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

Child-Specific Reference Doses (chRDs) for Atrazine and Deltamethrin

Final
October 2007

Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Introduction

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).

This document is a summary of OEHHA's evaluation of atrazine and deltamethrin. In developing these chRDs, OEHHA has followed the requirements set forth in Health and Safety Code Section 57003 for receiving public input. The first draft document was posted on the OEHHA Website (www.oehha.ca.gov) in January 2006. A public workshop was held in February 2006 to discuss the scientific basis and recommendations in the draft report. After considering public comments and input from external peer review, OEHHA revised the document for another public review in July 2007. No additional comments were received during the second public review period. The release of the final document is a culmination of this public input process.

The Introduction serves as a background for the technical evaluation atrazine and deltamethrin. For those that are not familiar with this OEHHA program, it is advisable to review this chapter prior to analyzing the following technical chapters.

Each technical chapter is a focused document that summarizes the chRD derivation. Recent reviews of the chemical by various entities, such as the U.S. Environmental Protection Agency (U.S. EPA), Agency for Toxic substances and Disease Registry (ATSDR), and California Department of Pesticide Regulation (CDPR), serve as a baseline for OEHHA to conduct additional literature search. In the document, OEHHA identifies relevant information from the baseline and from literature search for discussion. OEHHA will not reiterate basic data on environmental fate, pharmacokinetics, and pharmacodynamics that have been adequately covered in the cited baseline documents. Because these two technical chapters concern chRD derivations, non-cancer studies using an oral route of administration and studies that provide information regarding age-sensitivity are the primary focus of the OEHHA review. ChRDs will be applied for assessing health risk from oral or dermal exposure; whereas, chRCs derived from inhalation studies will be applied for assessing risk from inhalation exposure.

The purpose of establishing these child-specific health criteria is to provide improved means for consultants of school districts or the Department of Toxic Substances Control (DTSC) to conduct

school site-specific risk assessment. The process here is similar to that used by U.S. EPA in developing reference doses (RfDs) for superfund site risk assessment. Thus, OEHHA is not considering exposure issues here. They will be dealt with in the site-specific risk assessment, specifically in the exposure assessment portion, which can be found in the "Guidance for Assessing Exposures and Health Risks at Existing and Proposed School Sites Pursuant to Health and Safety Code §901(f)," February 2004. Exposure assessment will be performed based on site-specific sampling. The appropriate chRDs will be applied to characterize the risk only if the sampling and analysis data indicate the occurrence of the corresponding chemicals.

Developing a chRD or chRC

Challenge

The use of appropriate HGVs and exposure parameters is essential to provide an unbiased assessment of the health risk at an existing or a proposed school site. Since school children have higher air, food and water intake relative to their body weight compared to adults; and have activity or behavioral patterns that may lead to higher exposure to environmental contaminants than adults, these higher intakes and unique activity patterns need to be considered in developing a set of child-specific exposure parameters for use in the risk assessment. OEHHA has analyzed these exposure parameters in issuing the report, Guidance for Assessing Exposures and Health Risks at Existing and Proposed School Sites (OEHHA, 2004).

With respect to evaluating non-cancer risk by comparing the potential chemical exposure against the corresponding health criteria in the school setting, HGVs in the form of child-specific reference doses or concentrations should be used. Until the inception of the HSC Section 901(g) program, these child-specific HGVs were not available. For the most part, existing reference doses or concentrations for non-cancer endpoints, which were based on adult human or animal data, were used. The Food Quality Protection Act of 1996 (http://www.epa.gov/opppsps1/fqpa/) was an attempt to address the issue of children sensitivity. In addition to the traditional interspecies and intra-species uncertainty factors, it mandated a safety factor of 10 for the protection of children unless data existed to indicate that children were not more sensitive than adults. Thus, a question has been raised that the intra-species uncertainty factor of 10 would not adequately protect children because it was mainly designed to account for genetic variability such as metabolizing isoenzyme variations.

A case can be made for the development and application of child-specific HGVs based on studies in young animals or epidemiological analysis of pertinent data rather than relying solely on a safety factor or uncertainty factor. While locating the appropriate data is a challenge, OEHHA has strived to do so because children can be more (or less) susceptible to chemical effects due to pharmacodynamic and pharmacokinetic differences between them and adults, and thus empirical data in the young would be preferable. U.S. EPA and the March of Dimes sponsored a workshop -- Identifying Critical Windows of Exposure for Children's Health -- in September 1999 to systematically review the state of knowledge on prenatal and postnatal exposures and subsequent outcomes (Selevan *et al.* 2000). The workshop focused on the nervous, immune, respiratory, reproductive, and endocrine systems—organ systems that are still undergoing development and maturation in children and thus deemed to be potentially more vulnerable to chemical insults. Workshop participants noted that data pertaining to children's

sensitivities to environmental contaminants during various critical developmental periods are limited. In particular, little attention has been given to studying peripubertal/adolescent exposures or adult consequences from childhood exposure. Thus, the state of scientific knowledge pertaining to chemical effects on children is and will continue to be a limiting factor in OEHHA's ability to develop child-specific HGVs for these contaminants.

The evaluation of empirical data in the young can be a complex task. Vulnerability of the young often depends on the organ system in question and its developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, including adolescence. During its critical period(s), a particular structure or function is most sensitive to disruption due to interactions between a toxicant and target tissues that are undergoing biochemical changes. Damage may not be evident until a later stage of development (DeRosa et al., 1998; Bigsby et al, 1999). The brain, for example, is an organ with distinct neurodevelopmental stages that occur in distinct time frames across different regions, so the specific chemical, dose, and time of exposure during development determine if a specific function in the brain will be altered (Faustman et al, 2000).

Differences also exist between children and adults with respect to their absorption, distribution, metabolism, and elimination of chemical contaminants. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC, 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman PL, 1974; Fomon, 1966; Fomon *et al*. 1982; Owen G.M., 1966; Widdowson E.M., 1964). The infant also has an immature blood-brain barrier (Adinolfi, 1985) (Johanson, 1980) and probably an immature blood-testis barrier (Setchell B.P., 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori *et al*. 1990; Leeder and Kearns, 1997; NRC, 1993; Vieira *et al*. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns, who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman PL, 1974; NRC, 1993; West J.R., 1948). Children and adults may differ in their capacity to repair damage from chemical insults.

OEHHA faces an additional challenge when evaluating chemicals that are potential endocrine disruptors. The topic of endocrine disruption during development has been the subject of much scientific and regulatory debate (Colborn *et al*. 1993a; Colborn *et al*. 1993b; Cranmer *et al*. 1984; US EPA, 1998). While not all chemicals selected for the OEHHA review are endocrine disruptors, the endocrine disruptors do pose a greater concern because not only could they directly impact the maturation and proper functioning of the endocrine system, they could also interfere with hormonal signal transduction that leads to abnormal growth and functioning of other target organs (e.g., immune and nervous systems) in school children. Exposure to endocrine disruptors during critical "programming" periods in development, in contrast to exposure during adulthood,

may produce irreversible effects on the reproductive, nervous, and/or immune systems (Bigsby *et al.* 1999). In adulthood, these endocrine disruptors might only produce reversible effects by participating in the "seesaw" process of stimulation and feedback inhibition.

Given the complexity of hormone signaling processes, it is also not surprising to find the evaluation of the dose and response relationship to be another challenge. The shape of the dose response curve may not be linear, but rather shaped like an upright U or an inverted U (Markowski *et al*. 2001; vom Saal *et al.* 1997). This makes data interpretation difficult when the study does not include sufficient treatment doses to span the entire range of interest.

In summary, the use of a study in children or young animals as the basis for a child-specific HGV is preferred. In cases when epidemiological studies involving an adult population, or studies involving adult animals, are used, the challenge is to integrate other experimental studies that suggest a greater sensitivity in the young with adult studies to justify the application of appropriate safety factors.

Process

In June 2002, OEHHA issued a report, "Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code, Section 901(g): Identification of Potential Chemical Contaminants of Concern at California School Sites," documenting the process by which OEHHA identifies chemicals and presenting a compilation of 78 chemicals (OEHHA, 2002). The compilation, whose sole purpose is to provide OEHHA staff with a manageable list of chemicals to work from, has no regulatory status and is a living document – chemicals may be added or removed as new information becomes available.

The chRD development process begins with the prioritization of chemicals from the compilation described in the June 2002 report. OEHHA has employed the following criteria, recognizing that often the availability of health effect data may be the overriding consideration in the selection of chemicals for evaluation.

1. Chemicals having a strong indication of their presence at school sites according to monitoring studies or other reliable sources.
2. Chemicals cited to have possible adverse effects in three or more of the systems that are undergoing critical development during childhood: the nervous, immune, respiratory, reproductive, or endocrine systems.
3. Chemicals that other OEHHA programs have identified as a concern.

OEHHA has adopted the following procedures in evaluating and developing chRDs or chRCs. First, in order to protect children from infancy through the time they leave school, chRDs must consider school-aged children up to age 18, and infants and toddlers in daycare facilities located at school sites. Second, OEHHA opts to consider the most sensitive species and endpoints in our evaluations. When evaluating various studies that use different test parameters to measure the same endpoint such as the nervous system, the lowest LOAEL (lowest observed adverse effect level) or NOAEL (no observed adverse effect level) from these studies would be selected. Third, the paucity of data has underscored the reality that the databases for sensitive endpoints may be incomplete. An uncertainty factor for database deficiency will be considered when there is sufficient information to suggest child-specific sensitivity but insufficient quantitative data from

young animal studies to permit the use of these data. Fourth, because quantifying differences in susceptibility between a developing organ system and a mature one are hampered by the availability of studies that intentionally compare an effect in young animals with one in adult animals and available data are mainly from developmental toxicity studies that limit dosing to the mother during pregnancy, OEHHA staff have deemed that these studies can be used for development of a child-specific health guidance value (chRD or chRC) if it is reasonable to assume that the effect of the chemical on the target organ in the offspring animal would likely occur on the same target organ undergoing development after birth in humans. If studies that include gestational dosing of the mother and lactational dosing of the pups (a protocol of the U.S. EPA Developmental Neurotoxicity Health Effects Test) are available, OEHHA will also consider these studies acceptable for establishing a chRD or chRC if the development of the critical organ system continues to occur during childhood.

Finally, these prenatal and perinatal studies are frequently part of a series of studies to elucidate a "mechanism of toxicity". These studies may not have used a large number of animals or dose ranges. However, due to the critical windows in which cell proliferation and differentiation are occurring in specific organ systems during childhood, a study in young animals is usually preferred over one in adults, even adult humans. With corroborating studies showing a mechanism of action and biological plausibility, OEHHA will consider using these studies as appropriate. However, data from adult animals may be used, if they are from high quality studies and if there are data to provide a means of inference to vulnerability of development in young animals so that an appropriate uncertainty or safety factor can be applied.

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Atrazine

Summary

OEHHA has identified atrazine as a contaminant of concern pursuant to Health and Safety Code Section 901(g). In an updated review of available literature, OEHHA has not found additional critical studies with a NOAEL or LOAEL that is comparable to, or lower than, those used in establishing the existing health criteria, which could serve as a basis for developing a child-specific reference dose (chRD) for atrazine. OEHHA determines that it is appropriate to apply the NOAEL derived from the Morseth (1996) study for the luteinizing hormone (LH) endpoint in establishing a chRD of 0.006 mg/kg-day for assessing the non-cancer risk of atrazine at existing or proposed school sites. This chRD will also protect the cardiomyopathy endpoint discussed in OEHHA's 1999 Public Health Goal document.

What is atrazine?

Atrazine, 6-chloro-N-ethyl-N'-(1-methylethyl)-triazine-2,4-diamine, is a herbicide that is widely used to kill weeds. It is used in agricultural areas and on highway and railroad right-of-ways for weed control (ATSDR, 2003). Table 1 provides a summary of atrazine use in California. The data do not indicate an increasing or a decreasing use trend, but rather, suggest a sustained use of atrazine.

Table 1

Atrazine Use Trend in California Pesticide Use Report, California Department of Pesticide Regulation							
	POUNDS APPLIED						
	1997	1998	1999	2000	2001	2002	2003
ATRAZINE	48,482	57,003	72,175	57,403	62,872	59,292	58,245

What characteristics make atrazine of concern pursuant to Health & Safety Code Section 901 (g)?

OEHHA has identified atrazine as a contaminant of concern pursuant to HSC Section 901(g) (OEHHA, 2002). Atrazine is of concern to schoolchildren because available data indicate that atrazine could adversely impact the development of both the male and female reproductive systems. Various animal studies have shown that atrazine affects the hypothalamus, pituitary,

gonads, and/or pubertal maturation (ATSDR, 2003). In addition, atrazine could potentially affect the cardiovascular, immune, and nervous systems.

Atrazine is also likely to be found at school sites that have a history of agricultural activities. While atrazine is relatively mobile in the surface soil, it becomes immobilized once leached into the subsoil and degrades slowly (OEHHA, 1999). No leaching of atrazine or its metabolites was observed below soil layers of 15-30.5 cm in California, Minnesota, and Tennessee soils (U.S. EPA, cited in OEHHA, 1999). Thus, atrazine may accumulate in upper subsoil layers after years of its application. Atrazine has been found in current or former National Priorities List (NPL) sites (ATSDR, 2003). ATSDR notes that the total number of NPL sites evaluated for this herbicide is not known. However, ATSDR feels that the number of sites with atrazine found would increase as more atrazine sampling and analysis are performed. Likewise, the total of school sites evaluated for atrazine is not known; nevertheless, it will likely be found as more atrazine sampling and analysis is included.

What are the existing health guidance values for atrazine?

U.S. EPA Reference Dose (RfD)

U.S. EPA has established an RfD of 0.035 mg/kg-day for atrazine (U. S. EPA., 1987). The RfD is based on a study involving Sprague-Dawley rats (Ciba-Geigy, 1986). Dietary doses of 0, 0.5, 3.5, 25 and 50 mg/kg-day of atrazine were given to rats (20/sex/dose) for two years. Mean body weights were significantly depressed ($p<0.01$) in males and females receiving 25 and 50 mg/kg-day of atrazine. Based on decreased body weight gain, the LOAEL for systemic toxicity is 25 mg/kg-day and the NOAEL 3.5 mg/kg-day. U.S. EPA applied an uncertainty factor of 100 (10 for interspecies and 10 for intraspecies) to the NOAEL in calculating the RfD.

It should be noted that atrazine is no longer being reassessed under the Integrated Risk Information System (IRIS) Program (See Federal Register February 9, 2004 Volume 69, Number 26). Updates are performed by the Office of Pesticide Program (OPP).

U.S. EPA OPP Health Criteria

More recently, U.S. EPA's OPP has established two health criteria for use in a human health risk assessment in support of the re-registration eligibility decision for atrazine (U.S. EPA, 2002c). These health criteria are based on a study on adult rats, which evaluated the effect of atrazine exposure on the proestrus luteinizing hormone (LH) surge (Morseth, 1996). Atrazine, 97.1 percent a.i.(active ingredient), was administered to 360 female Sprague Dawley rats in the diet for 26 weeks (approximately six months). Dose levels were 0 (negative control), 25, 50, and 400 parts per million (ppm) (0, 1.80, 3.65, 29.44 mg/kg/day). Body weight, body weight gain and food consumption were significantly ($p\leq0.05$) decreased in animals at the high dose tested compared to controls (body weight decreased 8.5 percent at the end of the study and food consumption decreased 3.75 percent for the entire study). The percentage of days in estrus was significantly increased ($p\leq0.01$) during the 21-22 and 25-26 week time periods at the high-dose level. Percent days in estrus were also increased during the 21-22 and 25-26 week time periods at the mid dose, but the increase was only significant ($p\leq0.05$) for the 21-22 week time period. The

proestrus afternoon LH surge was severely attenuated at the high dose (29.44 mg/kg-day) (LH levels at most sampling time points were actually decreased compared to baseline) and less so at the mid dose (3.65 mg/kg-day) (maximum increase in the mid dose group over baseline was 157% compared to maximum increase over baseline in controls of 273%). Pituitary weights were increased at the high dose (absolute weight increased 22% and weight relative to body weight was increased 28%). Pituitary weights at the other two doses were not affected. At the high dose, there was a slight increase in animals displaying enlarged pituitaries (0% in controls compared to 3.4% at 29.44 mg/kg/day) and thickened mammary glands (0% in controls compared to 6.7% at 29.44 mg/kg/day). There were no other gross necropsy findings in the high dose that could be attributed to compound exposure and there were no compound-related gross pathology findings at the mid- or low-dose. Selected tissues were saved for histopathology but those results have not been reported. There were no compound-related effects in mortality or clinical signs. The proestrus afternoon prolactin surge was not affected by compound exposure at any dose. The low dose (1.8 mg/kg-day) had no effects on the estrous cycle and LH surge. Based on these data, U.S. EPA determines that the attenuation of LH surge is the most sensitive endpoint, with a LOAEL of 3.65 mg/kg-day and a NOAEL of 1.8 mg/kg-day.

The NOAEL of 1.8 mg/kg-day was used in conjunction with uncertainty and child safety factors to calculate the two health criteria - one for assessing dietary (including drinking water risk) and the second for assessing the risk from ingestion of, or dermal contact with, contaminated soil. An uncertainty factor of 100 (10 for interspecies and 10 for intraspecies) was uniformly applied; however, a different child protection factor was applied in developing the dietary and the soil health criteria. U.S. EPA's Health Effects Division (HED), Food Quality Protection Act (FQPA) Safety Factor Committee (SFC) determined that there is not sufficient reliable data to assign a different safety factor than the 10X default factor to dietary exposure scenarios but that there is reliable data demonstrating that the safety of infants and children will be protected by use of an additional safety factor of 3X for soil exposure scenarios (U.S. EPA, 2002b).

The following is a summary of U.S. EPA's analysis in support of its respective 10X and 3X factor determinations. Other atrazine testing using young rats has been limited to short periods of dosing in specific developmental periods. Uncertainties are raised for susceptibility during earlier developmental periods as well as for consequences of earlier developmental exposure with longer duration of dosing throughout development. The effects of neurotransmitters/peptides (known to be critical for normal development and which could potentially translate into severe effects in children that may not be manifested until later in life) have not been fully characterized. As the Federal Insecticide Fungicide Rodenticide Act (FIFRA) Scientific Advisory Panel noted, there are concerns for behavioral effects in the young resulting from atrazine's mode of action on the nervous system and the dose level at which these effects might occur. As such, U.S. EPA concluded that the default 10X FQPA safety factor for the dietary scenario is statutorily required in the absence of reliable evidence showing that a safety factor different than the statutory 10X default would be protective of infants and children. In addition to the neuroendocrine uncertainties, U.S. EPA felt that there are data gaps especially pertaining to the extent of atrazine exposure via drinking water. Although it is known that there is significant, widespread exposure to atrazine and its metabolites in drinking water, limitations in the extent, frequency, and compounds tested for in the monitoring data raise significant uncertainties regarding the level of exposure to atrazine and its metabolites.

U.S. EPA used the following rationale to conclude that an additional Special FQPA Safety Factor of 3X would be adequate in the soil exposure scenario. The toxicology endpoints reviewed (e.g., delayed puberty in males and females, suppressed LH surge, and decreasing hypothalamic norepinephrine (NE) and gonadotropin releasing hormone (GnRH), to be elaborated in the next section) are all consistent with atrazine's mode of action on the neuroendocrine system. Using the most sensitive endpoint with the lowest NOAEL (1.8 mg/kg-day) as a basis for the health criteria is appropriate, albeit that this NOAEL is derived from an adult rat study. When comparing the effects observed in adults to those observed in the young, U.S. EPA noted that clear NOAELs were established for delayed puberty in both male and female offsprings (6.25 mg/kg-day in males; 12.5 mg/kg-day in females). If the offspring NOAEL of 6.25 mg/kg-day from this study is protected by a factor of 3X, the extrapolated NOAEL is 2.0 mg/kg-day. Comparing this value to the adult NOAEL of 1.8 mg/kg-day from the 6-month LH Surge study indicates that the young are not likely to be an order of magnitude more sensitive than the adult. A 3X safety factor applied to the NOAEL from the adult study would provide infants and children with an order of magnitude (10X) level of protection from the lowest offspring NOAEL. Therefore, U.S. EPA concluded that, given the half-log (3X) protection provided children by the more sensitive endpoint in adults and the relatively tight pattern of NOAELs for adults and children from existing studies, a half-log reduction in the default Special FQPA Safety Factor (3X) is considered to be sufficiently protective of the concerns for this CNS mode of action in the young.

Using the NOAEL of 1.8 mg/kg-day, an uncertainty factor of 100, and a child safety factor of three or 10, U.S. EPA has developed a health criterion of 0.006 mg/kg-day for the soil scenario and a criterion of 0.002 for the dietary/drinking water scenario.

ATSDR Minimal Risk Level (MRL)

ATSDR (2003) has established a MRL of 0.003 mg/kg/day, which was derived from a 19-day pig study (Gojmerac *et al*. 1999). Groups of nine female Swedish Landrace/Large Yorkshire cross pigs (6 to 7-month-old gilts) were administered 0 or 1 mg/kg-day atrazine in the feed for 19 days beginning with the onset of estrus (day 0). Blood samples were drawn three times daily at 3-hour intervals on five post-treatment days (this corresponded to the two days before [days -1 and -2] the next estrus, the expected day of the next estrus [day 0], and two days [days 1 and 2] after the expected estrus). Serum 17β-estradiol (E2) concentrations in the blood samples were determined, and histopathological examination of the uterus was performed. E2 concentrations were statistically significantly different ($p<0.001$) from controls on all five days measured. In controls, E2 concentrations were high on days -2 and -1, then dropped on day 0 (beginning of estrus) and remained low on days 1 and 2. In treated animals, E2 concentrations were lower than controls on days -2 and -1, and higher than controls on days 0 through 2. Treated pigs failed to exhibit overt signs of estrus onset and uterine histopathology indicated a state of uterine rest (diestrus) at the end of the observation period. A slight, but steady increase of E2 hormone level was seen in the treated animals on day 24 of the estrus cycle (day 2). The authors suggested that the balance of the E2 hormone level was being gradually restored, which is the pattern that would be anticipated if the animals were about to go into estrus. Similar results were seen after administration of 0 or 2 mg/kg/day atrazine (Gojmerac *et al*. 1996). The oral MRL of 0.003

mg/kg-day was calculated based on the LOAEL of 1.0 mg/kg-day and an uncertainty factor of 300 (10 for LOAEL to NOAEL conversion, 10 for extrapolation from animals to humans, and 3 for human variability). An uncertainty factor of three for human variability was used instead of 10 because the critical effect was identified in a sensitive population (young, developing female pigs).

CDPR Risk Characterization

CDPR has issued a risk characterization document in support of its regulatory activity on atrazine (CDPR, 2001a). The most sensitive endpoint, cardiomyopathy, with a chronic NOAEL of 0.48 mg/kg-day (rounded to 0.5 mg/kg-day) was identified from a one-year dog study for use in characterizing the chronic, non-cancer risk from atrazine exposure (O'Connor et al., 1987). Atrazine (97 percent pure) was given to 5-month-old, pre-pubertal, beagles (6 dogs/sex in the control and high dose groups; and 4 dogs/sex in the low-and mid dose groups) for one year at dietary levels of 0, 15, 150, and 1000 parts per million (ppm) (equivalent to male: 0, 0.48, 4.97, and 33.65 mg/kg-day; female; 0, 0.48, 4.97 and 33.8 mg/kg-day). Three animals were killed during the study in moribund condition: one 150 ppm male on day 75; one 1000 ppm female on day 113 and one 1000 ppm male on day 250. Cardiomyopathy (discrete myocardial degeneration) was the most significant effect observed in animals fed 1000 ppm. Clinical signs associated with cardiac toxicity were: ascites, cachexia, labored/shallow breathing, and abnormal EKG (irregular heart beat and increased heart rate, decreased P-II values, atrial premature complex, atrial fibrillation). These were first observed as early as 17 weeks into the study. Gross pathological examination revealed moderate-to-severe dilation of the right atrium (and occasionally the left atrium), microscopically manifested as atrophy and degeneration of the atrial myocardium. Other effects observed were: decreased food consumption and body weight gain at 1000 ppm, decreased red blood cell (RBC) count, hemoglobin (Hb), hematocrit (HCT), total protein and albumin, as well as an increase in platelet counts, P, Na, glucose and liver and ovary relative weights at 1000 ppm. The authors of the study concluded that 150 ppm (4.97 mg/kg-day) was the NOAEL. However, CDPR, in analyzing the data, came to the conclusion that the NOAEL is 15 ppm (0.48 mg/kg-day) (CDPR, 2001b). The following is an excerpt of CDPR's toxicological summary:

> "At 150 and 1000 ppm, females experienced increased heart weights and in both sexes treatment related electrocardiographic changes in the heart accompanied by gross and histologically detectable pathology were observed. Previously reviewed as having a NOAEL of 15 ppm (Silva, 5/20/88), the study has been re-evaluated based upon information submitted to CDPR by Ciba-Geigy. The status, however, remains unchanged."

Gammon et al. recently reviewed the human health and ecological aspects of atrazine use in California (Gammon et al., 2005). The article further elaborates CDPR's conclusion in the re-review of the dog data. Although 5.0 mg/kg-day may be a more appropriate NOAEL based on group data, CDPR's consensus was to use 0.5 mg/kg-day because one of the three dogs in the 5.0 mg/kg-day showed moderate atrial dilation and altered heart weight. Furthermore, Gammon et al. elaborated that the selection of 0.5 mg/kg-day as the NOAEL is supported by a benchmark dose for increased extra-medullary hematopoiesis in the spleen of the female SD rat in a two-year study.

OEHHA Public Health Goal (PHG)

OEHHA has developed a cancer-based PHG of 0.00015 mg/L (0.15 µg/L or 0.15 ppb) for atrazine in drinking water (OEHHA, 1999). In that process, OEHHA also reviewed non-cancer endpoints of atrazine. The most sensitive endpoint identified was cardiomyopathy, observed in a one-year dog study (O'Connor et al., 1987). This is the same study the CDPR used in characterizing the chronic, non-cancer risk of atrazine (CDPR, 2001a). OEHHA adopted CDPR's analysis as a basis for calculating a reference dose for the non-cancer endpoint. An uncertainty factor of 100 (10 for interspecies and 10 for intraspecies) was applied to the NOAEL of 0.48 mg/kg-day in calculation.

What data indicate a critical effect of atrazine in school-age children?

Reviews performed by ATSDR, U.S. EPA, and CDPR (ATSDR, 2003; U.S. EPA, 2002c; and CDPR, 2001a) were examined to establish a baseline for atrazine's non-cancer effects on humans, particularly children. There were a number of worker incidents reported. It appears that the majority of cases involved skin illnesses such as dermal irritation and pain, rashes, and welts; and eye illnesses such as eye damage, blurred vision, conjunctivitis, irritation, and pain. Incidents involving children were also reported. Dermal and ocular effects accounted for the majority of symptoms associated with exposure to atrazine, though a few cases also reported gastrointestinal, neurological, and respiratory effects. Moreover, OEHHA examined available literature and did not locate any additional human studies. Because there are so few studies on humans and the exposure levels are usually unknown, OEHHA depends primarily on animal data to assess the potential effects of atrazine on children.

Atrazine can adversely impact the hepatic, renal, cardiovascular, immune, nervous, or reproductive system (ATSDR, 2003; OEHHA, 1999). Cardiovascular and reproductive systems are sensitive endpoints, and are of special concern to young children because these organ systems are vulnerable to chemical injuries. As discussed above, cardiomyopathy was identified from a pre-pubertal dog study used by CDPR in characterizing the chronic, non-cancer risk of atrazine (O'Connor et al., 1987). Cardiomyopathy can, and often does, occur in young children (Lucile Packard Children's Hospital, 2007). While the cardiovascular (CV) system begins to develop within two weeks after conception and is one of first organ systems to become functional, postnatal growth continues, which includes the hypertrophy of myocytes, increase in the number of DNA copies (polyploidy) in myocytes, and increase in capillary density (Penney, 2004). Prenatal and postnatal development of the CV system could confer critical windows of vulnerability to chemical injury. A review from the Journal of The American Academy of Pediatrics further elaborates the windows of vulnerability of the heart, which include fetal life, childhood, and adolescence (Mone et al., 2004). Cardiomyopathy tends to be progressive and sometimes worsens fairly quickly; it is a leading cause for heart transplantation (Lucile Packard Children's Hospital, 2007). Exposure to toxins is a known etiology of cardiomyopathy. Most of the human data came from chemotherapy given to fight cancer. High incidence of cardiomyopathy in children, for example, was observed in adriamycin and DTIC ((3,3-dimethyl-1-triazeno)- imidazole-4-carboxamide) combination chemotherapy (Smith et al., 1977). Following 10 patients with ages between four and 14, the authors observed four of these patients developed drug-related cardiomyopathy. Three of the effected patients had acute cardiac failure

while the fourth had mild symptoms of congestive cardiac failure. Aside from the pre-pubertal dog model, at least one other animal model provides additional evidence that the heart is a sensitive endpoint for children. TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) was shown to induce postnatal cardiac hypertrophy in mice following perinatal exposure (Thackaberry et al., 2005).

Data on young animals indicate that the reproductive system is another target of atrazine. As discussed above, atrazine interrupted the estrous cycle through its action of attenuating LH surge. The mid-menstrual cycle LH surge is necessary for ovulation (Guraya *et al*., 1992) and thus atrazine could suppress ovulation and create fertility issues.

Other animal studies also indicate that atrazine affects the maturation of both the male and female reproductive systems. Rat studies have demonstrated that atrazine induced a delay in female sexual maturation. Female Wistar rats were dosed by oral gavage from postnatal days 22 thorough 41 with 0, 12.5, 25, 50, 100 or 200 mg/kg of atrazine. Vaginal opening, an indicator of female sexual maturation, was significantly delayed in a dose-dependent manner (Ashby *et al*. 2002). Laws *et al*. (2000) observed a similar delay of vaginal opening. Studies have also shown that atrazine could adversely impact the male reproductive system. Serum and intra-testicular levels of testosterone were significantly reduced when juvenile male rats were exposed to atrazine by gavage (Friedmann, 2002); the ventral prostate and seminal vesicle weights of peripubertal rats were reduced (Trentacoste *et al.,* 2001); and preputial separation, an indicator of male sexual maturation, was also delayed in atrazine treated juvenile rats (Stoker *et al*., 2000).

In discussing the mechanism of toxicity, U.S.EPA cited several studies in proposing that atrazine acts on the hypothalamic-pituitary-ovarian axis (U.S.EPA, 2002a). Atrazine affected the hypothalamus, leading to a decreased secretion of hypothalamic norepinephrine and a decreased release of gonadotropin releasing hormone (GnRH) (Cooper *et al*., 1998). Atrazine caused an attenuation of LH surge (presumably via its action on the hypothalamus) (Cooper *et al*., 2000; Morseth, 1996). Perturbation of LH, in turn, affected the aforementioned pubertal development.

There is an important implication of the animal data on human sexual maturation. LH plays a significant role during puberty in girls to ensure their sexual maturation (Plant et al., 1995). At puberty, as the amplitude of LH pulses increases, the theca cells of the ovaries begin to produce testosterone and smaller amounts of progesterone. Much of the testosterone moves into nearby granulosa cells. Smaller increases of follicle stimulating hormone (FSH) induce an increase in the aromatase activity of these granulosa cells, which converts most of the testosterone to estradiol for secretion into the circulation. Rising levels of estradiol produce the characteristic estrogenic body changes of female puberty: growth spurt, acceleration of bone maturation and closure, breast growth, increased fat composition, growth of the uterus, increased thickness of the endometrium and the vaginal mucosa, and widening of the lower pelvis.

LH also plays an important role during puberty in boys to ensure their sexual maturation (Plant et al., 1995). LH stimulates the Leydig cells of the testes to make testosterone. Testosterone is converted into dihydrotestosterone in target tissues, which in turn mediates the maturation of males' secondary sexual characteristics. In addition, a portion of testosterone in adolescent boys

is converted to estradiol. Estradiol mediates the growth spurt, bone maturation, and epiphyseal closure in boys just as in girls.

In summary, attenuating LH during the pubertal window by atrazine could potentially delay or interrupt sexual maturation in children. This would have an important ramification on reproductive health.

Which study should be used as a basis for establishing the child-specific reference dose for atrazine?

From literature search and review, OEHHA did not find additional critical studies with a NOAEL or LOAEL that is comparable to, or lower than, those used in establishing the existing health criteria, which could serve as a basis for developing a child-specific reference dose for atrazine. Table 2, which presents these existing health criteria and a potential chRD, provides a framework for discussion.

OEHHA does not recommend using U.S. EPA's RfD because the study endpoint, body weight, is not a good measure of potential critical effects on children. Moreover, the numerical value of the RfD is the highest (least protective) among those values compared. While U.S. EPA's health criterion for dietary assessment (in support of the re-registration eligibility decision for atrazine) is most health protective, OEHHA feels that the use of this criterion is not appropriate in the context of school-site risk assessment. Because the health criterion was intended for dietary assessment, U.S. EPA was statutorily required to use the default 10X FQPA safety factor in the absence of scientific certainty. The school-site risk assessment program does not pertain to dietary assessment and is not subject to FQPA. As such, OEHHA does not recommend using this health criterion, which is based on a 10X FQPA factor, for school-site assessment. OEHHA concurs with U.S. EPA that the application of a 3X child safety factor would suffice for non-dietary assessments.

With respect to U.S. EPA's criterion for residential assessment (in support of the re-registration eligibility decision for atrazine), ATSDR's MRL, and the reference dose derived from CDPR's Risk Characterization, these values fall within a narrow range (0.003-0.006 mg/kg-day). Their supporting studies and respective endpoints are relevant to children. The MRL is based on a study of immature female pigs (Gojmerac *et al*. 1999). The reference dose derived from CDPR's Risk Characterization is based on a study of young dogs. While the health criterion for residential assessment is based on a study of adult rats, the young rat study cited by U.S. EPA support the view that the critical effect on the reproductive system observed in adult rats could also be triggered by atrazine in young animals. Thus, this adult rat study is pertinent to children.

Table 2

	Health Criteria (mg/kg-day)	Inter-species Factor	Intra-species Factor	LOAEL-to-NOAEL Factor	Child Safety Factor	LOAEL* or NOAEL** (mg/kg-day)	Study	Endpoint
U.S. EPA RfD	0.035	10	10	1	1	3.5**	2 yr rat	Decreased body weight gain
U.S. EPA Criterion for dietary assessment	0.002	10	10	1	10	1.8**	6 mo female rat	attenuation of LH surge
U.S. EPA Criterion for residential assessment	0.006	10	10	1	3	1.8**	6 mo female rat	attenuation of LH surge
ATSDR MRL	0.003	10	3	10	1	1*	19 day gilts	Decreased estrogen levels; delayed onset of estrus
Reference dose derived from CDPR Risk Characteri-zation	0.005	10	10	1	1	0.48**	1 yr juvenile dogs	Increased heart weight ; myocardio pathy

Regarding the endpoints, OEHHA feels that the endocrine/reproductive system effects observed from the rat study (Morseth, 1996) or the pig study (Gojmerac *et al*. 1999) as well as the cardiovascular effects observed in the dog study (O'Connor et al., 1987) are clearly relevant. However, the pig study is less preferable because it did not identify a NOAEL. The rat study employed larger group sizes; it yielded a smaller LOAEL-to-NOAEL ratio (3.65/1.8) when compared to that (4.97/0.48) of the dog study. The "tightness" of this ratio observed in the rat study provides an increased confidence of its NOAEL. Thus, OEHHA is using the rat study in establishing its chRD. This chRD will be protective of both the endocrine/reproductive and cardiomyopathy endpoints. Calculation of this chRD is given below:

$$chRD = \frac{\text{NOAEL}}{\text{UF}} = \frac{1.8\ \text{mg/kg - day}}{300} = 0.006\ \text{mg/kg - day}$$

Where,

UF = Uncertainty factor of 300 (10 for interspecies extrapolation, 10 for human variability, and three for child protection based on U.S EPA's analysis).

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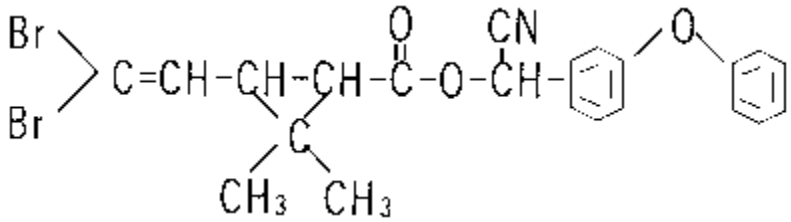
Deltamethrin

Summary

OEHHA has identified deltamethrin as a contaminant of concern pursuant to Health and Safety Code Section 901(g). OEHHA has reviewed available data in developing a chRD for deltamethrin for school site risk assessment. The nervous system is the primary target for deltamethrin toxicity. Available information indicates that neurotoxicity is the most sensitive endpoint, and OEHHA is recommending a chRD of 0.0001 mg/kg-day for deltamethrin based on that endpoint (Goldenthal, 1980).

What is deltamethrin?

Deltamethrin is a type II pyrethroid insecticide, with the following structural formula:



The pyrethroids are synthetic chemicals with structure similar to the pyrethrins, which are naturally occurring chemicals found in certain chrysanthemum flowers. The pyrethroids are generally more toxic to insects and mammals, and more persistent in the environment than pyrethrins (ATSDR, 2003). The type II pyrethroids are generally characterized by having a cyano group in the structure; and by producing effects that may include pawing and burrowing behavior, salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremors that progress to sinuous writhing (choreoathetosis).

In addition to being manufactured as a pesticide, deltamethrin is also a breakdown product of tralomethrin, another pyrethroid. Environmental fate studies have indicated that tralomethrin is unstable under either an aerobic or anaerobic condition, and rapidly undergoes debromination to form deltamethrin (CDPR, 2000).

Table 1 summarizes the use trend of deltamethrin in California. The data indicate that deltamethrin is largely used in structural pest control, and its use has increased by an 80 fold in six years. Other uses include the treatment of cotton, non-food/feed areas of food/feed processing plants, granaries, and ornamental plants (CDPR, 2000).

Table 1

Deltamethrin Use Trend in California Pesticide Use Report, California Department of Pesticide Regulation						
	POUNDS APPLIED					
	1998	1999	2000	2001	2002	2003
STRUCTURAL PEST CONTROL	212	3,305	10,606	17,107	12,458	17,690
Chemical Total	214	3,343	10,910	17,721	13,001	18,301

What characteristics make deltamethrin of concern pursuant to Health & Safety Code Section 901 (g)?

The nervous system is a primary target for deltamethrin toxicity. Its potential effects on the developing brain in children are of concern.

A recent California portable classroom study has identified deltamethrin and tralomethrin as contaminants in floor dust (ARB and DHS, 2003). Floor dust from 39 portable classrooms and 38 traditional classrooms were analyzed. Deltamethrin/tralomethrin were detected in 29 percent of the portable classrooms and 39 percent of the traditional classrooms. Contaminated floor dust is especially a concern in rooms used by very young children, who spend a substantial amount of time on the floor and may be exposed to deltamethrin through ingestion, inhalation, and even through dermal absorption. Carpets can serve as a reservoir of dust and particles.

What are the existing health guidance values for deltamethrin?

U.S. EPA Health Criterion for Chronic Dietary Risk Assessment

U.S. EPA, in 40 Code of Federal Regulations, Part 180, establishes tolerance levels for deltamethrin on a number of agricultural commodities (U.S. EPA, 2004). U.S. EPA summarized those guideline and non-guideline studies that the agency had reviewed in defining a chronic NOAEL of 1.0 mg/kg-day from a dog study (Ryle et al., 1993) for use in a dietary assessment to support the promulgated tolerance levels. In the Ryle study, beagles (4 males and 4 females per group) were orally dosed with a capsule containing 0, 1, 10 or 50 mg/kg-day of deltamethrin for 52 weeks. The increased incidences of chewing and scratching of extremities, and liquid feces were observed in the higher dose groups and U.S. EPA determined that 1.0 mg/kg-day is the NOAEL. An uncertainty factor of 100 (10 for interspecies and 10 for intraspecies) and a 3X Food Quality Protection Act (FQPA) safety factor based on difference in brain concentration of deltamethrin between weanling and adult rats (Sheets et al., 1994) were applied to the NOAEL in developing the health criterion of 0.003 mg/kg-day for the dietary risk assessment.

ATSDR Minimal Risk Level (MRL)

In the draft Toxicological Profile for Pyrethrins and Pyrethroids, the Agency for Toxic Substances and Disease Registry (ATSDR) proposes a MRL of 0.002 mg/kg/day for deltamethrin (ATSDR, 2001). This MRL is based on results of a study that indicate altered motor behavior in adult mice treated with deltamethrin neonatally (Eriksson and Fredriksson, 1991). However, ATSDR withdrew this MRL from the final Toxicological Profile (ATSDR, 2003), noting that other investigators (Ray et al. 2002) were unable to replicate the results of the Eriksson study.

In the 1991 Eriksson study, groups of 10-day-old male NMRI mice were treated with 0 (vehicle control) or 0.7 mg deltamethrin/kg in a fat emulsion vehicle by gavage daily for seven consecutive days. Following treatment cessation, 17-day- and 4-month-old mice were tested for habituation to novel stimuli provided by the test chamber. Decreasing spontaneous behaviors in locomotion, rearing, and total activity are used as a measure for habituation. The habituation test, in turn, is a measure for cognitive abilities. This type of tests is used by psychologists in the assessment of children (University of Bistol, 2007). The habituation test is based on the premise that the amount of time an infant spends looking at (non-threatening) novel stimuli before losing interest reflects information processing efficiency in that infant. Thus, an infant who "habituates" (quiets down) to a stimulus quickly would be assumed to be more efficient at processing information than one who takes a long time looking at this stimulus before losing interest. Recent research using the habituation paradigm has pointed towards some degree of continuity in development from early infancy to later childhood, with habituation measures in early infancy correlating with later developmental assessments such as IQ tests.

In Eriksson's experiment, habituation tests were conducted for one hour, and scores were summed for three 20-minute periods. Behavior in the 17-day-old mice was not significantly different from that in controls. However, when tested at four months of age, deltamethrin-treated mice exhibited significantly increased locomotion and total activity during the last 20 minutes of the test period. This was interpreted as disruption of a simple, non-associative learning process, (i.e., habituation), or a retardation in adjustment to a new environment. Receptor assays, performed one–two weeks following behavioral testing at four months of age, revealed a significant trend toward a decrease in muscarinic acetylcholine (MACh) receptor density in the cerebral cortex of deltamethrin-treated mice. No significant treatment-related changes in this parameter were seen in two other brain regions, the hippocampus and striatum. The authors concluded that disturbances of the cholinergic system during rapid development in the neonatal mouse could lead to permanent changes in cholinergic and behavioral variables in the animals as adults.

As observed by ATSDR, the study shows that oral exposure of neonatal mice to deltamethrin levels below those resulting in overt signs of acute neurotoxicity may cause changes in receptor densities within the brain that can be observed at maturation. Neonatal exposure can also cause changes in behavioral patterns that are first apparent in adulthood. On that basis, the LOAEL of 0.7 mg/kg-day is divided by an uncertainty factor of 300 (10 for LOAEL-to-NOAEL conversion, 10 for interspecies extrapolation and three for human variability; three instead of 10 for human

variability was used because ATSDR feels that the neonatal mouse is a sensitive subject.) to derive the proposed MRL.

ATSDR did not explicitly discuss the basis for not finalizing the proposed MRL. Since the Ray et al. study, in which the authors concluded that they could not replicate the results of Eriksson's study on deltamethrin, was cited in the final ATSDR report, this could be interpreted as a reason for not promulgating a MRL for deltamethrin. However, OEHHA noted that the Ray et al. study results were published as an abstract (Ray et al. 2002) and as a letter to the editor (Muhammad et al. 2003), rather than as a full article in a peer review journal. Aside from not having the benefit of peer review, the brevity of the information rendered does not permit one to follow the experimental set up and discern how the receptor binding and behavioral studies were conducted. The authors also acknowledged that they did not follow Eriksson's original experimental conditions in its entirety. In particular, the male and female mice were not separately housed, as done in the original study. This condition may influence the outcome of these behavioral studies. In comparing habituation data between the two studies, the Ray et al. study noted that the rate of habituation in their controls was markedly slower than the controls in the Eriksson and Fredriksson study. This reduced their ability to detect any delay in habituation in the treatment group.

CDPR Risk Characterization

In its Risk Characterization Document for deltamethrin, the California Department of Pesticide Regulation (CDPR) identified both acute/sub-chronic and chronic No Observed Effect Levels (NOELs) for calculating margins of exposure (MOE)(CDPR, 2000). An MOE is defined as the ratio of absorption-adjusted NOEL to the estimated human absorbed dose. MOEs are calculated for various exposure scenarios.

An acute/subchronic LOEL of 0.1 mg/kg-day and an estimated acute/subchronic NOEL of 0.01 mg/kg-day were identified based on a 13-week oral study in dogs (Chesterman, 1977). Deltamethrin was dissolved in a solvent and inserted into gelatin prior to administration. Treatment doses were 0, 0.1, 2.5, or 10 mg/kg-day. Three animals/sex/group were used for controls and 0.1 mg/kg-day. All other dose groups had five animals per sex. The endpoints including liquid feces, vomiting, and tremors, which are characteristic of autonomic nervous system dysfunction, were reported during the first week of treatment.

A chronic NOEL of 0.1 mg/kg-day was identified based on a two-year oral study in rats (Goldenthal, 1980). Deltamethrin without a solvent carrier was administered in the feed to Sprague-Dawley rats at levels of 0, 2, 20 or 50 ppm (equivalent to 0, 0.11, 1.1, or 2.8 mg/kg/day). Ninety animals per sex per dose were used, with 10 animals/sex /dose for interim sacrifice at 6, 12, and 18 months. Dose-related increases in the degeneration of sciatic, tibial, and plantar nerves were observed at 18 months.

What data indicate a critical effect of deltamethrin in children?

Reviews of human data and illness reports by CDPR (2000) and ATSDR (2003) documented deltamethrin toxicities from agricultural use and accidental or suicidal poisoning. Effects from oral ingestion included epigastric pain nausea, vomiting, coarse muscular fasciculation, and coma. Workers exposed to deltamethrin during its manufacture experienced cutaneous and mucous membrane irritation. These reviews and OEHHA's literature review, however, have not identified children specific data. Thus, the potential effects of deltamethrin are based on animal data.

The developmental neurotoxicity of pyrethroids was recently reviewed, which offers some insight on the potential effects of deltamethrin (Shafer et al. 2005). While the mechanisms of action on the developing brain have not been completely worked out, the review presented some evidence to suggest the vulnerability of children to pyrethroids. Specifically, pyrethroids could disrupt voltage-sensitive sodium channel (VSSC) function and expression during development, leading to irreversible neurotoxic effects. Pyrethroids are known to bind the α-subunit of VSSCs. Different forms of the α-subunit are expressed during neurodevelopment. For example, high expression of $Na_v1.3$ during the embryonic period diminishes as expression of $Na_v1.2$ increases in the early postnatal period. The latter α-subunit is replaced by $Na_v1.6$ as myelination proceeds. The authors concluded that given the previously reported differences in α-subunit sensitivity to pyrethroids, the complex ontogeny of VSSC expression could result in altered sensitivity and perturbation of the developing nervous system by pyrethroids. Phenytoin, an anticonvulsant having a mode of action similar to that of pyrethroids in interfering with the activity of VSSCs, was further used to illustrate the potential effect of pyrethroids. In humans, the use of phenytoin during pregnancy has been associated with a number of defects in offspring including microcephaly and intellectual impairment. Studies in animal models support the human findings. However, the authors were careful to underscore that there are currently no data to suggest that developmental exposure to pyrethroids results in similar effects.

OEHHA also reviewed the literature specific to deltamethrin, including the Eriksson and Ray studies cited by ATSDR. Pertinent studies from the targeted review are summarized in Table 2. Collectively these studies provide a picture that prenatal or early postnatal exposure to deltamethrin, at doses below those that cause overt neurotoxic symptoms, could alter normal brain development and maturation. The effects of deltamethrin could manifest themselves later in life. Thus, infants in daycare centers and young school children would be vulnerable to deltamethrin exposure.

In the Aziz et al. (2001) study, deltamethrin (grade not reported) at a dose of 1 mg/kg-day was orally given to pregnant albino Wistar rats from GD 14-20. No gross abnormality was observed in deltamethrin exposed or unexposed rats. Body weights of treated and control pups were not significantly different. Acetylcholinesterase (AchE) in the hippocampal region was increased by 28 and 16 percent ($P<0.05$) in exposed progeny at 6 and 12 weeks of age, respectively. MACh receptors, on the other hand, were significantly reduced in the hippocampus when measured at those same time periods. A significant decrease in relearning performance (memory) of the exposed progeny was also noted when they were subjected to a Y maze test at 6 and 12 weeks.

Table 2

Study	Test Species	Exposure Route & Duration	Testing Time & Critical Effects	LOAEL (mg/kg-day)
(Eriksson and Fredriksson, 1991)	NMRI mice	Oral; postnatal day (PND) 10-16	At PND 17, no significant behavioral effects. At 4 months old, significant increase in locomotion & total activity and significant decrease in cholinergic receptors in cerebral cortex.	0.7
(Aziz et al. 2001)	Albino Wistar rats	Oral; gestational days (GD) 14-20	Significant increase in cholinesterase activity and decrease in cholinergic receptors in hippocampus, and decrease in learning and memory performance observed at both 6 and 12 weeks old,	1.0
(Patro et al. 1997)	Wistar rats	Intraperitoneal injection; PND 9-13	Histopathology at PND 12, 15, 21 or 30. Observed delay in cytogenesis and morphogenesis of neurons in cerebellum, and damage of developing vasculature.	0.7
(Husain et al. 1994)	Albino Wistar rats	Oral; PND 22-37	At PND 38 observed significant decrease in hippocampus weight, increase in cholinesterase, decrease in cholinergic receptors, impaired learning function and increased locomotion.	7.0
(Lazarini et al. 2001)	Wistar rats	Oral, GD 6-15	At PND 60, a anxiogenic swimming procedure followed by open-field behavior testing indicated treated male rats having a significantly increased in emotional state.	0.08

Patro et al. (1997) exposed young Wistar rats to 0.7 mg/kg-day of deltamethrin (grade not specified) by Intraperitoneal injection between PND 9-13. The animals were weighted and histopathology was performed on the cerebellum at PND 12, 15, 21, and 30. The body and brain weights of the treated rats were significantly lower than the controls. The authors observed a delay in cytogenesis and morphogenesis of neurons in the cerebellum. Damage to the developing vasculature, and focal degeneration and spongy appearance of the tissues in the vicinity of the damaged blood vessels were also noted.

Husain et al. (1994) administered deltamethrin formulation orally to 50 albino Wistar male rats from PND 22-37 at a dose of 7 mg/kg-day. Various assays and behavioral testing were performed on PND 38. There were no significant differences in body and whole brain weights

of treated and untreated rats, except for a significant decrease in the wet weight of the hippocampus. A significant elevation of the activity of monoamine oxidase and AchE , a slight but significant increase in spontaneous locomotor activity, and impaired, learning performance as measured by the conditioned avoidance response test, were observed in treated rats. A significant enhancement in dopaminergic and lowering of MACh receptors in the corpus striatum were noted in comparison to controls.

In the Lazarini et al. (2001) study, deltamethrin formulation was orally administered to nine pregnant Wistar rats from GD 6-15 at a dose of 0.08 mg/kg-day. Prenatal exposure did not affect maternal and offspring body weight. At PND 60, rats were subject to a swimming test and open-field behaviors were measured 15 minutes after the swimming test. The swimming test, in which rats were plunged individually into a vertical glass cylinder to induce anxiety, was used as a challenge to detect possible subtle effects of low-dose deltamethrin during open-field testing. Treated male rats showed significantly decreased peripheral, median and central locomotion frequencies, as well as significantly increased immobility duration. At PND 140, animals were sacrificed and striatal monoamine levels were measured. Treated males exhibited a significantly higher striatal DOPAC (3,4-dihydroxyphenylacetic acid, a dopamine metabolite) levels and DOPAC/dopamine ratio. However, the authors expressed the concern that the deltamethrin formulation used may have included xylene as a solvent, which could potentially enhance the effects of deltamethrin.

In summary, all studies listed in Table 2 have limitations. For example, there is some concern that lower body weight gain in the treatment group may confound the observed results in the Patro study. Studies, which used a deltamethrin formulation or did not report the grade of deltamethrin, also present some challenge in terms of interpreting the dose and response. However, the use of formulations may provide a more realistic exposure scenario. It should be emphasized, nevertheless, that these studies from Sweden, India and Brazil help paint an overall picture of the effects of deltamethrin or its formulation on the developing brain.

Which study should be used as a basis for establishing the child-specific reference dose for deltamethrin?

While collectively the studies in Table 2 provide suggestive evidence on the developmental neurotoxicity of deltamethrin, OEHHA shares the views of Shafer et al. (2005) regarding the study limitations. Thus, OEHHA is not using any of the studies in Table 2 as the critical study for developing the chRD for deltamethrin. Table 3 summarizes those studies that have been used by CDPR and U.S. EPA. These studies have gone through U.S. EPA, CDPR, and public reviews as part of the processes of registering deltamethrin, setting margins of exposure, and establishing tolerance levels. A description of them, which includes the endpoints, the number of animals per sex per test group, route of administration, exposure time and duration and pathological reporting, is given under the heading of "existing health guidance values for deltamethrin."

Table 3

Study	Use	LOAEL* or NOAEL** (mg/kg-day)	Test Species	Exposure Route and Duration	Endpoint
Goldenthal	For CDPR to calculate chronic margin of exposure	0.1 **	Rat, 90/sex/grp	Oral, two years	Degeneration of sciatic, tibial, and plantar nerves
Chesterman	For CDPR to calculate acute/subchronic margin of exposure	0.1 *	Dog, 3/sex/grp	Oral, 13 weeks	Neural-- liquid feces, vomiting, and tremors
Ryle	For U.S. EPA to establish tolerance levels	1.0 **	Dog, 4/sex/grp	Oral, 52 weeks	Neural-- chewing and scratching of extremities, and liquid feces

In comparison, the Goldenthal study has the largest sample size and longest exposure duration. The Ryle study produces the highest NOAEL. The Chesterman investigation, on the other hand, is a subchronic study with a LOAEL only. The use of the Chesterman study would confer a lower chRD because additional uncertainty factors would be applied for subchronic-to-chronic and LOAEL-to-NOAEL extrapolations. However, that increases the uncertainty of the chRD value. Moreover, in the Chesterman study, a carrier solvent for deltamethrin was used, which has the potential of enhancing deltamethrin's toxicity. In final analysis, OEHHA opts to use the 1980 Goldenthal study as a basis for developing the chRD.

In considering safety factors to be applied to the NOAEL of the Goldenthal study for the protection of children, OEHHA agrees with U.S. EPA's approach in establishing deltamethrin tolerance levels that a 3X factor be applied to account for age- related sensitivity (brain concentration of deltamethrin in weanling rats was higher than in adult rats (Sheets et al., 1994)); however, OEHHA disagrees with U.S. EPA that a database deficiency factor is not needed. There is suggestive evidence that deltamethrin adversely impacts the developing brain. Since the non-guideline developmental neurotoxicity studies listed in Table 2 have a range of LOAEL values between 0.08 and 1.0 mg/kg-day, additional developmental neurotoxicity studies, which include functional tests and span the dose range below 1.0 mg/kg-day, should be conducted to adequately quantify the impact and establish a NOAEL. In the interim, a database deficiency factor should be applied. The lowest LOAEL observed from the non-guideline developmental neurotoxicity studies is 0.08 mg/kg-day (Lazarini et al. 2001), and yields an estimated NOAEL of 0.008 mg/kg-day. In comparing this estimated NOAEL from the Lazarini study using young

animals to the chronic NOAEL of 0.1 mg/kg-day from the Goldenthal study that dosed animals throughout their adulthood, an inference can be drawn that children could potentially be 12.5 times (0.1/0.008) more sensitive to deltamethrin. Since OEHHA agrees with U.S. EPA pertaining to the use of the 3X factor to account for pharmacokinetics (brain concentration difference), that factor will be applied in deriving the chRD. In addition, OEHHA proposes to apply another factor of 3 to account for possible pharmacodynamic sensitivity, which cannot be ascertained at this point due to deficiencies in the developmental neurotoxicity database. In combining these two factors of three, OEHHA derives a safety factor of 10 to address the overall 12.5 fold increase in children sensitivity.

The calculation of the chRD for deltamethrin is given below:

$$chRD = \frac{NOAEL}{UF} = \frac{0.1\,\text{mg/kg - day}}{1000} = 0.0001 mg/kg - day$$

Where,

UF = Uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for human variability, and 10 from combining a factor of three for neurotoxicity database deficiency and a factor of three for age-difference in brain concentration).

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APPENDIX 1: OEHHA Response to Public Comments

Response to Syngenta's Comments

Comment 1: OEHHA's assignment of a high priority to atrazine for establishing a chRD under HSC Section 901(g) is unwarranted based on the following reasons: (1) it is minimally used in California and the main use is in forestry, (2) it does not accumulate or persist in upper layers of soil and should present little or no exposure to children, and (3) there is an absence of health-related complaints associated with atrazine exposure in California.

Response 1: It is important to understand the purpose of HSC Section 901(g), which is to provide a mechanism to ensure that any contaminant present in the school environment will not pose a health risk to school children. The law requires OEHHA to develop a school site risk assessment method and chRDs for use as a risk assessment tool. A chRD will be applied in the site-specific risk assessment only if the corresponding chemical has been identified as a contaminant of concern for that site. Accordingly, the chRD for atrazine will not be applied unless it is definitively identified as a site-specific contaminant of concern.

The process of site-specific exposure assessment takes away any guesswork. It does not rely on atrazine use information or field studies to predict the exposure potential. Instead, it demands the positive identification of atrazine at the site through sampling and analysis before the application of the chRD for risk assessment.

In page four of the draft report, OEHHA has discussed the process for prioritizing chemicals for review. OEHHA has specifically indicated that while prioritization is usually made on the basis of exposure and health effect potential, the availability of health effect data is often the overriding consideration in the selection of chemicals. The OEHHA model is similar to that of U.S. EPA in its development of RfDs , and of ATSDR in its establishment of MRLs. OEHHA strives to develop as many chRDs as appropriate to provide the necessary tools for risk assessors who will likely encounter different contaminants at different school sites.

Syngenta contended that there are no health-related complaints associated with atrazine. OEHHA also noted very minor complaints and has indicated in the draft report: "Because there are so few studies on humans and the exposure levels are usually unknown, OEHHA depends primarily on animal data to assess the potential effects of atrazine on children."

In its review of a mammalian toxicology database, Syngenta also contended that there is no evidence that environmentally relevant exposure to atrazine would have any direct effect on the hepatic, renal, immune or reproductive system. Syngenta stated that studies cited by ATSDR and OEHHA used extremely high doses of atrazine and did not reflect environmentally relevant exposure. OEHHA would like to point out that the nature of toxicity testing requires testing at relatively high doses. Testing at high doses are necessary to detect adverse effects when a limited number of animals and animal species are used, which is usually the case to minimize the cost of testing. Testing at environmental relevant doses, which would require large studies, utilizing thousands of animals and at extreme costs, are an infeasible proposition.

Comment 2: OEHHA listed the RfD for atrazine from the Integrated Risk Information System (IRIS), which is no longer relevant because U.S. EPA has stated that atrazine is no longer being reassessed under the IRIS program. Instead, the latest information from the U.S. EPA's Office of Pesticide Program (OPP) should be used. Syngenta suggested the replacement of the RfD of 0.035 mg/kg-day with a value of 0.018 mg/kg-day.

Response 2: The intent of listing the RfD and other pertinent health-based values is to provide a baseline for the OEHHA review. In fact, both IRIS and OPP efforts were summarized in the OEHHA report. It should be noted that OPP has derived a dietary/drinking water reference dose of 0.002 mg/kg-day (round up from 0.0018) and a soil reference dose of 0.006 mg/kg-day, and did not include a value of 0.018 mg/kg-day suggested by Syngenta. To provide a better transition between the IRIS and OPP discussions, OEHHA will include a statement in the report indicating that atrazine is no longer being reassessed under the IRIS Program (See Federal Register February 9, 2004 Volume 69, Number 26).

Comment 3: OEHHA in its draft report indicated that it has developed a cancer-based PHG of 0.00015 mg/L (0.15 µg/L or 0.15 ppb) for atrazine in drinking water. Knowledge of atrazine's mode of action in Sprague-Dawlegy rats, the lack of relevance of this mode of action in human, and supportive epidemiological data all point to the conclusion that atrazine is not carcinogenic in humans.

Response 3: The carcinogenic issue had been discussed when the PHG was established. OEHHA will re-visit this issue during the update of this PHG. The information provided by Syngenta will then be reviewed in that process. In this phase of the school site risk assessment program, OEHHA is focusing on the non-cancer endpoint, and thus, is limiting the discussion on non-cancer issues.

Comment 4: Developing rats have been shown to be less sensitive to atrazine than adult rats. These data suggest that children do not have greater sensitivities.

Response 4: Syngenta attempted to integrate different studies, data sets and endpoints in drawing an inference that children do not have greater sensitivities. OEHHA disagrees with the approach of commingling qualitative and quantitative data sets in drawing this inference. As U.S. EPA observed, atrazine testing using young rats has been limited to very short periods of dosing in specific developmental periods. As such, the NOAEL or LOAEL from these studies may not reflect the "true" NOAEL or LOAEL. The decision of U.S. EPA's OPP to use an adult rat study in establishing its reference doses is an indication of that concern.

However, young animal studies do provide qualitative support for the concern of atrazine's effects on children. OEHHA provided a summary discussion of this topic under "What data indicate a critical effect of atrazine in school-age children?" In addition to the potential endocrine disruption effects, the Federal Insecticide Fungicide Rodenticide Act (FIFRA) Scientific Advisory Panel noted that there are concerns for behavioral effects in the young resulting from atrazine's mode of action on the nervous system and the dose level at which these

effects might occur. U.S. EPA has applied appropriate safety factors for protection of children in developing its reference doses.

Comment 5: The NOAEL of 6.25 mg/kg-day from a study on developing rats should be used to establish the chRD for atrazine.

Response 5: OEHHA evaluates the appropriateness of studies on a case-by-case basis. This study, which also has a short period of dosing, may not provide a "true" NOAEL or LOAEL. Compared to other studies identified by OEHHA, this study does not provide the most sensitive endpoint with the lowest NOAEL. U.S. EPA's OPP also did not choose this as the critical study for its reference doses.

Comment 6: OEHHA should not use the pig studies identified in its draft report to establish the chRD.

Response 6: OEHHA has not considered these as critical studies for developing the chRD. OEHHA agrees that there are some limitations in these studies, such as small sample size and using a single dose. They do, however, provide added information regarding the possible endocrine disruption effects of atrazine in a second animal species.

Comment 7: The proposed chRD is based on the original observation of cardiotoxicity in a dog study submitted to regulatory agencies. Supplemental information, which supported a higher NOAEL, was provided to both CDPR and U.S. EPA. In this subsequent review, U.S. EPA agreed that the NOAEL should be 5.0 mg/kg-day rather than 0.5 mg/kg-day. OEHHA should further review these data in determining the NOAEL.

Response 7: OEHHA and CDPR were aware of U.S. EPA's 1989 re-evaluation memo in Appendix 9 of Syngenta's comments. In developing the draft report, OEHHA had also reviewed all relevant information, including the supplemental information on the dog study, CDPR's 2001 review, and the 2005 review article by Gammon et al., 2005, that was cited in the OEHHA report. OEHHA agrees with CDPR staff's conclusion stated in the 2005 article. Although 5.0 mg/kg-day may be a more appropriate NOAEL based on group data, CDPR's consensus was to use 0.5 mg/kg-day because one of the three dogs in the 5.0 mg/kg-day showed moderate atrial dilation and altered heart weight. Furthermore, the selection of 0.5 mg/kg-day as the NOAEL is supported by a benchmark dose for increased extra-medullary hematopoiesis in the spleen of the female SD rat in a 2-year study.

As indicated in the OEHHA draft report, either the dog study (used by CDPR) or the rat study (used by U.S. EPA) could be used to derive the chRD. Using the dog study, the chRD would be 0.005 mg/kg-day. With the rat study, the chRD would be 0.006 mg/kg-day. The outcome from using either study is basically the same. In rethinking the overall scientific basis, OEHHA concludes that the rat study should be used in establishing the chRD (see responses to Dr. Matsumura's comments). That chRD would be protective of both the endocrine/reproductive and cardiomyopathy endpoints.

Response to California Citrus Mutual's Comments

Comment 1: Atrazine is not a material of concern at school sites based on exposure potential and it is not a health hazard to children.

Response 1: It is important to understand the purpose of HSC Section 901(g), which is to provide a mechanism to ensure that any contaminant present in the school environment will not pose a health risk to school children. The law requires OEHHA to develop a school site risk assessment method and chRDs for use as a risk assessment tool. A chRD will be applied in the site-specific risk assessment if only if the corresponding chemical has been identified as a contaminant of concern for that site. Accordingly, the chRD for atrazine will not be applied unless it is definitively identified as a site-specific contaminant of concern.

Atrazine could have been used in areas adjacent to school sites, or could occur as a contaminant if a school were to be built on a former agricultural area. We are not here to predetermine if atrazine is a material of concern at school sites. Instead, the process of site-specific risk assessment will objectively determine if atrazine is a chemical of concern. The process does not rely on atrazine use information or field studies to predict the exposure potential. It demands the positive identification of atrazine at the site through sampling and analysis before the application of the chRD for risk assessment.

OEHHA disagrees that atrazine is not a health hazard to children. As discussed in the report, while human data are sparse, there is enough scientific information from animal studies to indicate that atrazine could adversely impact children. Atrazine could effect the hepatic, renal, cardiovascular, immune, nervous, or reproductive system (ATSDR, 2003; OEHHA, 1999). Cardiovascular and reproductive systems are sensitive endpoints, and are of special concern because these organ systems are not fully developed in children and are vulnerable to chemical injuries.

Comment 2: OEHHA notes U.S. EPA applied a safety factor for children protection under the Food Quality Protection Act of 1996, and then selectively cites certain studies that would justify that a 10X factor is not sufficient.

Response 2: At no point has OEHHA indicated that a 10X factor for protection of children is not sufficient. On the contrary, OEHHA indicated that a 10X child safety factor is not necessary in the context of school site risk assessment. In the final draft, OEHHA proposes a 3X child safety factor in conjunction with the use of the adult rat study in establishing the chRD, which is consistent with the view of U.S. EPA's OPP.

Comment 3: OEHHA in its draft report indicated that it has developed a cancer-based Public Health Goal (PHG) of 0.00015 mg/L (0.15 µg/L or 0.15 ppb) for atrazine in drinking water. Knowledge of atrazine's mode of action in Sprague-Dawlegy rats, the lack of relevance of this mode of action in human, and supportive epidemiological data together indicate that atrazine is

not carcinogenic in humans. This seems to be the conclusion of IARC and other authoritative bodies.

Response 3: The carcinogenic issue had been discussed when the PHG was established. OEHHA will re-visit this issue during the update of this PHG. The information provided by the California Citrus Mutual will then be reviewed in that process. In this phase of the school site risk assessment program, OEHHA is focusing on the non-cancer endpoint, and thus, is limiting the discussion on non-cancer issues.

Comment 4: OEHHA ignores data that suggest children do not have greater sensitivities.

Response 4: This comment appears to be based on Syngenta's analysis. Syngenta attempted to integrate different studies, data sets and endpoints in drawing an inference that children do not have greater sensitivities. OEHHA disagrees with the approach of commingling qualitative and quantitative data sets in drawing this inference. As U.S. EPA observed, atrazine testing using young rats has been limited to very short periods of dosing in specific developmental periods. As such, the NOAEL or LOAEL from these studies may not reflect the "true" NOAEL or LOAEL. The decision of U.S. EPA's OPP to use an adult rat study in establishing its reference doses is an indication of that concern.

However, young animal studies do provide qualitative support for the concern of atrazine's effects on children. OEHHA provided a summary discussion of this topic under "What data indicate a critical effect of atrazine in school-age children?" In addition to the potential endocrine disruption effects, the Federal Insecticide Fungicide Rodenticide Act (FIFRA) Scientific Advisory Panel noted that there are concerns for behavioral effects in the young resulting from atrazine's mode of action on the nervous system and the dose level at which these effects might occur. U.S. EPA has applied appropriate safety factors for protection of children in developing its reference doses.

Comment 5: OEHHA ignores that U.S. EPA's IRIS system has not been updated with newer review materials.

Response 5: The intent of listing the RfD from IRIS is to provide a baseline for the OEHHA review. It should be noted that OEHHA has considered the most recent peer review journals, data from ATSDR, CDPR and U.S. EPA's OPP in evaluating atrazine.

APPENDIX 2: Syngenta Crop Protection, Inc. Comments on Draft

The text of Syngenta's comments is contained in Appendix 2. The comments are summarized in Appendix 1 along with the OEHHA responses to those comments. The Syngenta comments and the Appendices associated with Syngenta's comments can be obtained upon request in writing to the Integrated Risk assessment Branch, Office of Environmental Health Hazard Assessment, P.O. Box 4010, MS-12B, Sacramento, California 95812-4010, through an e-mail to answers@oehha.ca.gov or by phone 916-324-2829. Please provide the name of the document, and the specific parts of the document needed, and the format (e.g., paper copy, electronic file, etc.). If there is a specific format needed to assist the reader in obtaining the information, please be specific and OEHHA will make an effort to provide the information in the appropriate format.

syngenta

State Regulatory Affairs
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March 13, 2006

Mr. Leon Surgeon
Integrated Risk Assessment Section
Office of Environmental Health Hazard Assessment
P.O. Box 4010
1001 I Street
Sacramento, California 95812-4010

Subject: Response to the Office of Environmental Health Hazard Assessment (OEHHA) for Public Comments on Proposed Atrazine Child-specific Reference Dose (ChRD) for use in Assessing Health Risks at Existing and Proposed School Sites

Dear Mr. Surgeon:

Enclosed please find Syngenta Crop Protection's comments to the OEHHA draft report titled: "Development of Health Criteria for School Site Risk Assessment Pursant to Health and Safety Code Section 901 (g): Proposed Child-specific Reference Dose (chRD) for School Site Risk Assessment, Atrazine and Deltamethrin." The comments are specifically limited to atrazine and not deltamethrin. Syngenta appreciated the opportunity to provide comments at the public workshop held on February 17, 2006 and more extensively through the enclosed written comments.

We were informed that comments could be submitted electronically and as instructed by Ms. Susan Luong of OEHHA, we have submitted these comments to Dr. David Siegel, Branch Chief of the Integrated Risk Assessment Branch at dsiegel@oehha.ca.gov.

For technical questions please contact Dr. Tim Pastoor at 336-632-2226. For general questions please contact me at 336-632-2449.

Sincerely yours,

Debbie Stubbs

Debbie Stubbs
Sr. Regulatory Manager

VOLUME ___ OF ___ OF SUBMISSION

ATRAZINE: RESPONSE

TITLE

RESPONSE TO THE CALIFORNIA EPA OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT'S (OEHHA'S) DRAFT PROPOSED CHILD-SPECIFIC REFERENCE DOSE FOR ATRAZINE (DECEMBER 2005)

DATA REQUIREMENT

Not Applicable

AUTHOR

Charles Breckenridge, Ph.D.

COMPLETION DATE

March 13, 2006

PERFORMING LABORATORY

Human Safety Department
Syngenta Crop Protection, Inc.
Greensboro, NC

LABORATORY STUDY IDENTIFICATION

Syngenta Number T001712-06

SUBMITTER/SPONSOR

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Post Office Box 18300
Greensboro, NC 27419

VOLUME 1 OF 1 OF STUDY

PAGE 1 OF 202

STATEMENTS OF DATA CONFIDENTIALITY CLAIMS

1) *The following statement applies to submissions to regulatory agencies in the United States of America.*

STATEMENT OF NO DATA CONFIDENTIALITY CLAIM

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10 (d) (1) (A), (B), or (C).

Company: Syngenta Crop Protection, Inc.

Company Representative: Debra S. Stubbs

Title: Senior Regulatory Manager

Signature: Debra S. Stubbs Date: 3-13-06

These data are the property of Syngenta Crop Protection, Inc. and, as such, are considered to be confidential for all purposes other than compliance with the regulations implementing FIFRA Section 10.

Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other provision of common law or statute or in any other country.

2) *The following statement applies to submissions to regulatory agencies other than in the United States of America.*

THIS DOCUMENT CONTAINS INFORMATION CONFIDENTIAL AND TRADE SECRET TO SYNGENTA LIMITED.

It should not be disclosed in any form to an outside party, nor should information contained herein be used by a registration authority to support registration of this product or any other product without the written permission of Syngenta Limited.

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

As this volume contains a summary statement and interpretation of information in reports previously submitted to CDPR and is not a study, per se, a Good Laboratory Practice Compliance Statement is not appropriate.

Study Director: There is no GLP study director for this volume

Timothy Pastoor, Ph.D., D.A.B.T.
Head, Human Safety
Representative of Submitter/Sponsor

13 March 2006
Date

Submitter/Sponsor: Syngenta Crop Protection, Inc.
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Greensboro, NC 27419

REPORT APPROVAL

Timothy Pastoor, Ph.D., D.A.B.T.
Head, Human Safety
Representative of Submitter/Sponsor

13 March 2006
Date

Pastoor for CBB

Charles Breckenridge, Ph.D.
Science & Tech. Senior Fellow
Syngenta Crop Protection, Inc.

13 March 2006
Date

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EXECUTIVE SUMMARY

The California Office of Environmental Health Hazard Assessment's (OEHHA) assignment of a high priority to atrazine for establishing a child-specific reference dose (chRD) under Section 901(G) is unwarranted based on the following reasons:

1. Atrazine is minimally used in the State of California and the majority of use (by poundage) is in forestry where applications are only made at planting and not continually during the maturation of the trees.

2. Atrazine does not accumulate or persist in upper layers of agricultural soil. Therefore, agricultural land developed for school playgrounds presents little or no atrazine exposure to children.

3. There is an absence of health-related complaints associated with atrazine exposure in California.

Each of these points is discussed in this document.

In addition, OEHHA should correct its draft report with regard to atrazine's…

1. lack of cancer risk to humans,

2. no greater sensitivity to children, and

3. updated reviews of the chronic dog study.

Therefore, on the basis of a minimal chance for childhood exposure to atrazine at schools, atrazine should not be prioritized for establishment of a chRD. In the event that this document is finalized, the most up to date data and findings from EPA as well as other authoritative regulatory and scientific bodies should be used.

1.0 EXPOSURE TO ATRAZINE IS MINIMAL OR NONE

1.1 Atrazine use is minimal in California

OEHHA proposes to establish a child-specific reference dose for atrazine based on the assumption that children in California will be exposed to atrazine on agricultural land that has been converted to school play grounds. However, atrazine is not used extensively in California and its use in the state is almost exclusively on non-residential, forestry, forage production and row-crop lands.

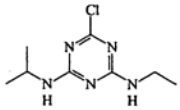
Reported use of atrazine in California during the period from 1990 to 2004 indicates that use has been low, with recent fluctuations in the range from ~38,700 pounds in 2004 to a high of ~69,500 pounds in 1999. At this low use rate, atrazine does not even rank in the top 100 pesticide active ingredients used in the state of California.

The draft report should be revised to reflect that the potential for schools to be constructed on atrazine-treated land is minimal.

1.2 Atrazine Does Not Accumulate in Upper Sub-Soil Layers

OEHHA states that, "...atrazine is also likely to be found at school sites that have a history of agricultural activities," and that, "...atrazine may accumulate in upper subsoil layers after years of its application." The hypothesis that atrazine accumulates and resides in upper soil layers of land that has had past agricultural use is inconsistent with published data on mobility, bioconcentration potential, soil adsorption and degradation by aerobic and anerobic processes.

Atrazine (G-30027) is an s-chlorotriazine herbicide, 2-chloro-4-ethylamino-6-isopropyl-amino-s-triazine with the following chemical structure:



At 25°C, its vapor pressure is 2.9×10^{-7} mm Hg; at 22°C its water solubility is 33 ppm (pH = 7). It is not lipophilic, and therefore does not bioconcentrate, as indicated by a relatively low octanol/water partition coefficient (K_{ow} = 481).

Atrazine is moderately mobile in soil as indicated by Kd and K_{oc} (Kd = 0.2 - 2.4 and K_{oc} = 39-155). The photolytic half life in soil is relatively short (45 days).

Burnett et al., 2002 evaluated field dissipation of atrazine from published and Syngenta studies conducted for EPA. In these 72 studies, the half-life for atrazine was variable, ranging

from 5 to 140 days, with an average half-life of 55.75 days. Figures 1 and 2 illustrate the dissipation of atrazine based on a half-life of either 55.75 days or the longest derived half-life of 140 days.

Figure 1. Predicted Atrazine Soil Concentration as a Function of Application Rate and Soil Dissipation Half Life (55.75 Days)

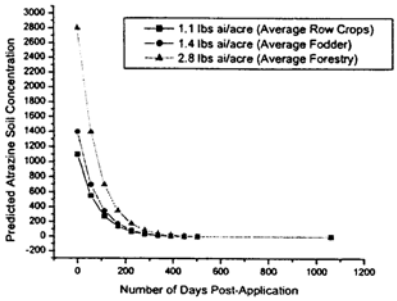
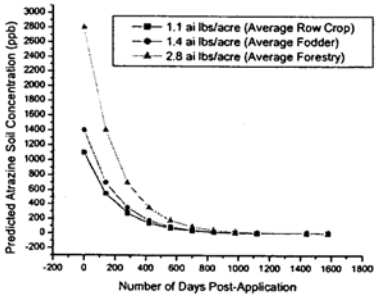


Figure 2. Predicted Atrazine Soil Concentration as a Function of Application Rate and Soil Dissipation Half Life (140 Days)



OEHHA's criteria for prioritizing the development of a chRD includes the identification of, "…those chemical contaminants commonly found at school sites and determined by OEHHA to be of greatest concern based on criteria that identify child specific exposure and child-specific physiological sensitivities."[1]

The low use of atrazine and its dissipation indicate that atrazine would not be found on school sites and is unlikely to be found on land to be used for school construction.

[1] HSC Section 901 (g)

1.3 Health-Related Complaints Do Not Indicate a Problem with Atrazine

In the first paragraph of this section, OEHHA discusses reviews of the pesticide exposure incidence reporting data reported by CDPR 2001, US EPA, 2002 and ATSDR, 2003 and states that the majority of complaints deal with skin or eye irritation, largely in agricultural workers. OEHHA characterizes skin and eye irritation as "illnesses" and infers that these "illnesses" were caused by atrazine.

Syngenta has extracted reports of illnesses or injury reported by California (http://www.cdpr.ca.gov/docs/whs/pisp.htm) for the years from 1996 to 2003 (See Appendix 10). These reports show zero incidence of an association between atrazine exposure and systemic, skin and or eye effects.

In the second paragraph of this section, OEHHA states that "Atrazine could adversely impact the hepatic, renal, cardiovascular, immune, nervous or reproductive systems (ATSDR, 2003, OEHHA, 1999)." Based on an extensive mammalian toxicology database and a review of the literature, there is no evidence that environmentally-relevant exposure to atrazine would have any direct effect on the hepatic, renal, immune or reproductive system. Literature citations by ATSDR and OEHHA, where secondary effects are reported at extremely high doses of atrazine, do not reflect environmentally relevant exposures. Therefore, OEHHA's comment is speculation about potential adverse effects that have not been shown as realistic hazard end-points in regulatory studies.

2.0 THE OEHHA DRAFT REPORT SHOULD REFLECT CURRENT TOXICOLOGY DATA AND INTERPRETATIONS

2.1 Updated Information Should Be Used For the Reference Dose (RfD)

OEHHA obtained some of its atrazine information from the outdated Integrated Risk Information System (IRIS), which is no longer relevant nor used by the EPA to set the current RfD for atrazine.

Currently, EPA states[2] that atrazine, "…is no longer being reassessed under the IRIS Program. See Federal Register February 9, 2004 (Volume 69, Number 26)" (see Appendices 1 and 2). The last update to IRIS for atrazine was in 1995, thus the IRIS database is significantly outdated with regard to toxicological studies on atrazine.

Based on this information, the draft should reflect the latest information from OPP (rather than IRIS) and replace the RfD of 0.035 mg/kg/day with EPA's current chronic reference dose of 0.018 mg/kg/day

[2] IRIS Section VII – Revision History (http://www.epa.gov/iris/subst/0209.htm) – Appendix 1.

2.2 Atrazine Does Not Pose a Cancer Risk

OEHHA states in the section entitled "OEHHA Public Health Goal (PHG)" that mammary tumors observed in female Sprague-Dawley rats may be relevant to humans and that it was appropriate to use a linear, low-dose extrapolation method (Q_1^*) to calculate the potential cancer risk for man. However, atrazine's mode action for inducing mammary tumors in the Sprague-Dawley rat is well understood and this mode of action is not relevant to humans.

Since 1999 a number of authoritative bodies (USEPA 2000, 2003; UK 1996, 2000; Australia 1997, 2004; IARC 1999), relying on the expertise of scientists from around the world, concluded that mammary tumors observed in the female Sprague-Dawley rat are not relevant to humans. For example, EPA concluded that atrazine is not likely to be a human carcinogen and is not mutagenic. A summary of regulatory conclusions from a wide international range is as follows:

IARC, 1999	"there is strong evidence that the mechanism by which atrazine increases mammary tumours in Sprague-Dawley rats is not relevant to humans"
USEPA, 2000, 2003	"…atrazine is classified as 'not likely to be a human carcinogen'"
UK (Rapporteur for the EU), 2000	"The non-genotoxic mode of action of Atrazine is concluded to be adequately explained, and to be without consequence for human health. Classification of Atrazine as a carcinogen is not appropriate."
Australia, 1997, 2004	"…the atrazine response in SD rats is not an appropriate surrogate for the assessment of human risk for mammary tumour development."

2.3 Human Epidemiological Data

In addition, the most recent epidemiological studies also support the fact that atrazine is "not likely to be carcinogenic to humans". Notably, the US government-sponsored Agricultural Health Study, involving a large cohort of licensed pesticide applicators in the states of North Carolina and Iowa, concluded that atrazine is not associated with increases in human cancer (Alavanja et al. 2003; Rusiecki et al. 2004). Blair et al. (2005) further state that, "No exposure-response gradient was noted for any cancer among farmers exposed to atrazine, including prostate."

Knowledge of atrazine's mode of action in Sprague-Dawley rats, the lack of relevance of this mode of action to human health (Simpkins, 2000, Appendix 5), and supportive epidemiological data all point to the conclusion that atrazine is not carcinogenic in humans.

2.4 Reference to "USEPA Health Criteria"

The title of this section of OEHHA's document is unclear because the USEPA does not refer to any toxicity endpoints for regulating exposure to chemicals as "health criteria". Instead, EPA's revised Interim Re-registration Decision (IRED) document for atrazine (USEPA 2003) discusses toxicity endpoints as a function of exposure duration and route as modified by uncertainty factors. Therefore, the most scientifically relevant method to establish a child-specific reference dose and risks from exposure of children in school play yards is to use the endpoints presented by USEPA in Table 6 (see Appendix 3).

The endpoints and safety/uncertainty factors used by EPA are highly conservative. Although the USEPA has data to show that the adult female Sprague-Dawley rat is highly sensitive to atrazine and the carcinogenic mode of action in the Sprague-Dawley rat is not considered relevant to humans[3], EPA nonetheless uses this most sensitive species to set the chronic, population-adjusted dose (cPad) = 0.00018 mg/kg/day), based on a NOEL of 1.8 mg/kg/day and a 1000-fold uncertainty factor (Appendix 4). This supports the conclusion that the risk assessment is conservatively health protective.

2.5 Developing Rodents are Less Sensitive than Adult Rodents

Developing rats have been shown to be less sensitive to atrazine than adult rats. The no observed effect level (NOEL) for developing (young) rats (pubertal delay as a surrogate of LH surge suppression) is approximately 3.5 fold higher than in adult rats (LH suppression), confirming that developing rats are less sensitive than the adult. This is shown graphically in Figure 3, which is based on the US EPA's IRED (USEPA 2003) and shows the NOELs and LOELs based on effects of atrazine from animal studies of various durations.

Figure 4, shows the time period and duration of dosing in the animals studies on atrazine in relationship to human development and further demonstrates that the developing animal is less sensitive to the effects of atrazine than is the adult.

[3] USEPA 2000, 2003; IARC 1999, UK, 1996, 2000, Australian Pesticides and Veterinary Medicines Authority 1997, 2004

Figure 3: NOAEL/LOAELS for Atrazine

From EPA Interim Re-registration Eligibility Decision for Atrazine (USEPA 2003)

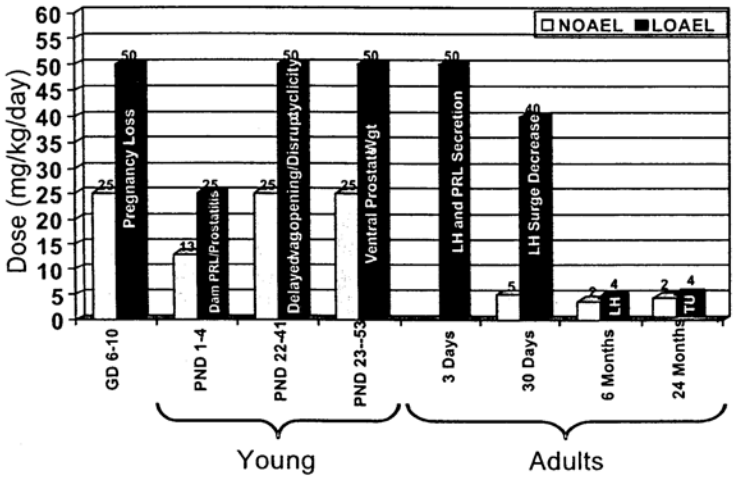
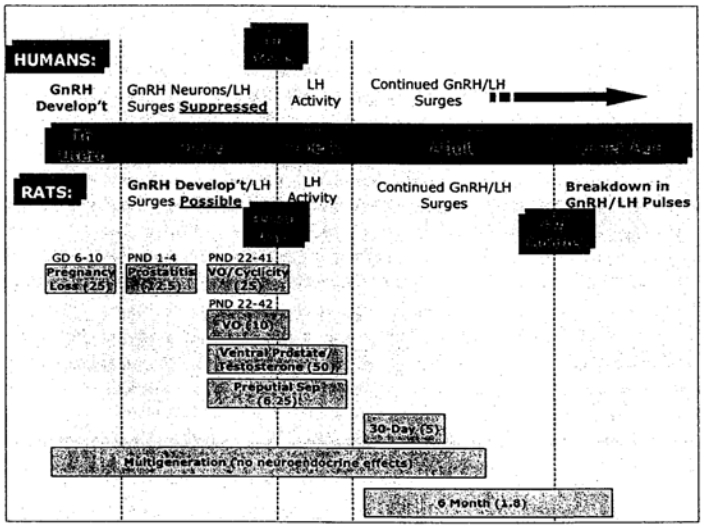


Figure 4. Schematic Representation of Atrazine Treatment Periods



2.6 Non-Cancer Endpoints

2.6.1 Endpoints from Studies in Rat Should Be Used

A detailed discussion of the rat studies has been presented. The conclusion from this discussion is that the most appropriate endpoint for risk estimation associated with short- to intermediate-term exposure to atrazine (as might arise from contact with soil in playgrounds at school) is pubertal delay as indicated in EPA's IRED (USEPA 2003). The most sensitive NOEL in the developing animal is 6.25 mg/kg/day, and an appropriate, age-specific uncertainty factor would be 100. Therefore, it is scientifically appropriate to establish the non-cancer chRD for atrazine at 0.0625 mg/kg/day.

2.6.2 Endpoints from Studies in the Pig Should Not Be Used

OEHHA cites the ATSDR review of the pig study conducted by Gojmerac et al., 1996 in the section entitled ATSDR Minimal Risk Level (MRL) beginning on page 12.

There are three atrazine studies on pigs that have been reported in the open literature by Gojmerac and associates (Gojmerac et al., 1996, 1999 and Curic et al., 1999). The studies and the respective detailed reviews by independent experts are provided in Appendices 6, 7, & 8, respectively. Because of serious technical limitations and clear flaws in these three pig studies, OEHHA should not use them in developing a scientifically valid chRD.

2.7 Complete and Up-To-Date Reviews of the Chronic Dog Study Should Be Used

The proposed chRD is based upon the original observation of cardiotoxicity in the top two of three dose levels administered to dogs. These data were subsequently reviewed by a canine cardiologist and that review was submitted as supplemental information to the US EPA. The US EPA considered this information and both concluded that the observations at the middle dose level were "not related to treatment." Therefore the NOAEL for cardiotoxicity is 5 mg/kg/day rather than 0.5 mg/kg/day as reported by OEHHA. The findings are discussed in more detail below.

On August 4th, 1989, EPA sent a data call-in notice requesting that the Agricultural Division of Ciba-Giegy Corporation (now called Syngenta, Crop Protection, Inc.) conduct an additional, follow-up chronic dog study on atrazine because of potential for cardiac effects of atrazine in the mid- (150 ppm; 5 mg/kg/day) and the high-dose (1000 ppm; 43 mg/kg/day) groups in the existing chronic dog study on atrazine. On November 6th, 1989, Ciba-Giegy submitted new information on the potential cardiac findings in this study, which included an evaluation by Dr. D.K. Detweiler, an expert canine electrocardiologist, (Wetzel, 1989).

After reviewing the new data and interpretation provided by Ciba-Geigy, the EPA withdrew the data call-in notice for a new study and established the no observed adverse effect level in this study at 150 ppm; 5 mg/kg/day (Appendix 9).

Since EPA has determined that the NOAEL for this study to be 150 ppm, Syngenta encourages OEHHA to thoroughly review the relevant and current information, particularly the expert interpretation of the changes in canine electrocardiographs. Syngenta is including the canine electrocardiography review (Wetzel, 1989) and EPA's Data Evaluation Report (DER) (Appendix 9) for OEHHA's consideration in making their judgment on the critical issue of the no observed effect level in this study.

3.0 CDPR'S CITATION OF AUTHORITATIVE REVIEWS (OEHHA TABLE 2, P13)

CDPR should expand its consideration of authoritative reviews on atrazine beyond US-based governmental agencies. Syngenta suggests that scientific reviews of atrazine conducted by other authoritative regulatory bodies around the world should be added to this table in the draft document to give a full perspective on what other authoritative scientific bodies have concluded. Most significantly, not a single other reviewing agency has concluded that atrazine affects the heart at the mid-dose level in the chronic dog study in contrast to conclusions reached by California Department of Pesticide Registration. Furthermore, no authoritative regulatory body has concluded that atrazine is mutagenic nor has any agency utilized a low-dose extrapolation procedure for risk quantification relating to cancer.

4.0 CONCLUSIONS

OEHHA has been charged with identifying "…those chemical contaminants commonly found at school sites and determined by OEHHA to be of greatest concern based on criteria that identify child-specific exposure and child-specific physiological sensitivities." OEHHA should not assign a high priority to establishing a child-specific reference dose for atrazine because child-specific exposure to atrazine is minimal to none nor are there child-specific sensitivities.

Virtually no childhood exposure is expected on school sites because atrazine is not used extensively in the State of California and it does not accumulate or persist in upper layers of agricultural soil.

Furthermore, the Public Health Goal for Atrazine cited in the OEHHA draft report of 0.15 ppb should be revised to reflect the latest atrazine scientific assessments. The cited PHG is based upon the incorrect assumption that atrazine may induce cancer in humans at any dose. USEPA (2000, 2003), IARC (1999), the UK (2000), and Australian authorities (1997, 2004) all conclude that the mode action for inducing mammary tumors in the Sprague-Dawley rat is well understood and that this mode of action is not relevant to humans. EPA has classified atrazine as "not likely to be carcinogenic to humans."

OEHHA has incorrectly concluded that atrazine induced cardiotoxicity in the dog at the mid-dose of 150 ppm and thereby incorrectly defined the chronic dog No Observe Effect Level

(NOEL) as 0.5 mg/kg/day to be used as a basis for establishing the child-specific reference dose. This is not the NOEL in this study, as established in EPA reviews and should not be used as the definitive endpoint for risk assessment. US EPA has established the NOEL of 6.25 mg/kg/day to assess short- and intermediate-term exposure to atrazine.

Finally, the draft document also lacks a discussion of the evidence showing that developing (young) rats are in fact, less sensitive to the effects of atrazine than adults, obviating the need for a "child-specific" reference dose for atrazine. Less sensitivity in children should ensure OEHHA that atrazine is not "of greatest concern" for development of a chRD.

Therefore, on the basis of a minimal chance for childhood exposure to atrazine at schools, atrazine should not be prioritized for establishment of a chRD. In the event that this document is finalized, the most up to date data and findings from EPA as well as other authoritative regulatory and scientific bodies should be used.

5.0 REFERENCES

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APPENDIX 3: California Citrus Mutual Comments on Draft

The text of California Citrus Mutual's comments is contained in Appendix 3. The comments are summarized in Appendix 1 along with the OEHHA responses to those comments. The California Citrus Mutual comments can be obtained upon request in writing to the Integrated Risk assessment Branch, Office of Environmental Health Hazard Assessment, PO Box 4010, MS-12B, Sacramento, California 95812-4010, through an e-mail to answers@oehha.ca.gov or by phone 916-324-2829. Please provide the name of the document, and the specific parts of the document needed, and the format (e.g., paper copy, electronic file, etc.). If there is a specific format needed to assist the reader in obtaining the information, please be specific and OEHHA will make an effort to provide the information in the appropriate format.

February 23, 2006

Mr. Leon Surgeon
Integrated Risk Assessment Section
Office of Environmental Health Hazard Assessment
P.O. Box 4010
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Sacramento, Ca 95812-4010

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Dear Mr. Surgeon,

California Citrus Mutual is a citrus producers trade association with a statewide grower membership approaching 2000 producers. They farm over 100,000 acres of citrus. The industry employs an estimated 14,000 people and enjoys a reputation as a safe, wholesome and nutritious food product. The gross revenue for the industry exceeds $1.5 billion.

Members of Citrus Mutual use a derivative of atrazine called simazine. Atrazine is the base compound for wide spread weed control throughout the United States. Our interest is quite transparent, as goes atrazine, so goes simazine.

Citrus Mutual has been a member, and serves on the executive committee, for the Triazine Network. The Network consists of farming organizations in over 25 states. We banded together to participate in an EPA initiated Special Review for Atrazine over a decade ago. Our role as a Vice Chair has enabled CCM leadership to become intimately involved with the science promulgated by the Review and decisions reached by EPA throughout this process.

This knowledge base is the foundation of our comments. It is our view that OEHHA is making a grievous error in determining that Atrazine is a health hazard to children. We are amazed that OEHHA has ignored a decision by EPA that clearly indicates that Atrazine is not a health hazard.

Why has OEHHA determined that Atrazine is a material of concern at school sites when no such data exists to warrant this conclusion? In fact it would appear that just the opposite would be true based upon DPR use statistics. We believe that OEHHA has made selective use of this same data by simply citing annual statistics and thereby extrapolating that into a negative .

A closer examination would yield the following information. Almost 45% of the material was applied in forestry. Forage had received 40% of the material. Row crops constituted slightly more than 13% of the pounds applied. Given this breakdown one can readily conclude that applications on or around school grounds would be rare, if at all. The total poundage used is far below other materials that could be considered a concern as well.

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CCM is also perplexed by conflicting statements in the OEHHA designation document. "OEHHA is not considering exposure issues here." Then: "OEHHA has analyzed these exposure parameters in the risk assessment." Conflicts and inconsistencies are plentiful throughout the document.

Later OEHHA notes that under the Food Quality Protection Act of 1996 the issue of children sensitivity was addressed. The Act mandates a safety factor of 10x for the protection of children unless data existed that children were not more susceptible. Thus an authoritative body such as EPA makes a determination and then OEHHA selectivity cites certain studies that would justify that a 10x safety factor is not sufficient.

OEHHA notes that children can be "more (or less) susceptible to chemical effects" but only cites those studies that support a desired conclusion. By ignoring the collective weight of the science promulgated by the Special Review, let alone EPA's conclusion, OEHHA reaches a contrary conclusion. Furthermore the "health hazard of concern" is not relevant to school age children.

OEHHA ultimately relies upon studies that conclude negative effects or results under certain conditions for a broad array of crop protection materials. It ignores ignores positive studies specific to this material, the studies for the Special Review and the decision in the IRED.

The studies specific to Atrazine cited in the proposed decision include those promulgated in 1986 which have since been updated several times. Furthermore, lab tests using Sprague-Dawley Rats EPA has found unsuitable for this family of materials. The bottom line is this: the OEHHA toxicology review ignores the scientific foundation EPA's Special Review and the resulting decision. OEHHA is using dated material that is not consistent with current data and/or other assessments and it ignores the weight of scientific evidence.

OEHHA ignores or misinterprets dissipation rates for soil concentration. OEHHA ignores or misinterprets time and soil disturbance studies. For toxicology purposes, OEHHA ignores the fact that children are less sensitive to atrazine. Throughout the document OEHHA ignores the fact that the EPA Integrated Risk Information System (IRIS) has never been updated with the Special Review material and EPA has announced that the IRIS will never be updated.

OEHHA dismisses or ignores the fact that EPA's worst case scenarios for exposure to children are not plausible for OEHHA's school site evaluation. One could therefor argue that there is an even greater safety factor in California.

OEHHA ignores conclusions reached by IARC in 1999, USEPA in 2000 and 2003, the UK in 1996 and 2000, and Australia in 1997 and 2004. Can it be that all those authoritative bodies have reached one conclusion and OEHHA a different one? And, that OEHHA is the right one?

CCM believes the weight of evidence and OEHHA's reliance on selective and/or dated material requires an opposite determination. Therefore CCM disagrees that Atrazine is commonly found in school sites and should be designated as a material of concern for children.

Cordially,

Joel Nelsen

cc: Kahn, Soares & Conway
GHS

APPENDIX 4: OEHHA Response to External Peer Review Comments

Response to comments of Dr. Fumio Matsumura, U. C. Davis, on atrazine

Comment 1: While the overall approach is adequate, it is important to provide proper documentation by providing detailed information from original publications. While government agencies should adopt a conservative approach, their approaches should not be solely based on "worst-case scenarios."

Response 1: Since a number of the specific comments center on the issue of proper documentation, it is more appropriate for OEHHA to address this issue in context of those specific comments.

In the draft report, OEHHA analyzed different scenarios under "Which study should be used as a basis for establishing the child-specific reference dose for atrazine?" Table 2 in the text provides a comparison of potential studies for use. The young female pig study, which ATSDR used for establishing its MRL, would have been chosen under the "worst-case scenario" approach. The use of that study would result in a chRD of 0.003 mg/kg-day. In comparison, the use of the dog or rat study would yield a chRD of 0.005 mg/kg-day or 0.006 mg/kg-day, respectively. The dog or rat study presented a NOAEL; whereas, the pig study only conferred a LOAEL. Moreover, multiple doses were used in the dog or rat study; whereas, only one dose was used in the pig study. OEHHA has considered the scientific basis, rather than a "worst-case scenario approach" in proposing the chRD.

Comment 2: The summary statement in the last paragraph of page10 gave the impression that the author is exaggerating the toxicity of atrazine. The statement should be referenced.

Response 2: An appropriate reference has been added to the text.

Comment 3: The second paragraph of page 11 on environmental fate and exposure is somewhat speculative. The best approach is to find the actual data on soil samples from school yards, playgrounds and backyards. If not, ask experts on soil fates to conduct a reasonable fate assessment based on well-accepted model.

Response 3: The intent of this paragraph is to summarize very basic information. As discussed in the report's Introduction, the purpose of establishing these chRDs is to provide improved means for consultants of school districts or the Department of Toxic Substances Control to conduct school site-specific risk assessment. The process here is similar to that used by U.S. EPA in developing reference doses (RfDs) for superfund site risk assessment. Thus, OEHHA is not considering exposure issues here per se. They will be dealt with in the individual site-specific risk assessments, where soil samples will be taken for contaminant analysis.

Comment 4: The discussions on U.S. EPA's RfD and Office of Pesticide Program's health criteria are important. Citation of the original publications of critical studies should be given, and experimental parameters such as number of rats per group and method of treatment should be summarized. In addition, the issue of accurate dosing, particularly at high doses where a decrease in food consumption was observed, should be discussed.

Response 4: OEHHA noted that the study used in establishing OPP's health criteria was properly cited; however, the study used in developing the RfD was not. This omission has been corrected. OEHHA has also re-checked to ensure that all relevant study parameters have been included. Accurate dosing becomes an issue if the dose in question is the LOAEL or NOAEL and it is to be used to establish a health criterion. This is not the case; a decrease in the consumption of atrazine treated feed was observed only in the high-dose group.

Comment 5: The implication of attenuation of LH surge to children should be discussed and the determination of LOAEL and NOAEL from the data should be better explained.

Response 5: The discussion on the implication of attenuation of LH surge to children during the pubertal window has been expanded. The paragraph pertaining to the determination of LOAEL and NOAEL has been revised.

Comment 6: OEHHA should consider using the 6-month rat study rather than the 1-year dog study as a basis for establishing the chRD. The rat study appears to be preferable because of the sample size and relevance of the endpoint (endocrine disruption—attenuation of LH surge) to children. The relevance of the endpoint in the dog study could not be established without a discussion on the implication of cardiomyopathy to children. In addition, the rat study has been extensively reviewed by other governmental agencies; however, it was unclear if the dog study has received a similar level of review by CDPR or OEHHA?

Response 6: The process employed by CDPR for reviewing and regulating pesticides is given in *Regulating Pesticides: The California Story, A Guide to Pesticide Regulation in California, October 2001*. Before a pesticide may be marketed and used in California, CDPR evaluates it thoroughly, under guidelines of the Food and Agricultural Code (FAC), to ensure that it will not harm human health or the environment. Pesticides that pass this scientific, legal, and administrative process are granted a license that permits their sale and use according to requirements set by CDPR to protect human health and the environment. The Toxicological Summary and Risk Characterization reports produced by CDPR are subject to external peer reviews by other state agencies, and U.S. EPA. The entire evaluation along with a proposed action to register a pesticide or deny a registration is subject to public review. Thus, the dog study reviewed by CDPR has received a similar level of attention as compared to the rat study evaluated by U.S. EPA. In developing the draft report, OEHHA had also reviewed all relevant information, including the supplemental information on the dog study, CDPR's 2001 review, and the 2005 review article by Gammon et al., 2005, that was cited in the OEHHA report. OEHHA agrees with CDPR staff's conclusion stated in the 2005 article. Although 5.0 mg/kg-day may be a more appropriate NOAEL based on group data, CDPR in considering all comments decided to use 0.5 mg/kg-day because one of the three dogs in the 5.0 mg/kg-day showed moderate atrial dilation and altered heart weight. Furthermore, the selection of 0.5 mg/kg-day as the NOAEL is supported by a benchmark dose for increased extra-medullary hematopoiesis in the spleen of the female SD rat in a 2-year study.

OEHHA agrees that the discussion on relevance of cardiomyopathy to children should be expanded and has done so in the text. Briefly, cardiomyopathy can, and often does, occur in the

young. An article in the Journal of Pediatrics provides a review of the windows of vulnerability of the heart, which include fetal life, childhood, and adolescence. Cardiomyopathy is a leading cause for heart transplantation. Exposure to toxins is known to cause of cardiomyopathy. Most of the data came from chemotherapy given to treat cancer. For example, high incidence of cardiomyopathy in children was observed in adriamycin and DTIC ((3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide) combination chemotherapy. Moreover, TCDD, an environmental contaminant, was shown to induce postnatal cardiac hypertrophy in mice following perinatal exposure. Thus, the endpoint, cardiomyopathy, from the dog study is deemed relevant for use in establishing the chRD.

However, OEHHA agrees that the rat sample size is larger than that of the dogs. Moreover, the rat study yielded a smaller LOAEL-to-NOAEL ratio (3.65/1.8) when compared to that (4.97/0.48) of the dog study. The "tightness" of this ratio observed in the rat study provides an increased confidence of its NOAEL. From this perspective, OEHHA concludes that the use of the rat study is more preferable.

As indicated in the OEHHA draft report, there is no practical difference in the outcome with using either the dog study or the rat study (used by U.S. EPA) to derive the chRD. Using the dog study, the chRD is 0.005 mg/kg-day. With the rat study, the chRD would be 0.006 mg/kg-day. The end result from using either study is basically the same. However, since the rat study provides a better overall scientific basis and its use will lead to the protection of both the endocrine/reproductive and cardiomyopathy endpoints, OEHHA will use the NOAEL of 1.8 mg/kg-day from the rat study in developing the chRD.

Response to comments of Dr. Fumio Matsumura, U. C. Davis, on deltamethrin

Comment 1: While the overall approach is adequate, it is important to provide proper documentation by providing detailed information from original publications. While government agencies should adopt a conservative approach, their approaches should not be solely based on "worst-case scenarios."

Response 1: Since a number of the specific comments center on the issue of proper documentation, it is more appropriate for OEHHA to address this issue in context of those specific comments.

OEHHA has evaluated the science in selecting the Goldenthal study as the basis for the chRD for deltamethrin. Table 3 in the text provides a comparison of potential studies for use. The Chesterman study would have been chosen under the "worst-case scenario" approach. As a subchronic study with a LOAEL, the use of the Chesterman investigation would have conferred a lower chRD because additional uncertainty factors would have been applied for subchronic-to-chronic and LOAEL-to-NOAEL extrapolations. The Chesterman study was not selected because of the added uncertainties assigned to such a chRD and the potential of the carrier solvent in enhancing deltamethrin's toxicity.

Comment 2: The discussion on the finding of deltamethrin and tralomethrin in classroom floor dust in California is important. OEHHA should also indicate their concentrations if the data are available. Moreover, relevant peer-reviewed articles, such as Heudorf et al., 2001 (Environmental Health Perspectives 109:213-7), which discuss the occurrence of pyrethroids such as permethrin, should be included.

Response 2: While OEHHA would also like to include more exposure data on deltamethrin and tralomethrin, as discussed in the report's Introduction, the purpose of establishing these chRDs is to provide improved means for consultants of school districts or the Department of Toxic Substances Control (DTSC) to conduct school site-specific risk assessment. The process here is similar to that used by U.S. EPA in developing reference doses (RfDs) for superfund site risk assessment. Thus, OEHHA is not considering exposure issues here per se. They will be dealt with in the individual site-specific risk assessments. Moreover, the objective of the Air Resources Board's portable classroom study cited in the text was to identify various contaminants in California schools and thus they were reported as detects or non-detects. We have not found peer-reviewed articles on deltamethrin or tralomethrin in the school environment, especially in California. The Heudorf article pertains to a study in the former U.S. Forces housing estates in Frankfurt, Germany. As part of the study, household dust from about 300 homes was analyzed for different pyrethroids; only permethrin was found. Because this study pertains to a different setting and country, and to a pyrethroid that may have a different mode of action (permethrin is a Type I pyrethroid and deltamehtrin is a Type II pyrethroid), OEHHA has not included this study in the discussion.

Comment 3: OEHHA should further elaborate the study of Eriksson and Fredriksson (1992), as well as that of Ray et al. (2002). Study descriptions should include number of animals per test group, sex, strain, and age. The significance of the behavior test should also be discussed.

As written, the reader got the impression that the Eriksson study should be discredited and yet OEHHA has included this study in the evaluation process. Not being able to replicate Eriksson's results by Ray et al. does not necessarily mean Eriksson's work is flawed. A common reason for obtaining different results is that the original experimental protocol had not faithfully been followed.

Response 3: All experimental parameters except the number of animals per group have been included in the description. That exception arose because it was not given in Eriksson's paper. Pursuant to the suggestion, a discussion on the significance of the behavior test has been incorporated into the text.

Ray et al. published their study results as a Society of Toxicology abstract and a Letter to the Editor in the Archive of Toxicology. Detailed experimental procedures were not given in the abstract or Letter to the Editor. However, the authors acknowledged that Eriksson's protocol was not completely followed. OEHHA previously discussed this information and the significance of Ray's results in a different section. To improve the clarity of the manuscript, OEHHA has consolidated related discussions so that readers would not arrive at the impression that Eriksson's work should be disregarded.

Comment 4: It is unclear whether the decision of ATSDR to withdraw the MRL is related to Ray et al.'s study.

Response 4: OEHHA has added a statement in the text that ATSDR did not explicitly indicate the reason for withdrawing the MRL. However, because Ray's work was cited, it could be interpreted that this information could have been a reason.

Comment 5: OEHHA should provide more detailed information in Table 2, including the number of animals used per test group and frequencies of the treatment.

Response 5: All studies in Table 2 have been reviewed by Shafer et al.(2005), which was cited in the text. OEHHA feels that it is not necessary to repeat this analysis. In summarizing the review, OEHHA concurs that these studies have limitations; none of these studies became a candidate for further evaluation in establishing the chRD. The intent of Table 2 and its associated narration is to paint a picture that prenatal or early postnatal exposure to deltamethrin, at doses below those that cause overt neurotoxic symptoms, could alter normal brain development and maturation. Adhering to a tiered evaluation process, OEHHA feels that detailed information need not be presented for studies that had dropped out of the evaluation in an earlier tier.

Comment 6: Specify the learning test method used in the Husain study presented in Table 2. Is this method commonly used and accepted by others?

Response 6: Pursuant to the suggestion, OEHHA has specified the learning test method used, which is a conditioned avoidance response test. As OEHHA understands, it is a commonly used method. A literature search seems to have affirmed this view. However, the Husain study was not considered as a candidate for further evaluation because deltamethrin formulation rather than deltamethrin was used to conduct the experiment.

Comment 7: The explanation given to justify the final selection of the Goldenthal study as a basis for deriving the chRD was brief and not convincing. More detailed comparison of the listed studies is required. Since the listed studies were not published in peer-reviewed journals but were submitted by industry for purposes of registering deltamethrin, the public will have difficulty in obtaining the details, including the endpoints, the number of animals per sex per test group, route of administration, exposure time and duration and pathological reporting, necessary to comprehend and accept OEHHA's selection.

Response 7: OEHHA concurs that this section should be expanded to put in context that these studies have gone through U.S. EPA, CDPR, and public reviews as part of the processes of registering deltamethrin, setting margins of exposure, and establishing tolerance levels, and that a description of these studies (which included the suggested details) has been provided under the heading of "What are the existing health guidance values for deltamethrin?" Additionally, OEHHA expanded the discussion on study selection; however, the focus remains as a salient comparison in rationalizing the choice of the Goldenthal study.

Comment 8: The paragraph on deriving a database deficiency factor cannot be clearly followed, including the estimation of NOAEL to LOAEL. As a result, there is a problem is visualizing the derivation of the total uncertainty factor of 1000.

Response 8: This paragraph has been re-written to improve its clarity. OEHHA did not disagree with U.S. EPA regarding the application of a 3X factor for age-difference in brain concentration (pharmacokinetics). OEHHA, however, did disagree with U.S. EPA in terms of the need for a database deficiency factor for developmental neurotoxicity (pharmacodynamics). The rationalization of an additional 3X to account for database deficiency is given in this paragraph. Thus, the total uncertainty factor of 1000 consists of 10X for interspecies extrapolation, 10X for human variability, and 10X from combining a factor of three for neurotoxicity database deficiency and a factor of three for age-difference in brain concentration.

APPENDIX 5: External Peer Review

Dr. Fumio Matsumura
Professor of Environmental Toxicology and Entomology
University of California, Davis

Atrazine reviewed

I have read this document thoroughly from the viewpoint of an active scientist, toxicologist, as well as that of an expert in pesticide risk assessment.

Overall Comments

This reviewer has found that the authors/OEHHA scientists followed well-established procedures of risk assessment in general. They have cited the precedents of risk assessments conducted by the US EPA and other governmental agencies, including the processes employed to arrive at their final recommendations. This document is easy to read and to understand the criteria used by the OEHHA to come to the final recommendation.

Critiques

Having acknowledged the overall adequacy of the basic approach adopted for this document, I must also emphasize the importance of proper documentation by citing actual scientific information from the original publications. We all understand that government regulatory agencies must make decisions even when there are not sufficient data, and that, for the protection of the public, they must also adopt conservative approaches in their interpretation of the available data. However, their efforts should not be solely based on "worst case scenarios." To arrive at the recommendation/final decision, therefore, they should document the critical background materials to reasonably justify their interpretations and actions.

Page 10, Last paragraph: I know that this is a kind of summary statement, but it gives the impression that the authors are exaggerating the toxicity of atrazine. My recommendation is to delete it or, if you decide to keep it, cite each reference indicating the exact sources of the information.

Page 11, Second Paragraph: This statement needs better justifications or documentation. The KOC values cited in literature range around 100, meaning that this compound does not show tight binding (adsorption) or high affinity to surface soils. While it does not appear to show high mobility, judging by the absence of residues in deep soil only atrazine has been found in ground water in some cases. Moreover, horizontal surface leaching is very likely. The half-life of atrazine in surface soil is cited to be 5-14 days (HSDB). The best approach is to find the actual data on soil samples from school yards, playgrounds, and backyards. If not, ask experts on soil fates to conduct a reasonable fate assessment based on a well-accepted model. Avoid statements such as "ATSDR feels that…".

Page 11, US EPA R+D and OPP: This is an important source of information. First, cite the original publication. Second, mention the number of rats used per group, method of treatments (how did they ensure the accurate dosing, particularly at high doses where the amounts of food consumed decreased).

Page 12, First Paragraph: Since LH or prolactin surges are the key criterion, explain more in detail how US EPA arrived at LOAEL and NOAEL values and what their implications are.

Pages 14-15, CDPR and OEHHA PHG: Since this is the main source of information leading to the final recommendation, it is very important to present the details of analyses by both CDPR and OEHHA. I, for one, would like to know whether the results were published, and were assessed by other scientific groups or not. Also important is to explain the process through which CDPR decided that NOAEL is 15 ppm. Again, the details are important (e.g. how accurate their estimate of food-consumption/dosing, etc.). How sensitive/accurate are the electrocardiographic methods (what were their positive controls?)? My main criticism on this work is that the number of animals (dogs) was low: only 4 per test groupand in some cases only 3 were chosen for the final health studies. Also, since the final criterion adopted here is myocardiopathy, I would like to see some discussion added on its implication of myocardiopathy to children. Are there any epidemiological evidence of recent rises in the incidence of cardiomyopathy among children?

Pages 16-17, Selection of the key study: Frankly, if I were to choose the best study from the table, I would have selected the 6 month female rat study, basing on the number of animals studied per test group, the relevance of the endpoint on the development, and the existence of extensive records of deliberations by other governmental agencies. Given that health criteria values delivered from that study are not so different from this OEHHA PHG, it is easier to defend the choice by using the rat study rather than this dog study. The reason I cite the above opinion of mine is to stress that OEHHA should do a better job of defending its final choice with ample justifications (the more scientific data they present, the better chance of the acceptance by others).. I recall that I indeed participated in similar FQPA/FIFRA Science Advisory Panel meetings, where we discussed the health criterion of several pesticides (in the case of atrazine the value adopted was 0.006 mg/kg-day). That was based on the propensity of young children to ingest soil from playgrounds and backyards, which should also be relevant in this case. OEHHA would be wise to add a sentence to explain the reason why those recommendations were not adopted in this decision.

Dr. Fumio Matsumura
Professor of Environmental Toxicology and Entomology
University of California, Davis

Deltamethrin reviewed

I have read this document thoroughly from the viewpoint of an active scientist, toxicologist, as well as that of an expert in pesticide risk assessment.

Overall Comments

This reviewer has found that the authors/OEHHA scientists followed well-established procedures of risk assessment in general. They have cited the precedents of risk assessments conducted by the US EPA and other governmental agencies, including the processes employed to arrive at their final recommendations. This document is easy to read and to understand the criteria used by the OEHHA to come to the final recommendation.

Critiques

Having acknowledged the overall adequacy of the basic approach adopted for this document, I must also emphasize the importance of proper documentation by citing actual scientific information from the original publications. We all understand that government regulatory agencies must make decisions even when there are not sufficient data, and that, for the protection of the public, they must also adopt conservative approaches in their interpretation of the available data. However, their efforts should not be solely based on "worst case scenarios." To arrive at the recommendation/final decision, therefore, they should document the critical background materials to reasonably justify their interpretations and actions.

Page 22, Second paragraph: Finding deltamethrin and tralomethrin in floor dust is very important. If possible, cite the actual levels of those pyrethroids (ppb?) in those dust samples. Also, if there is any publication in peer-reviewed scientific journals, this is the place to cite. Additionally, some data on other pyrethroids (e.g. Permethrin is very frequently found in house dust; e.g. Heudorf U and Angerer J, 2001. Environmental Health perspectives 109:213-7) would help, since those pyrethroids act in the same manner.

Page 23, First and Second Paragraphs: Explain more fully the study by Eriksson and Fredriksson (1991) (e.g. the number of animals per test group, the nature of motor behavior test, sex strain, age, etc.) as well as those of Ray et al. (2002). It is common that, even when some other group failed to repeat, the latter do not faithfully replicate the exact experimental protocols. The way it is presented it gives an impression that the former should be discredited, and yet later the reader finds that OEHHA used the former study in the process of risk assessment of deltamethrin.

Page 23, Third Paragraph: It is not clear whether the decision of ATSDR (Paragraph 1) to withdraw MRL is related to this statement, or not.

Page 25, Table 2: Indicate the number of animals used per test group in all cases. Also important is to indicate the frequency of the treatment (if single dosing, just state so).

Page 26, Husain study: Specify the learning test method. Is this a method commonly used and accepted by others?

Pages 27-28, Which Study: The explanation given to justify the final selection of the Goldenthal study (Table 3) as the basis for arriving at the chNOAEL is so brief, and not convincing. The only reasons given are the non-use of solvent and the lower NOAEL. It is important to describe the details of this study as compared to others to justify the final choice by your agency. This is particularly important, since all 3 studies have not been published in peer-reviewed scientific journals. Furthermore, all of these were submitted by AgrEVO Environmental Health, Inc. for the purposes of registering deltamethrin . The public (including the scientific public) will have difficulty obtaining the details, and therefore will have a difficult time in accepting the recommendation by OEHHA. The main questions are the method of assessing the endpoints, the number of animals per test group, the procedure of animal treatments, the life stage of the test animals (at the beginning), sex tested, and pathological reporting.

Page 28, last paragraph: It is not clear what methods of extrapolation were used in estimating NOAEL from LOAEL. Also it is important to explain the basis of the statement of "inference can be drawn that children could potentially be 12.5 times more sensitive to deltamethrin (than adults)." My guess is that the 0.1 mg/kg figure was derived from adults (if so, state clearly). Moreover, the statement of "the lowest LOAEL … is 0.08 mg/kg-day" needs further explanations. Where did the authors get that figure and what were the scientific bases for such a statement.

Page 29, The Last Sentence, "UF=…": It appears from this description that UF=1000 was derived by 10 x 10 x 10 x 3 (which cannot be true). Furthermore, the statement of "age-difference in brain concentration" needs additional explanation if this is indeed an additional factor. My guess is that this one comes from Sheets et al. (1994), but in page 28, OEHHA disagreed with US EPA in this point. In any case, it would be better to clarify this point.