DEVELOPMENT OF HEALTH CRITERIA FOR SCHOOL SITE RISK ASSESSMENT PURSUANT TO HEALTH AND SAFETY CODE SECTION 901(g):

Malathion Evaluation

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Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment
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Background and Summary

Health and Safety Code (HSC) Section 901(g) requires the Office of Environmental Health Hazard Assessment (OEHHA), in consultation with the appropriate entities within the California Environmental Protection Agency, to identify those chemical contaminants commonly found at school sites and determined by OEHHA to be of greatest concern based on child-specific physiological sensitivities. HSC Section 901(g) also requires OEHHA to annually evaluate and publish, as appropriate, numerical health guidance values (HGVs) for five of those chemical contaminants until the contaminants identified have been exhausted. HGVs established by this mandate are intended for use in the assessment of risk at proposed or existing California school sites. At this time, OEHHA focuses its evaluation on non-cancer effects of the identified chemicals, pending the completion of a new method for developing HGVs based on child-specific carcinogenic effects. Accordingly, current HGVs are in the form of a child-specific reference dose (chRD) or child-specific reference concentration (chRC).

Malathion has been reviewed by the U.S. Environmental Protection Agency (U.S. EPA), Agency for Toxic Substances and Disease Registry (ATSDR), and the California Department of Pesticide Regulation (CDPR). This report summarizes OEHHA's evaluation of malathion based on those reviews and on our additional literature search, and discusses the appropriateness of developing a chRD. The reader is referred to the cited reviews for basic data on chemical use, environmental fate, pharmacokinetics, and pharmacodynamics.

In reviewing existing health criteria from ATSDR, CDPR, U.S.EPA (Integrated Risk Information System (IRIS) and Office of Pesticide Programs (OPP)) and pertinent literature, OEHHA concludes that the immune system could be a sensitive target of malathion and this chemical could potentially impact children at very low, non-cholinergical doses. However, there is insufficient information to derive a chRD based on this endpoint. U.S. EPA (2005) is requiring the registrant to develop additional immunotoxicity data as part of the re-registration process. When the immunotoxicity data become available, OEHHA will review and determine the applicability of those data to establishing a chRD. In the interim, it is recommended that OPP's chronic RfD of 0.003 mg/kg-day for malathion, based on the plasma and red blood cell (RBC) cholinesterase endpoint, be used for assessing health risk at school sites (U.S.EPA, 2005). The OPP's RfD value mirrors that of CDPR's reference dose (CDPR, 1993); however, these two identical values were derived from a different study.

Malathion is of concern because it has been detected in California schools (CARB and CDHS, 2003). The nervous and immune systems are the main targets of malathion. These organ systems, which are still undergoing development and maturation in children, are especially vulnerable to chemical insults. Existing health criteria discussed below are largely based on studies with cholinesterase inhibition as an endpoint. In addition, a

number of papers provide evidence that malathion doses exceeding 25 mg/kg-day induced oxidative stress in animal brains (Brocardo et al., 2005; Delgado et al., 2006; Fortunato et al., 2006; Haque et al., 1987). Existing data on oxidative stress are, nevertheless, equivocal; da Silva et al. (2006) showed that lactational exposure of mice to malathion inhibited brain cholinesterase but did not produce oxidative stress. While oxidative stress does not appear to be a sensitive endpoint, it remains as an important issue from the viewpoint of cumulative impacts from exposure to multiple oxidative stress inducers or exposure to a single inducer for long durations. The issue is also significant because strong associations were observed between oxidative stress and autism (Chauhan and Chauhan, 2006; James et al., 2004; Kern and Jones, 2006), and between oxidative stress and schizophrenia (Mahadik et al., 2001; Reddy and Yao, 1996; Yao et al., 2001).

In reviewing the immunotoxicity of organophosphates including malathion, Galloway et al. (2003) observed that in most experimental models malathion, at levels high enough to inhibit acetylcholinesterase, caused immunosuppression. However, the chemical produced immuno-enhancement at low, non-cholinergic doses. Perturbation of the neuroendocrine system leading to dysregulation of glucocorticoid was implicated as a cause of immunosuppression. The stimulatory effect on immune function at low, non-chloinergic doses could also produce adverse ramifications, such as hypersensitivity or autoimmunity. It is this low-dose effect that requires further scrutiny.

Existing Health Criteria

U.S. EPA IRIS

The Integrated Risk Information System of EPA (1992) has derived an RfD of 0.02 mg/kg-day for malathion based on a subchronic human study (Moeller and Rider, 1962) This human oral exposure study was conducted with experimental groups of five subjects (23 to 36 years of age), each of whom received daily doses of 8, 16, or 24 mg (0.12, 0.23, or 0.34 mg/kg) malathion for 32. 17. or 56 days, respectively. Plasma and red blood cell cholinesterases were measured prior to administration, 24 hours after receiving the first dose, and twice weekly for the next 11 weeks. Inquiries and clinical observations were made daily throughout the study to identify possible toxic effects. The NOAEL of 0.23 mg/kg-day and the LOAEL of 0.34 mg/kg-day were based on inhibition of plasma and red blood cell cholinesterase activities. An uncertainty factor of 10 was used for the protection of sensitive human groups. No uncertainty factor was taken for subchronic to chronic extrapolation.

CDPR

CDPR (1993) also used the Moeller and Rider study in establishing a chronic reference dose for its risk assessment. Instead of the plasma and RBC cholinesterase endpoint, CDPR selected cholinergic signs or symptoms as the endpoint. The NOAEL for that

endpoint was 0.34 mg/kg-day, which was the LOAEL for the plasma and RBC cholinesterase endpoint. An uncertainty factor of 100 (10 for intraspecies and 10 for subchronic to chronic extrapolation) was applied in deriving a chronic reference dose of 0.003 mg/kg-day.

ATSDR

ATSDR (2003) employed the Daly (1996) study in establishing its chronic Minimal Risk Level (MRL) of 0.02 mg/kg-day. This was a combined chronic toxicity/carcinogenicity study in rats. Fischer 344 rats, grouped by sex and treatment dose, were used. Malathion was administered to each treatment group, which consisted of 90 rats, via the diet for up to 24 months at dose levels of 100/50 (100 ppm for first 3 months of study, 50 ppm for duration of study in both sexes due to finding of plasma and RBC cholinesterase inhibition in females only at 3 month assay), 500, 6,000 or 12,000 ppm [equivalent to respective mean values of 4/2, 29, 359 and 739 mg/kg-day (males) and 5/3, 35, 415 and 868 mg/kg-day (females)]. Thus, the NOAEL for the cholinesterase inhibition endpoint was 2 mg/kg-day based on the male rat or 3 mg/kg-day based on the female rat. ATSDR applied an uncertainty factor of 100 (10 for extrapolation from animal to humans and 10 for the protection of sensitive populations) to the NOAEL of 2 mg/kg-day (based on male rat) to derive the MRL.

U.S. EPA OPP

The Office of Pesticide Programs of EPA (2005) used the same Daly study to establish a population adjusted dose of 0.003 mg/kg-day for use in a human health risk assessment that served as a support for the re-registration of malathion. OPP selected the NOAEL of 3 mg/kg-day (based on female rat) and applied an uncertainty factor of 1000 (10 for interspecies, 10 for intraspecies, and 10 for child protection under the Food Quality Protection Act (FQPA)) to derive the population adjusted dose.

Immunotoxicity--a Critical Effect

Repeated aerial spaying of urban areas in Southern California to control fruit flies and reports of cases of allergic responses (CDHS, 1991) prompted a number of studies to examine the possible immune effects of exposure to low levels of malathion. Rodgers and Ellefson (1992) showed that a single acute administration of 0.25 mg/kg of purified malathion (>99% purity) orally to mice enhanced the hydrogen peroxide production and phagocytic activity of peritoneal leukocytes, and caused the degranulation of mast cells. In a 90-day study, Rodgers and Xiong (1997) demonstrated that phagocytic capability of peritoneal macrophages from treated mice was elevated at the dose of 0.1 mg/kg-day, but was suppressed at higher doses (1 or 10 mg/kg-day). Commercial grade malathion was administered orally to inbred female SJL/J mice, 5-6 weeks of age, at environmentally relevant doses of 0.018, 7.2, or 180 mg/kg on alternate days for 28 days. Malathion enhanced primary IgM antibody response to sheep RBCs by approximately 150% ($P<0.02$) at all doses tested; however, splenic macrophage phaocytosis, B-cell

blastogenesis induced by lipopolysaccharide, and T-cell balstogenesis induced by concanavalin A and phytohemagglutinin were not affected by treatment (Johnson et al., 2002).

While these studies provide an overall picture that malathion at low, non-cholinergic doses produces effects on the immune system, the disparity of the results makes interpretation difficult. For example, malathion seems to enhance activities of peritoneal macrophages but not of splenic macrophages. Malathion appears to enhance IgM activities but not B-cell or T-cell blastogenesis.

Another issue is the connection between the immune enhancement by malathion and disease outcome. To address that issue, Rogers (1997) demonstrated that malathion adversely affects the course and intensity of autoimmune disease in MRL-1pr mice, which are genetically predisposed to systemic lupus erythematosus.

The following table provides a comparison of existing health criteria to a hypothetical chRD based on the Johnson et al. (2002) study. The low dose of 0.018 mg/kg administered on alternate days is converted into a LOAEL of 0.01 mg/kg-day. This comparison illustrates that the immune system is a very sensitive endpoint even without the use of a child safety factor and a subchronic-to-chronic factor.

	L0AEL*/ NOAEL (mg/kg-day)	Subchronic -to- Chronic	LOAEL-to-NOAEL	Interspecies	Intraspecies	Children Protection	Health Criteria (mg/kg-day)
EPA IRIS	0.23				10		0.02
CDPR	0.34	10			10		0.003
ATSDR	2			10	10		0.02
EPA OPP	3			10	10	10	0.003
Hypotheti-cal chRD	0.01*		10	10	10		0.00001

Conclusion

OEHHA staff concludes that the immune system is a very sensitive endpoint for malathion. However, since U.S. EPA (2005) indicated that the database on immunotoxicity was incomplete, and has asked the registrant to conduct an additional study to clarify the picture, it is desirable to review the new data before considering any action. When the registrant's study results become available, OEHHA will update this evaluation to determine the appropriateness of establishing a chRD based on the immune endpoint.

In the interim, OEHHA recommends the use of OPP's chronic reference dose to assess the health risk of malathion at school sites in California. OPP's reference dose is as health protective as CDPR's reference value and more protective than the IRIS RfD. In

terms of the technical basis of the OPP and CDPR values, CDPR used a short-term human study with a smaller uncertainty factor, whereas OPP used a long-term animal study with a much larger sample size. Moreover, the human study that CDPR selected used signs or symptoms related to malathion exposure as an endpoint, rather than cholinesterase levels. Signs or symptoms, which are based on clinical observations, are deemed to be more subjective than cholinesterase levels as an indicator of health effects.

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