products and toxicity of methidathion is clearly warranted. Methidathion has been reported to travel a significant distance from application sites.

(5) Ambient air monitoring was done at four sites in June and July 1991 for methidathion and methidaoxon. These monitoring data were used to estimate seasonal and chronic human exposure to methidathion in ambient air.

(6) Application site monitoring was conducted in July 1991 near an application of methidathion. However, unanticipated changes in weather made it likely that the monitoring did not capture the highest concentrations. Because of this air concentrations during and after an application of methyl parathion to a walnut orchard in San Joaquin County in July 2003 were measured and used as surrogates to estimate airborne levels of methidathion. In this study, samplers were placed all around the field and the downwind samplers were used to estimate exposure. The methyl parathion study was considered an appropriate surrogate study for methidathion because of similarities in equipment used, timing of applications and vapor pressure. Exposure estimates were adjusted upward to account for differences in application rate in the methyl parathion study (2 lbs/acre) and the maximum application rate for methidathion on citrus (5 lbs/acre). In the methyl parathion study, the air was monitored for methyl paraoxon in addition to methyl parathion. These surrogates were used to estimate acute (one hour and daily), seasonal and annual human exposure at application sites (bystander exposure).

(7) Human exposure to atmospheric methidathion can occur by both inhalation and dermal routes, but the predominant exposure route for systemic doses is inhalation. Inhalation uptake was assumed in the RCD/TAC document to be 100 percent for these estimates. Dermal uptake of methidathion has not been quantitatively estimated in these studies, but DPR has estimated the dermal route is expected to provide less than one percent of the systemic dose received by inhalation. This assumption should be evaluated in persons at close proximity to application sites.

(8) Exposure values presented in the DPR document were estimated as follows:

a. One-hour absorbed doses and absorbed daily doses (ADDs) were calculated for acute exposures of bystanders based on the 11 hour and 21 hour time-weighted average (TWA) air concentration of methyl parathion, respectively. Air concentrations were adjusted to estimate a maximum application rate of 5 lbs AI/acre for methidathion;
b. Seasonal average daily doses (SADD) were calculated for seasonal ambient exposures from the average air concentration at the Jefferson site and from the unadjusted 21 hour TWA for bystander exposures; and
c. Annual average daily doses (AADD), based on nine-month annual use periods, were calculated for ambient chronic exposures and bystander chronic exposures from the respective SADDs.

Human doses were estimated for adults and infants (up to 12 months) and were based on generally accepted default values for body weights and breathing rates. Inhalation absorption was assumed to be 100 percent.

(9) The toxicokinetics of methidathion are complex. A wide range of metabolites have been proposed and the list may be incomplete. There is potential for covalent bond formation between active metabolites and macromolecules (electrophilic chemistry). The toxicity of methidathion metabolites is an important research area given evidence for chronic health outcomes unrelated to acetycholine effects including liver toxicity in the dog as well as lung ulceration and inflammation in a chronic feeding study.

(10) Numerous cases of acute pesticide illness involving methidathion have been reported in California in recent years. Between 1992 and 2003, a total of 39 incidents were reported associated with the use of methidathion. Ten incidents involved the use of methidathion as the sole active ingredient. Most of the illnesses were systemic in nature and derived from cholinesterase inhibition including: vomiting, nausea, abdominal cramps, headache and dizziness. The putative route of exposure for the majority of these acute illnesses is inhalation. The remaining cases were incidents of localized dermal irritation. Most of the cases were exposures to agricultural workers either as a direct result of their handling of the material (mixing or application) or field workers experiencing drift from nearby applications. Three incidents were non-occupational.

(11) Acute subacute and chronic toxicity of methidathion has been evaluated in a variety of animal species. Signs of acute intoxication which predominate are cholinergic in nature. Similar cholinergic signs occurred following subchronic exposure. Pathological observations included:

anemia, liver toxicity, reduced brain cholinesterase (ChE) activity, and lesions of the liver, stomach and heart.

(12) The No-Observed-Effect Level (NOEL) selected for evaluating acute exposure was 0.18 mg/kg based on a statistically significant reduction in acetylcholinesterase activity in the cerebral cortex of male rats. A similar value was obtained using benchmark methodology.

Brain acetylcholinesterase inhibition and cholinergic signs similar to those observed with acute exposures were also observed in laboratory animals after subchronic exposure. The subchronic NOEL was 0.18 mg/kg/day based on a 90-day neurotoxicity study in rats. The effects observed in laboratory animals with chronic exposure to methidathion were similar to those observed with subchronic exposure, except that evidence of liver toxicity was a target endpoint. The lowest NOEL in a chronic study of acceptable quality was 0.15 mg/kg/day based on elevated liver enzymes in the serum and microscopic lesions in the liver of dogs exposed to methidathion in the diet for one year.

(13) The results of a range of assays for gene mutation and chromosomal changes are mixed. There are no reported studies on metabolites for genotoxic potential. Chromosomal aberrations have been observed in an occupational study of men working in fields. Further follow up of this finding is warranted.

(14) Carcinogenicity: Increases in liver tumors (hepatocellular adenomas and carcinomas) were identified in two studies in male mice. A dose related trend was observed that was statistically significant ($p<0.01$ at the two highest doses) when analyzed separately or combined. No evidence of carcinogenicity was observed in female mice or rats. There is no evidence for a threshold or species specificity for these outcomes. As a result a cancer potency was derived and discussed below (18).

(15) Reference concentrations (RfCs) for each exposure duration: acute, seasonal, and chronic were determined by DPR by dividing the oral NOEL by the breathing rate and uncertainty factor. The calculated RfCs are found in Table 1 of this finding.

(16) The Panel agrees with DPR that the potential health risks from exposure to methidathion in application site and ambient air are of concern. The risk of non-carcinogenic health effects can be expressed as a margin of exposure (MOE), which is the ratio of the NOEL from the animal study to the human exposure dosage. Generally, an MOE of at least 100 is desirable assuming that humans are 10 times more sensitive than animals and that there is a 10-fold variation in the sensitivity between the lower distribution of the overall human population and the sensitive subgroup.

The margins of exposure for acute exposure in the application site air were less than 100 for both infants and adults. The margins of exposure for seasonal and chronic exposure at the application site were greater than 100 for both infants and adults, but less than 1,000 (except for chronic exposure in adults). See Table 2 for the calculated MOEs for application site and ambient air exposures.

(17) DPR acknowledges that "health risk estimates for methidathion were probably underestimated since they do not take into consideration cumulative exposure from other organophosphates." This is a finding of fundamental importance since, to date, the Panel has only received documents focusing on single chemicals from DPR. Clearly the issue of cumulative exposure to a range of pesticides is a matter of great importance.

(18) A quantitative risk assessment was conducted to assess carcinogenic risk from exposure to methidathion in ambient air. The values ranged from 7.1×10^{-6} at the maximum likelihood estimate (MLE) to 1.1×10^{-5} at the 95% upper confidence limit on the slope of the dose-response curve (95% UCL). The carcinogenic risk from exposure for bystanders ranged from 2.5×10^{-5} at the MLE to 3.9×10^{-5} at the 95% UCL. The Panel considers that lifetime exposure to methidathion in ambient air and to bystanders may constitute a carcinogenic risk and agrees with DPR that mitigation may be required (see Table 3).

(19) The Panel agrees with DPR in their conclusion that the health risks for methidathion were probably underestimated due to the lack of toxicity data for the oxygen analog, which is presumed to be the active metabolite. Further information on the toxicity of metabolites would be of value to assess the overall potential for adverse health effects.

(20) As required by law, the Panel has reviewed the scientific data on which the report is based, the scientific procedures and methods used to support the data, and the conclusions and assessments on which the report is based. The Panel concludes that the report, with the revisions specified by the Panel, is based on sound scientific knowledge, and represents a balanced assessment of our current scientific understanding.

(21) Upon review of the toxicity of methidathion including data on the carcinogenicity as well as the range of non-cancer outcomes, it is apparent that the available information supports the finding of its being listed as a Toxic Air Contaminant. The Panel recommends that the Director of DPR initiate regulatory steps to list methidathion as a toxic air contaminant pursuant to Food and Agricultural Code section 14023, and any further steps deemed necessary to reduce public exposure.

Findings of the Scientific Review Panel on the Proposed Identification of Methidathion as a Toxic Air Contaminant

I certify that the above is a true and correct copy of the findings adopted by the Scientific Review Panel on January 11, 2007.

/s/

John R. Froines, Ph.D.
Chairman, Scientific Review Panel

Attachments:
Table 1: Reference doses (RfDs) and concentrations (RfCs) calculated for to methidathion.
Table 2: Estimated margins of exposure for potential application site and ambient air exposure to methidathion for the general public.
Table 3: Carcinogenic risk for lifetime exposure as calculated for application site and ambient air.

Table 1. Reference doses (RfDs) and concentrations (RfCs) for methidathion*

Exposure Scenario	NOEL	Effects on LOEL	RfD	RfC	
				Infants[1]	Adults[2]
Acute	0.18 mg/kg	Reduced ChE activity in cerebral cortex of male rats	1.8 µg/kg	3.1 µg/m^3 (0.25 ppb)	6.4 µg/m^3 (0.52 ppb)
Seasonal	0.18 mg/kg/day	Reduced ChE activity in RBCs, cerebral cortex (M), striatum (F) and hippocampus (F) of rats	1.8 µg/kg/day	3.1 µg/m^3 (0.25 ppb)	6.4 µg/m^3 (0.52 ppb)
Chronic	0.15 mg/kg/day	Elevated liver enzymes in serum and liver histopathology in dogs	1.5 µg/kg/day	2.5 µg/m^3 (0.21 ppb)	5.4 µg/m^3 (0.43 ppb)
Lifetime	Potency 0.53 (mg/kg/day)$^{-1}$	Liver tumors in male mice	1.9 ng/kg/day	-----	6.8 ng/m^3 (0.6 ppt)

* **Adapted from Table 46, Methidathion Risk Characterization Document (Revision 1), Volume I, Health Risk Assessment, November 2006, at page 125, and OEHHA Findings, November 2006, page 7.**

1. Infant RfCs were calculated using DPR's assumed breathing rate for infants of 0.59 m^3/kg/day. An uncertainty factor of 100 was applied to all calculations.
2. Adult RfCs were calculated using DPR's assumed breathing rate for infants of 0.28 m^3/kg/day. An uncertainty factor of 100 was applied to all calculations.

Table 2. Estimated margins of exposure for potential application site and ambient air exposure to methidathion for the general public[a] (*)

Exposure Scenarios	Infants		Adults	
	MOE[b]	% RfC[c]	MOE	% RfC
Application Site				
Acute - 1 hr	39	250	220	45
Acute - 24 hr	22	440	47	210
Seasonal	190	51	400	24
Chronic	950	11	2,000	5
Ambient				
Seasonal	3,000	3	6,400	2
Chronic	3,300	3	7,100	1

a Margin of Exposure = NOEL / Exposure Dosage. Acute NOEL = 0.18 mg/kg (male rats, cortex ChE inhibition). Seasonal NOEL = 0.18 mg/kg/day (rats, RBCs and regional brain ChE inhibition). Chronic NOEL = 0.15 mg/kg/day (dogs, elevated liver enzymes in serum and histological lesions in the lever). Exposure dosages from Table 31. Values rounded to two significant figures.

b MOE = Margin of Exposure

c % RfC = Percentage of Reference Concentration. The acute, seasonal and chronic reference concentration for methidathion are 3.1 $\mu g/m^3$ (0.25 ppb), 3.1 $\mu g/m^3$ (0.25 ppb) and 2.5 $\mu g/m^3$ (0.21 ppb). See section VI. Reference Doses/Concentrations for explanation of calculations. Values rounded to two significant figures.

(*) Adapted from Table 39, Methidathion Risk Characterization Document (Revision 1), Volume I, Health Risk Assessment, November 2006, at page 100.

Table 3. Carcinogenic risk[1] for lifetime exposure as calculated for application site and ambient air

Exposure Scenario	Cancer Risk Estimate	
	Maximum Likelihood Estimate	95 percent Upper Bound
Application Site	2.5×10^{-5}	3.9×10^{-5}
Ambient Air	7.1×10^{-6}	1.1×10^{-5}

*** Adapted from OEHHA findings, November 2006, pages 6-7.**

1. Carcinogenic Risk = carcinogenic potency x exposure estimate. Potencies were calculated in the RCD/TAC and were: 0.34 $(mg/kg/day)^{-1}$ maximum likelihood estimate; 0.53 $(mg/kg/day)^{-1}$ 95 percent upper confidence limit estimate. Exposure estimates were the average annual daily doses as described in the RCD/TAC.