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

CHILD-SPECIFIC REFERENCE DOSES (chRDs) FOR SCHOOL SITE RISK ASSESSMENT

Manganese and Pentachlorophenol

Final
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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 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 chapter serves as a background for the technical evaluation of manganese and pentachlorophenol. For those that are not familiar with this OEHHA program, it is advisable to review this chapter prior to analyzing the following technological reports.

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/or 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.

It should be underscored that a chemical-specific risk assessment is not required to support the development of chRDs. 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. The appropriate chRDs will be applied only if site-specific sampling and analysis indicate the occurrence of the corresponding chemicals. The consultants will have the option to use, for example, default dermal or oral bioavailability factors provided in the exposure assessment guidelines, or proposed a departure from the default based on supporting data.

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 (http://www.oehha.ca.gov/public_info/public/kids/pdf/SchoolscreenFinal.pdf).

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 901(g) program, these child-specific HGVs were not available. For 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 and Protection Act of 1996 (http://www.epa.gov/opppsps1/fqpa/) was an attempt to address the issue of children sensitivity. It mandated a safety factor of 10 unless data existed to indicate that children were not more sensitive than adults. Moreover, a question has been raised that the intraspecies uncertainty factor of 10, the default factor, 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 pharmacokinetic and pharmacodynamic differences between them and adults, and thus empirical data in the young would be preferable. Vulnerability 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 temporally 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.

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 highly 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.

In summary, with rare exceptions the use of a study in children or young animals as the basis for a child-specific HGV is preferred, even when studies in adult humans or animals encompassing a greater dose range or a larger experimental population exist and a biological mechanism of action can be established from corroborating studies. If a study in the young does not exist, the challenge is to integrate studies supporting a biological mechanism for greater sensitivity in the young with studies on adults 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. The report can be found at http://www.oehha.ca.gov/public_info/public/kids/schoolsrisk.html. 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.

From a public health protection standpoint, the OEHHA scientists working on health guidance values for children as mandated by Health & Safety Code 901(g) have adopted the following procedures in 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 and scientifically supportable species and endpoints in our evaluations, meaning that the lowest Lowest-Observed-Adverse-Effect-Level (LOAEL) or No-Observed-Adverse-Effect-Level (NOAEL), preferably an effect on a developing organ system and judged to be scientifically supportable, 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 as appropriate. 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 decided 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, in rare cases, 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 critical windows of development in young animals.

Status

In December 2005, OEHHA issued a final report on chRDs for the first six evaluated chemicals: Cadmium, Chlordane, Heptachlor, Heptachlor Epoxide, Methoxychlor, and Nickel, which can be found at: (http://www.oehha.ca.gov/public_info/public/kids/schools1205.html).

In the current cycle, OEHHA selected 19 chemicals for which literature searches were performed. These chemicals included endosulfan, manganese, pentachlorophenol, toluene, lead, arsenic, aldrin, atrazine, DDE, DDT, dieldrin, endrin, hexachlorobenzene, lindane, malathion, perchloroethylene, permethrin, selenium, and trichloroethylene. The Public Health Library at the University of California at Berkeley assisted in literature search. OEHHA, in turn, reviewed the citations and abstracts, and evaluated relevant qualitative papers and quantitative studies. As a result, OEHHA is currently pursuing chRDs for endosulfan, manganese, pentachlorophenol, toluene, and lead. This report focuses on the development of manganese and pentachlorophenol chRDs.

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Manganese

Summary

OEHHA has reviewed human and animal data in developing a chRD for manganese for school site risk assessment. While manganese's effects on animals and humans are not identical, the rodent data do corroborate the neurotoxicity of manganese. It is also interesting to note that all calculated chRD values (based on animal or human data) fall within a narrow range. The comparative process has helped OEHHA in recommending a chRD of 0.03 mg/kg-day for manganese.

Basis for Selection

OEHHA has identified manganese as a chemical that is likely to be found in the school environment (OEHHA, 2002). Although it is an essential nutrient, manganese can also be toxic to humans after excess exposure. In particular, the potential neurological impact of manganese on school children is a concern.

Occurrence, Use, and Nutritional Value

Manganese is the 12th most abundant element, comprising about 0.1 percent of the earth's crust (ATSDR, 2000; Keen et al. 1994). It does not occur naturally as a base metal but is a component of over 100 minerals, including various sulfides, oxides, carbonates, silicates, phosphates, and borates. Pyrolusite (manganese dioxide) is one of the most common manganese-bearing minerals.

Manganese is used in the manufacturing of steel, carbon steel, stainless steel, cast iron, and superalloys to increase hardness, stiffness, and strength (HSDB, 1995). Manganese chloride is used in dyeing, disinfecting, batteries, and as a paint drier. Manganese oxide is used in textile printing, ceramics, paints, colored glass, and fertilizers.

Manganese is an essential nutrient involved in amino acid, cholesterol, and carbohydrate metabolism, and in bone formation (Food and Nutrition Board, 2002). Manganese is a cofactor in metalloenzymes such as arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, and manganese superoxide dismutase. Glycosyltransferases and xylosyltransferases, which are important in proteoglycan synthesis and thus bone formation, are also manganese dependent. Impaired growth, reproductive function, glucose tolerance, and skeletal development have been associated with manganese deficiency in various animal species. Decreased plasma manganese concentrations were reported in osteoporotic women, and a reduced dietary intake of manganese was associated with altered mood and increased pain during the premenstrual phase in young women. Accordingly, the Food and Nutrition Board has established Adequate Intake (AI) levels for men, women, and children.

Toxicology Summary

Manganese toxicity has been extensively reviewed (ATSDR, 2000). The nervous system is the primary target of manganese toxicity and is a sensitive organ with respect to school children. Manganese neurotoxicity in adult humans is well recognized in the occupational setting, where

workers inhale manganese dust. It especially impacts the extra-pyramidal motor system of the brain, producing lesions and symptoms similar to those of Parkinson's disease (Barceloux, 1999; Keen et al. 1994). Manganese is probably transported into the brain via transferrin (Aschner et al. 1999). Because the extra-pyramidal system (globus pallidus and substantia nigra) is efferent to areas with high transferrin receptor density, these authors hypothesize that these areas are the sources of manganese accumulation in the extra-pyramidal system. The exact mechanism for manganese accumulation in the extra-pyramidal system has not been worked out.

Neurotoxicity from ingested manganese has also been reported. In an aged population (average age, over 67 years), ingestion of drinking water with high concentrations of manganese (1.8–2.3 mg/L) was linked to the onset of unspecified neurological symptoms (Kondakis et al. 1989b). (Kawamura et al. 1941) reported that a small Japanese community (25 individuals) ingested high levels of manganese in contaminated well water over a three-month period. Manganese concentration in the water was not determined at the time, but months later, the water was estimated to contain 29 mg/L. Symptoms included lethargy, increased muscle tonus, tremor, mental disturbances, and even death. Children seemed to be less affected than adults. In contrast, two other studies indicated that oral exposure to excess inorganic manganese resulted in measurable signs of preclinical neurotoxicity in children. These studies show that children, who for three years drank water containing manganese at average concentrations greater than or equal to 0.241 mg/L (Zhang et al. 1995), or who ate food with increased manganese content (He et al. 1994), performed less well in school (as shown by mastery of their native language, mathematics, and overall grade average) and on the WHO neurobehavioral core test battery than students who drank water with a manganese level of 0.04 mg/L.

Central nervous system lesions and behavioral changes were observed following manganese ingestion in a number of animal studies (ATSDR, 2000). While rodents do not always exhibit the same type of neurologic deficits that humans do following exposure to manganese, the animal data corroborate the neurotoxicity of manganese. A recent neurobehavioral study of non-human primates (rhesus monkey infants) further illustrates the effects of manganese on the developing brain (Golub et al., 2005).

Existing Health Criteria

Food and Nutrition Board Upper Limit (UL)

The Food and Nutrition Board (FNB) of the National Academy of Science (Food and Nutrition Board, 2002) has established a UL (defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals) of 11 mg/day of total manganese intake from food, water, and supplements for an adult. The UL is based on the observation of no adverse effects (NOAEL) due to manganese intake in people consuming Western diets containing up to 10.9 mg/day of manganese (cited by (Greger, 1999)). The FNB at the time indicated that human data, even if sparse, provided a better basis for determining its UL for manganese than animal data. The low-dose animal studies were unable to establish a NOAEL. The adult UL of 11 mg/day (equivalent to 0.16 mg/kg-day based on 70 kg body weight) was adjusted based on relative body weight to derive children and adolescent ULs (Table 1). No uncertainty or modifying factors were applied to consider the potentially different sensitivity of children and adolescents.

Table 1 Food and Nutrition Board Tolerable Upper Intake Levels

	UL (mg/day)	*Body Weight (kg)*
Children 1-3 years	2	13
Children 4-8 years	3	22
Children 9-13 years	6	40
Adolescents14-18 years	9	57

U.S. EPA Reference Dose (RfD)

U.S. EPA's RfDs for manganese are 0.14 mg/kg-day (food) and 0.047 mg/kg-day (water or soil), are based on the three studies. First, the Food and Nutrition Board (FNB)of the National Academy of Science determined an "estimated safe and adequate daily dietary intake" (ESADDI) of manganese to be 2-5 mg/day for adults (Food and Nutrition Board, 1989). FNB also considered an occasional intake of 10 mg/day to be safe. Second, the World Health Organization reviewed several investigations of adult diets and reported the average daily consumption of manganese to range from 2.0-8.8 mg/day(WHO, 1973). The high end of this intake range is associated with diets high in whole-grain cereals, nuts, green leafy vegetables, and tea. From manganese balance studies, the WHO concludes that 2-3 mg/day is adequate and 8-9 mg/day is "perfectly safe" for adults. Third, Freeland-Graves et al. (1987) determined that standard Western diets provide an average intake of 2.3-8.8 mg Mn/day. From these studies, EPA concludes that an appropriate NOAEL for manganese is 10 mg/day (0.14 mg/kg-day based on 70 kg body weight). U.S. EPA applies an uncertainty factor (UF) of 1 to calculate the RfD for food because the supporting studies involved large populations consuming normal diets over an extended period of time with no adverse health effects. However, U.S. EPA recommends a modifying factor of 3 in computing the RfD for water or soil. The recommendation is mainly based on: (1) a concern about possible adverse health effects associated with a lifetime consumption of drinking water containing about 2 mg/L of manganese raised in the Kondakis *et al.* study (1999); and (2) evidence that neonates absorb more manganese from the gastrointestinal tract, are less able to excrete absorbed manganese, and absorbed manganese more easily passes their blood-brain barrier.

ATSDR Provisional Minimal Risk Level (MRL)

The upper range of the estimated safe and adequate daily dietary intake of 5.0 mg/day (Food and Nutrition Board, 1989) is the basis for a provisional MRL of 0.07 mg/kg-day (based on 70 kg body weight) for oral exposure to manganese. The agency indicates that the guidance is necessary because, although manganese is an essential nutrient, its prevalence at hazardous waste sites puts some individuals at risk for exposure to toxic levels.

OEHHA Reference Exposure Level (REL)

OEHHA's inhalation REL is based on the same study (Roels *et al.* 1992) that U.S. EPA used for its RfC. This cross-sectional investigation involved 92 male workers exposed to manganese dioxide and 101 matched controls. Exposed workers exhibited compromised neurological functions including visual reaction time, eye-hand coordination, and hand tremor. A LOAEL of 0.054 mg/m^3 was estimated for the general population. A UF of 300 (10 for intra-species variability, 3 for subchronic to chronic extrapolation, and 10 for LOAEL to NOAEL conversion) was applied to derive the REL of 0.2 μg/m^3.

Current Evaluation Results

The reviews by U.S. EPA (2002 and 1996), Food and Nutrition Board (2002), and ATSDR (2000) provide a very good coverage on the topic. Both U.S. EPA and ATSDR have used the FNB's analysis as a basis for their health criteria. OEHHA staff feels that the situation merits a further analysis of the FNB's recommendation on using human data, as well as an evaluation of more recent animal studies.

Human Data

FNB's 2002 NOAEL was used as a starting point in OEHHA's analysis for development of a chRD. Because the 11 mg/day NOAEL is based only on dietary intake, OEHHA reviewed the other uncontaminated manganese intake sources to evaluate the need for a background adjustment in proposing the chRD. The total manganese intake should be considered in deriving the NOAEL. Table 2 provides an exposure estimate for each source of contribution. OEHHA concludes that these uncontaminated sources contribute an insignificant amount of manganese to the total intake and therefore no adjustments are proposed.

Table 2 exposure estimate for each relevant source of contribution

Source	Intake	Manganese Concentration	Manganese Exposure	Data Source
Air	20 m^3/day	24.9 ng/m^3	0.0005 mg/day	Average of mean concentrations in California, 1989 2001(http://www.arb.ca.gov/adam/toxics/statepages/mnstate.html)
Drinking Water	2 L/day	0.15 mg/L	0.3 mg/day	Median conc. in CA public water systems (US EPA, 2002)
Soil	50 mg/day	3501 mg/kg	0.18 mg/day	Midpoint of the range of 2 to 7000 mg/kg (US EPA, 2002)

In the context of deriving a reference dose for manganese, it is important to determine the incremental amount of manganese from contamination that would cause an exceedance of the NOAEL that is based on the total intake. As demonstrated, the diet significantly contributes to the total manganese intake. Data compiled by Freeland-Graves *et al*. (1994) indicate a range of 2.14-7.1 mg/day of dietary manganese intake. OEHHA subtracted a mid-range dietary intake of 5 mg/day from the NOAEL of 11 mg/day to yield a non-dietary NOAEL of 6 mg/day (0.086 mg/kg-day based on 70 kg body weight). The non-dietary NOAEL underscores the potential adverse health effect of manganese from any contaminated source that results in an exposure of more than 6 mg/day of manganese.

Because the NOAEL is based on adult data, OEHHA recommends the use of an uncertainty factor of 3 in setting the chRD to protect infants and children. This is consistent with U.S. EPA's approach in deriving a manganese RfD for soil or water. Infants in daycare centers would be especially at a higher risk for manganese toxicity due to a higher absorptive capacity and/or immature excretory pathway (Chandra, 1983; Keen et al. 1994). U.S. EPA applied a factor of 3 in part because of evidence that neonates absorb more manganese from the GI tract, that they are less able to excrete manganese into the bile, and that the absorbed manganese passes more easily

through the neonatal blood-brain barrier. In addition, the developing brain may be particularly sensitive to manganese toxicity due to the high number of transferrin receptors in the nervous system (Keen et al. 1994). Transferrin is a transporter that carries manganese into the brain. While these data pertain to neonates and infants, it is also reasonable to assume that young school children may also be more vulnerable than adults. A recent case report supports this view: A family of four was exposed to manganese from drinking contaminated well water. The parents and their two sons (16 and 10 years old) subsequently had health assessments. Only the younger boy had abnormally high blood manganese levels (Woolf et al. 2002).

Animal Data

Although manganese does not necessarily produce the identical neurotoxic effects in rat (compared to human), they have been, and will continue to be, used because rodent data corroborate the neurotoxicity of manganese. In reviewing literature, OEHHA identified both the Dorman (Dorman *et al*. 2000) and Tran (Tran *et al*. 2002) studies, which targeted neonatal rats, as applicable for use in considering a chRD for manganese. The purpose of the Dorman study was to evaluate the relative sensitivity of neonatal and adult CD rats to manganese-induced neurotoxicity. Identical oral doses of 0, 25, or 50 mg manganese chloride/kg-day (0, 11, or 22 mg manganese/kg-day) were given to neonatal rats (10 litters per dose, greater than or equal to 8 pups per litter) from postnatal day (PND) 1 through 21, and to adult male rats (20 per dose) for 21 consecutive days. The manganese doses administered to neonates were about 100-fold higher than those resulting from the consumption of an equivalent volume of rat's milk. Dietary intake of manganese was excluded in computing the doses. An increased pulse-elicited acoustic startle response amplitude was observed in neonates from both manganese treatment groups on PND 21; whereas, a dose-response correlation was not demonstrated in adult rats. Manganese concentrations in the brain were also measured. A significant increase in manganese levels were detected in the cerebellum, hindbrain, hippocampus, hypothalamus, and striatum of neonate rats; whereas, a significant increase was demonstrated only in the cerebellum and striatum of adult rats. Dorman *et. al* concluded that neonates may be at greater risk for manganese-induced neurotoxicity. The startle response data indicated a LOAEL of 11 mg manganese/kg-day.

The objective of the Tran study was to analyze the potential neurological effect of manganese supplements on neonatal rats. The authors indicated that rat milk, which contains about 0.3 µg manganese/ml and gives a dietary intake of about 3 µg/day, was not included as a part of the oral dose computation. Manganese supplements consisting of manganese chloride were given in oral doses of 0, 50, 250 or 500 µg manganese/day, which are equivalent to 0, 1.6, 8.3, or 16.7 mg/kg-day (normalizing with a body weight of 0.03 kg derived from averaging PND 1 weight of 0.006 kg and PND 21 weight of 0.055 kg (U.S. EPA. 1988)). Neonatal Sprague-Dawley rats (10-12 pups per dam and a total of 12 dams) were dosed from PND 1 to 20. Behavioral assessment consisting of righting, homing, and passive avoidance tests was performed at PND 6, 10, and 32, respectively. Brain, liver, kidney, spleen and small intestine tissues were analyzed for manganese and other metals at PND 14, 21, and 40. Striatal dopamine levels were assayed on PND 40. As discussed by the authors, the study results seem to suggest the following—the increased in brain manganese may have caused the reduction in striatal dopamine levels in a dose-dependent fashion, which in turn may have caused the behavioral effects observed at various developmental stages as seen in the righting, homing, and passive avoidance tests. The homing test results indicate a NOAEL of 8.3 mg manganese /kg-day. Based on visual observation of the histograms that display the results of the passive avoidance test, it appears that

a NOAEL of 1.6 mg manganese/kg-day can be derived from this endpoint.

The above LOAEL and NOAELs derived from these two animal studies are used to compute a range of chRDs so that they can be compared with the one that is based on human data. Because the most sensitive age group (neonates) was used in these rodent studies, OEHHA is not recommending an additional uncertainty factor for infant and children protection.

Calculation of the ChRD

Calculation of the non-cancer ChRD for manganese is as follows:

Human Data

$$\text{ND} - \text{NOAEL} = \frac{\text{NOAEL} - \text{dietary Mn}}{\text{Body Weight}} = \frac{11\ \text{mg/day} - 5\ \text{mg/day}}{70\ \text{kg}} = 0.086\ \text{mg/kg–day}$$

Where:

NOAEL = No-observed-adverse-effect-level of 11 mg/day (FNB, 2002)

ND-NOAEL = Non-dietary NOAEL

$$\text{chRD} = \frac{\text{ND} - \text{NOAEL}}{\text{UF}} = \frac{0.086\ \text{mg/kg–day}}{3} = 0.03\ \text{mg/kg–day}$$

Where,

UF = Uncertainty factor of 3 to account for differences between children and adults in GI absorption, biliary excretion, blood-brain barrier, and transferrin receptors.

Animal Data

1. <u>Dorman Study</u>

$$\text{chRD} = \frac{\text{LOAEL}}{\text{UF}} = \frac{11\ \text{mg/kg–day}}{1000} = 0.01\ \text{mg/kg–day}$$

Where,

UF = Uncertainty factor of 1000 (10 for LOAEL-to-NOAEL conversion, 10 interspecies extrapolation, and 10 for human variability).

2. <u>Tran Study-</u> *Homing test endpoint*

$$\text{chRD} = \frac{\text{NOAEL}}{\text{UF}} = \frac{8.3\ \text{mg/kg–day}}{100} = 0.08\ \text{mg/kg–day}$$

Where,

UF = Uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability).

3. Tran Study- *Passive avoidance endpoint*

$$\text{chRD} = \frac{\text{NOAEL}}{\text{UF}} = \frac{1.6\ \text{mg/kg–day}}{100} = 0.02\ \text{mg/kg–day}$$

Where,

UF = Uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability).

Conclusion

It is interesting to note that the calculated values are all within a narrow range. From the school site risk assessment viewpoint, manganese would be present in a soil matrix. While data on GI absorption of manganese in a soil matrix are not available, OEHHA assumes that the amount of manganese absorbed from the soil matrix would be similar to that from the food matrix, but would be lower when compared to that from solution (the cited animal studies used manganese chloride solution). The human data, which are based on dietary studies, would reflect a similar GI absorption condition. Moreover, the chRD of 0.03 mg/kg-day, which is derived from a human NOAEL, is comparable to the value of 0.035 mg/kg-day, which is derived from averaging of all calculated values. Accordingly, OEHHA recommends the use of a chRD of 0.03 mg/kg-day for manganese in school site risk assessment.

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Pentachlorophenol

Summary

OEHHA has reviewed available data in developing a chRD for pentachlorophenol for school site risk assessment. For non-cancer endpoints, the liver, kidney, thyroid, nervous system, immune system, and reproductive system are the primary targets of pentachlorophenol toxicity. Most of these endpoints are relevant and applicable to school-age children. Available information indicates that thyroid/neurodevelopment is the most sensitive endpoint and OEHHA is recommending a chRD of 0.001 mg/kg-day for pentachlorophenol based on that endpoint.

Basis for Selection

The Office of Environmental Health Hazard Assessment (OEHHA) has identified pentachlorophenol as a chemical of potential concern pursuant to HSC 901(g) (OEHHA, 2002). Although the use of pentachlorophenol has been restricted, this persistent chemical has been found at proposed school sites in the Department of Toxic Substances Control's review of sampling and analysis data (personal communication with Sharon Fair, January 9, 2004). It has also been identified in at least 313 of the 1,585 hazardous waste sites that have been proposed for inclusion on the U.S. Environmental Protection Agency (U.S. EPA) National Priorities List (ATSDR, 2001a). Moreover, the potential endocrine and neurological impacts of pentachlorophenol on school children are a concern.

Use and Environmental Fate

Pentachlorophenol was one of the most widely used biocides in the United States. It was registered for use by U.S. EPA as an insecticide, fungicide, herbicide, molluscicide, algicide, disinfectant, and as an ingredient in antifouling paint, but it has been a restricted-use pesticide since July 1984 (ATSDR, 2001b). The current use of pentachlorophenol is as a wood preservative (registered by U.S. EPA for power poles, cross arms, fence posts, etc.). The treatment of wood for utility poles represents 80% of the U.S. consumption of pentachlorophenol. Pentachlorophenol is no longer contained in wood preserving solutions, insecticides, or herbicides available for home and garden use since it is a restricted-use pesticide. Pentachlorophenol is still used in the formulation of fungicidal and insecticidal solutions for incorporation into other manufactured pesticide products. These non-wood uses account for no more than 2% of U.S. pentachlorophenol consumption.

Commercial grade pentachlorophenol is 86% pure. Contaminants generally consist of other polychlorinated phenols, polychlorinated dibenzo-p-dioxins, and polychlorinated dibenzofurans, which are formed during the manufacturing process.

ATSDR (2001b) indicates that pentachlorophenol is stable to hydrolysis and oxidation. Adsorption to soils is likely, especially in acidic conditions. The compound has been found to bioaccumulate to moderate levels; however, food chain biomagnification has not been observed. Bioconcentration factors (BCF) of 100 to 10,000 have been reported by ATSDR (2001b) and

CDPR (1998). However, the Pentachlorophenol Task Force performed an independent review and suggested that BCF for pentachlorophenol should be in the range of 100-1000 (see Appendix 6). In recent decades, pentachlorophenol has been widely detected in human urine, blood, and adipose tissue among members of the general population.

Toxicology Summary

The health effects of pentachlorophenol have been reviewed (ATSDR, 2001b; OEHHA, 1997). Adverse health effects have been observed in humans and experimental animals following short- and long-term exposure to pentachlorophenol. Reports of inhalation and/or dermal exposure in humans and oral exposure studies in animals make up the bulk of the available toxicity data. U.S. EPA classifies pentachlorophenol as a group B2 (probable human) carcinogen and IARC classifies it as possibly carcinogenic to humans. Pentachlorophenol is on California's Proposition 65 list of carcinogens (January 1990, based on US EPA and National Toxicology Program (NTP) reports), and has a No Significant Risk Level of 40 micrograms/day (for a 70 kg person). For non-cancer endpoints, the liver, kidney, thyroid, nervous system, immune system, and reproductive system are the primary targets of pentachlorophenol toxicity. Most of these endpoints are relevant and applicable to school-age children. As discussed, OEHHA focused on the non-cancer endpoints in developing a chRD for pentachlorophenol.

Existing Health Criteria

California Department of Pesticide Regulation (CDPR) Chronic NOAEL

CDPR in its Risk Characterization Document (RCD) for pentachlorophenol estimated a chronic NOAEL based on a dog study for use to characterize the chronic exposure risks(California Department of Pesticide Regulation, 1998). In this study, four dogs of each sex received either an empty capsule or one containing the test compound at a daily dose of 1.5, 3.5, or 6.5 mg/kg-day for 52 weeks (TSI Mason Laboratories, 1996). A LOAEL of 1.5 mg/kg-day was defined based on liver effects (Granular cytoplasmic pigment accumulation and chronic inflammation). CDPR estimated a NOAEL of 0.15 mg/kg-day by applying a default uncertainty factor of 10. This approach would result in a chronic reference dose of 0.0015 mg/kg if an uncertainty factor of 100 (10X for interspecies and 10X for intraspecies) were applied.

U.S. EPA Chronic LOAEL for Risk Characterization in Pentachlorophenol Re-registration

In U.S. EPA's Human Risk Characterization study, the same dog study used by CDPR was used to assess chronic exposure risks (U.S. EPA, 2004). A 10X FQPA children safety factor was not applied because of the finding that children would not be susceptible, which was based on developmental toxicity studies in rats and rabbits as well as in the two-generation reproductive toxicity study in rats. A residential risk assessment was also not performed because U.S. EPA determined that there are no existing food uses for the wood preservative uses of pentachlorophenol (PCP); and wood treated with PCP is not available for sale to the general public and play activities in children around treated utility poles is not likely to occur. U.S. EPA used the LOAEL of 1.5 mg/kg-day from the dog study in this risk characterization study.

U.S. EPA Reference Dose (RfD)

U.S. EPA's RfD (U.S. EPA, 1993) is based on a chronic dietary study in rats by Schwetz *et al*. (1978) at dose levels of 0, 3, 10, 30 mg/kg-day. Rats fed a diet equivalent to 30 mg/kg-day of pentachlorophenol gained less weight and had increased urine specific gravity (females only) compared to controls. Pigmentation of the liver and kidneys was observed in females exposed at 10 mg/kg-day or higher and in males exposed to 30 mg/kg-day. The 3 mg/kg-day exposure level was deemed a chronic NOAEL. U.S. EPA applied an uncertainty factor of 100 to account for intra-human and inter-species variability in calculating the RfD of 0.03 mg/kg-day.

Agency for Toxic Substances and Disease Registry Minimum Risk Level (MRL)

The MRL, 0.001 mg/kg-day , (ATSDR, 2001), is based on a Lowest Observed Adverse Effect Level (LOAEL) of 1 mg/kg-day for decreased relative thyroid weight and decreased serum thyroxin concentrations in a three-generation investigation in mink (Beard and Rawlings, 1998). Mink were fed either an untreated diet or a diet treated with pentachlorophenol to achieve a daily dosage of 1 mg/kg. Although the report did not indicate the grade of pentachlorophenol used in the study, a follow-up communication clarified that analytical grade pentachlorophenol was used (D. Chan with S. Cook, assistant to N. Rawlings, November 3, 2003). All second and third generation mink were treated continuously from conception to maturity. Serum thyroxin was decreased in pentachlorophenol-treated mink. This decrease was statistically significant in both F_2 and F_3 exposed males but in only the F_3 exposed females ($P<0.05$). Thyroid mass was decreased in all generations of exposed mink but the decrease was statistically significant only in the F_3 females ($P<0.05$). ATSDR divided the LOAEL by an uncertainty factor of 1,000 (10 to account for the use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability) to derive the MRL. Deficiencies in thyroxin during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna *et al*. 1997; Birrell *et al*. 1983; Kooistra *et al.* 1994). As ATSDR indicates, it is not known if pentachlorophenol can adversely affect the CNS due to impaired thyroid function at exposures at or below 1 mg/kg-day. Neurobehavioral testing has not been performed on animals following either prenatal or postnatal exposure to pentachlorophenol.

OEHHA Public Health Goal (PHG)

OEHHA's PHG for pentachlorophenol, 0.00043 mg/L, (OEHHA, 1997), is based on a NTP two-year cancer bioassay in male and female B6C3F1 mice (NTP, 1989). OEHHA used a subchronic (12 weeks) feeding study in Wistar rats to compute a safe dose for the non-cancer endpoint, (Knudsen *et al*., 1974). The NOAEL of 1.21 mg/kg-day was based on anemia in the higher dose group. An uncertainty factor of 1000 (10 each for intra-human variability, interspecies extrapolation, and subchronic to chronic exposure extrapolation) was applied to calculate a safe dose of 0.0012 mg/kg-day.

Current Evaluation Results

Of particular interest is pentachlorophenol's impact on the thyroid. ATSDR cited several studies that have documented effects of pentachlorophenol on thyroid homeostasis (Beard *et al*. 1999a; Beard *et al*. 1999b; Beard and Rawlings, 1998; Jekat *et al*. 1994; van Raaij *et al*. 1991). These effects include decreased serum thyroxin concentration (Beard *et al.* 1999a; Beard *et al*. 1999b; Beard and Rawlings, 1998; Beard and Rawlings, 1999; Jekat *et al*. 1994; van Raaij *et al.* 1991), decreased thyroxin and triiodothyronine response to thyroid stimulating hormone (Beard and

Rawlings, 1999), and decreased uptake of thyroxin into cerebrospinal fluid (*van Raaij et al.* 1994). These effects may be linked with a demonstrated competition of pentachlorophenol with the thyroxin binding site on transthyretin, a major thyroxin transport protein (den Besten *et al.* 1991).

In reviewing existing literature, OEHHA notes that the effect of pentachlorophenol on thyroid hormones has been demonstrated in four different mammalian species. Altered thyroxin levels were seen in cattle administered both analytical and technical grade pentachlorophenol (McConnell et al., 1980). The reduction of thyroid hormones was observed in rat treated with pure and technical grade pentachlorophenol (Jekat et al., 1994). Both pure and technical grade pentachlorophenol was used to prove that the effect on thyroid hormones is caused by pentachlorophenol and not its contaminants. Beard and Rawlings contribute to the weight of evidence with their mink study cited in the ATSDR document and with a more recent study on lambs (Beard and Rawlings, 1999). Importantly, both the mink and lamb studies demonstrate that exposure to a low dose of 1 mg/kg-day pentachlorophenol can result in decreased serum thyroxin levels. In the 1999 study, ewe lambs and their dams were given feed treated with analytical grade pentachlorophenol to yield a daily dosage of 1 mg/kg from conception to necropsy at 67 weeks of postnatal age. The mean body weight and the thyroxin levels of treated lambs were reduced, indicating that pentachlorophenol adversely affected thyroid function. The exposure period for these studies spans the time window of interest. The implication of altered thyroid function on neurodevelopment is especially relevant to infants (in the daycare center of schools) or young schoolchildren.

The role of thyroid hormones in brain development and maturation have been reviewed (Howdeshell, 2002; Porterfield, 1994; Porterfield and Hendrich, 1993; Sher *et al.* 1998). Thyroid hormones were shown to increase neuronal proliferation; act as a time switch to end neuronal proliferation and stimulate differentiation; influence the pattern of neuron migrations; and stimulate both axons and dendrites development, including synapse formation. Moreover, in the absence of thyroid hormones, the myelination of neurons is delayed. Thus, impaired thyroid function during critical time periods could adversely impact the development of the nervous system. Porterfield and Hendrich discussed three phases or critical periods. Phase 1, which occurs during the first 10-12 weeks of gestation in human, is characterized by the neurogenesis of most of the brainstem and a portion of the cerebral cortex. Because the fetal thyroid is still undergoing development and not releasing hormones at that time, maternal thyroid hormones are the sole source of influence on the fetal brain. Phase 2 is the period in which the fetal thyroid is actively producing and releasing thyroid hormones. Fetal, as well as maternal, thyroid hormones act in concert to facilitate neuronal maturation, neurite formation, and synaptic development in the forebrain during Phase 2. Phase 3 denotes the period after birth. Postnatal releases of thyroid hormones are required for the continued maturation of the forebrain, and for gliogenesis and myelination. While most of the clinical data came from prenatal studies, observations have been made that children with spontaneous onset of hypothyroidism may manifest alterations in various disorders such as lethargy, dementia, depression, and psychosis (Sher *et al*. 1998). Sher *et. al* interpreted that these adverse effects reflect abnormalities in the prefrontal cortex, cortical interconnections, and the limbic system. These clinical data help strengthen the view that pentachlorophenol, which has been shown to impair thyroid function, could also pose a serious concern to brain development in the school environment.

The data on thyroid impairment; information on the role of thyroid hormones in brain development and maturation; and U.S. EPA's evaluation that neurotoxicity is suggested from the available scientific literature and a guideline study must be performed to properly assess this hazard (U.S. EPA, 2004) have led OEHHA to conclude that children susceptibility is an issue and that pentachlorophenol's impacts on thyroid hormone function and neurodevelopment is a valid concern. Moreover, OEHHA notes that a "safe" dose that protects against changes in thyroid hormones should also be protective against downstream neurodevelopmental effects. As such, OEHHA is recommending a chRD for pentachlorophenol based on the mink and lamb studies.

Calculation of the chRD

OEHHA has developed a chRD for pentachlorophenol based on the LOAEL of 1 mg/kg-day from Beard and Rawlings (1998; 1999). The following equation was used to calculate a non-cancer chRD for pentachlorophenol:

$$chRD = \frac{LOAEL}{UF} = \frac{1\ mg/kg\text{–}d}{1000} = 0.001\ mg/kg\text{–}d$$

Where: UF = Uncertainty factor of 1000 (10 for intra-human variability, 10 for interspecies extrapolation, and 10 for LOAEL to NOAEL extrapolation).

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APPENDIX 1: OEHHA Response to Pentachlorphenol Task Force Comments on Draft

Response to Pentachlorophenol Task Force (PTF) Comments

Comment1: Pentachlorophenol does not meet the Section 901(g) for chRD development. Given the current use of pentachlorophenol as a wood preservative in utility poles and cross-arms, PTF questions whether pentachlorophenol will be found at school sites. As such, pentachlorophenol could not be of concern if exposure potential is minimal.

Response: While pentachlorophenol is currently a restricted-use pesticide, it was one of the most widely used biocides. It is persistent in the environment. In its review of soil sampling and analysis data, the Department of Toxic Substance Control has also noted the occurrence of pentachlorophenol at proposed school sites. In addition, it has been identified in at least 313 of the 1585 hazardous waste sites that have been proposed for inclusion on the U.S. EPA National Priorities List. Thus, the potential for exposure at school sites is not minimal.

It is also important to understand the purpose of the criteria for identifying contaminant of concern pursuant to HSC Section 901(g), which is to facilitate the prioritization of chemicals for review rather than to accept or reject chemicals for consideration. The criteria are established from the perspective that a chRD is just a risk assessment tool and 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 pentachlorophenol will not be applied unless it is definitively identified as a site-specific contaminant of concern.

Comment2: Even if a chRD was warranted, the thyroid gland effects are not the appropriate toxicological endpoint. PTF takes issue with the selection of thyroid and associated effects as the relevant toxicological endpoint, and recommends the selection of the liver instead. PTF cites an NTP study (NTP Technical Report #483, 1999) as its basis for concluding that thyroid is not a particularly sensitive target organ.

Response: While OEHHA does not dispute that the liver is an important target organ, OEHHA deems the thyroid and its associated effects as the appropriate endpoint. Pentachlorophenol's effect on thyroid has been demonstrated in three different animal species: the mink and lamb studies cited by OEHHA, and supporting rat studies including the Jekat *et al*. (1994) study cited in the NTP Technical Report #483. Moreover, the thyroid effect has been shown to be the most sensitive endpoint because available data indicate that pentachlorophenol produces the lowest LOAEL in this target organ system.

The use of the NTP study to justify that thyroid is not a sensitive target organ is inappropriate. The primary objective of the NTP study was on pentachlorophenol carcinogenesis rather than on its effect on thyroid functions. While histopathology was performed on various tissues, including the thyroid, thyroid hormone levels (T_3, T_4, and TSH) were not monitored. The clinical chemistry tests assayed were for alanine aminotransferase, alkaline phosphatase, sorbitol dehydrogenase, and bile salts.

Comment3: OEHHA's selection of the thyroid is based on flawed studies. PTF questions whether sheep and mink are appropriate models for use in thyroid health hazard assessment. PTF uses the Jahnke et al., 2004 paper to support the view that the rat would be a better model.

However, PTF questions the rat studies cited by OEHHA to support the finding of the sheep and mink studies that pentachlorophenol adversely impacts thyroid functions. PTF feels that those cited studies, which employed intraperitoneal (I.P.) injection or gavage as a dosing method, may have produced misleading results. PTF suggests using studies such as the NTP rat study, which employed feed as a vehicle for pentachlorophenol administration, instead. In PTF's view, the NTP rat study demonstrates that the thyroid is not particlulary sensitive to pentachlorophenol.

Response: As discussed above, the NTP rat study is inappropriate for use to demonstrate that the thyroid is not sensitive to pentachlorophenol because carcinogenesis is the primary objective of the NTP rat study. While PTF criticizes the use of data based on I.P. injection or gavage, it has not provided any consensus report of the scientific community for documentation that such data should not be used. When the thyroid effects are demonstrated in three different animal species—mink, lamb, and rat, the only logical conclusion is that thyroid effects are a valid endpoint. Further, the use of larger animals such as mink and lamb are appropriate and actually preferred in the study of thyroid effects. As the Jahnke et al., 2004 paper points out: " separation of the thyroid gland from surrounding tissue and accurate weighing of the rodent thyroid gland is technically difficult, especially in pups…thyroid hormone assays often require larger blood volumes than are obtainable from rodent pups."

Comment4: Even if the references were valid, the thyroid still would not be appropriate for pentachlorophenol chRD development. PTF uses a finding of the 2002 conference, "Thyroid Hormone and Brain Development: Translating Molecular Mechanisms to Population Risk," that the effects of thyroid toxicants are not well studied and the relative sensitivities of various end points are not well characterized as a basis for this comment.

Response: The purpose of the conference is to review the status and make recommendations on thyroid research. It is in this context that the finding is issued. For example, the present approach to identify thyroid toxicants depends entirely on the ability of a chemical to reduce circulating levels of thyroid hormones. However, this single focus will not allow detection of chemicals in the environment that interfere with thyroid hormone action without affecting circulating levels of thyroid hormones. Clearly, other endpoints will need to be developed to define the complete universe of thyroid toxicants. For thyroid toxicants such as pentachlorophenol that can be defined by circulating thyroid hormone levels, they should be addressed. In the arena of preventive health, it is imprudent to wait for absolute certainty. To do so is contrary to a sound public health policy. Thus, OEHHA feels that the use of the thyroid as a critical effect for pentachlorophenol chRD development is appropriate.

Comment5: Pentachlorophenol developmental neurotoxicity is not a data gap. PTF provides excerpts from U.S. EPA's 2004 document entitled, " Toxicology," to support that view. The document is a part of the U.S. EPA docket for reregistration of pentachlorophenol. PTF also underscores U.S. EPA's determination that there is no issue with respect to increased sensitivity of infants and children from the available toxicology database. PTF feels that the 3X uncertainty factor for thyroid toxicant influenced neurotoxicity database deficiency to protect children is not warranted.

Response: OEHHA has reviewed this U.S. EPA document. The relevant sections that PTF cited to support its views are as follows. U. S. EPA in Section 6.1 of the report concluded that there was no evidence of children sensitivity. That conclusion was based on data including developmental toxicity studies in the rat and rabbit, as well as a two-generation reproduction toxicity study in rats. U.S. EPA, in Section 6.2 of that document, further indicated that based on no evidence of frank, unequivocal neurotoxicity, including changes in brain weight or incidence of neuropathology in the central nervous system tissues, and no evidence of abnormalities in the development of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats or rabbits, developmental neurotoxicity testing would not be required. U.S. EPA felt that the nervous system has not been generally considered as a target tissue.

OEHHA notes that the traditional developmental and reproductive studies do not provide adequate information to conclude pentachlorophenol developmental neurotoxicity is not a data gap. Gross morphological and histopathological examinations do not provide a complete picture. Biochemical and appropriate behavioral tests will also be needed to fully assess the neurotoxic effects of pentachlorophenol. This is in light of the role of thyroid hormones in brain development and maturation (discussed in the OEHHA document); and the call by participants of the 2002 international conference, Thyroid Hormone and Brain Development: Translating Molecular Mechanisms to Population Risk, to focus research to fill data gaps.

In addition, U.S. EPA's literature review and analysis given in Section 4.8 of its report strongly suggest that the nervous system is also a target tissue of pentachlorophenol. In Section 4.8, U.S. EPA indicated that because the Pentachlorophenol Task Force had not committed to perform neurotoxicity studies on pentachlorophenol, U.S. EPA provided a summary of literature reviewed on the neurotoxicity of pentachlorophenol. U.S. EPA concluded that available data suggested pentachlorophenol could adversely affect the nervous system. *In vitro* systems showed that pentachlorophenol caused a decrease in neuromuscular and ganglionic conduction, and inhibition of human red cell cholinesterase. *In vivo* animal data demonstrated some possible effects after subchronic administration. Clinical signs associated with occupational exposure to pentachlorophenol are suggestive of neurotoxicity, but not definitive. Pentachlorophenol is structurally related to known neurotoxicants such as hexachlorobenzene and hexachlorophene, which have been demonstrated to cause swelling of the myelin sheath and/or convulsions after stimulation with auditory or physical stimuli.

In summary, OEHHA determines that PTF has not provided convincing evidence that there are no data gaps on the neurodevelopment endpoint. However, based on Dr. David Eastmond's comment on the necessity of the 3X uncertainty factor for database deficiency, OEHHA agrees with that observation and has withdrawn the application of this 3X factor (see Response1 to Dr. Eastmond's comment).

APPENDIX 2: Pentachlorophenol Task Force Comments on Draft

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January 27, 2005

Mr. Leon Surgeon
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Re: Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code Section 901(g): PROPOSED CHILD-SPECIFIC REFERENCE DOSE (chRD) FOR SCHOOL SITE RISK ASSESSMENT, Manganese and Pentachlorophenol

Dear Mr. Surgeon:

These comments are submitted by the Pentachlorophenol Task Force (PTF or the Task Force) in connection with the draft report entitled "Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code Section 901(g): PROPOSED CHILD-SPECIFIC REFERENCE DOSE (chRD) FOR SCHOOL SITE RISK ASSESSMENT, Manganese and Pentachlorophenol," that was posted on the Office of Environmental Health Hazard Assessment (OEHHA) website for comment until January 31, 2005. OEHHA has proposed a non-cancer chRD for penta of 0.0003 mg/kg-d, based on purported thyroid gland effects and the role of thyroid hormones in brain development and maturation.

The PTF is comprised of the two North American manufacturers of the wood preservative pentachlorophenol (penta) – Vulcan Chemicals, a business unit of Vulcan Materials Company, and KMG-Bernuth, Inc. Part of the mission of the PTF is to ensure that regulations implicating penta are based on the most current and robust science.

Pentachlorophenol Does Not Meet the Section 901(g) Criteria for chRD Development

California Health and Safety Code (HSC), Section 901(g) requires 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 901(g) also requires OEHHA to annually evaluate and publish, as appropriate, numerical health guidance values (HGVs) in the form of child-specific reference doses (chRDs) for the identified chemical contaminants.

In the first instance, the PTF questions whether pentachlorophenol contamination is "commonly found" at school sites. Pentachlorophenol is used almost exclusively in California in the production of utility poles and cross-arms. A small amount of penta-treated wood is also used as highway dividers and traffic sign posts. There are currently no wood preservation facilities in California that use penta. In light of the specific and narrowly-defined use pattern for penta-treated wood, we have difficulty understanding the circumstances that would lead to penta contamination being "common" at school sites.

Similarly, the Task Force has difficulty understanding how OEHHA could determine that penta contamination at school sites is "of greatest concern," because concern implicates not only potential hazard, but potential exposure. To the extent a penta-treated utility pole was present at a school site, the potential for exposure would be exceedingly low. The U.S. Environmental Protection Agency (EPA) has carefully considered the use of utility poles in home/school or other residential sites and has determined "child contact via the dermal or oral routes is not anticipated since play activities with or around these pole structures would not normally occur."

Even If a chRD Was Warranted, the Thyroid Gland Effects Are Not the Appropriate Toxicological End point.

With respect to the draft numerical health guidance value or chRDs developed by OEHHA, the PTF takes issue with the selection of thyroid gland effects and the potential association between thyroid function and neural development as the relevant toxicological end-points. The Task Force does not believe that doing so is consistent with OEHHA's obligation under law to "use appropriate HGVs and exposure parameters" in order to "provide an unbiased assessment of the potential health risk at an existing or a projected school site." Numerous peer reviewed publications and documents indicate that the liver is the most important target tissue of penta in animal studies. Accordingly, both the U.S. EPA and California Department of Pesticide Regulation has established RfDs for penta on the basis of liver effects. OEHHA similarly should select liver effects as the appropriate toxicological end-point for chRD development.

OEHHA has offered no convincing rationale for its conclusion that the "*available information indicates that thyroid/neurodevelopment is the most sensitive end point...*" In point of fact, one of the most recent and comprehensive studies on penta was conducted by the National Toxicology Program (NTP Technical Report # 483) (NTP, 1999) in rats. This testing program combined toxicology assessments of penta and a lifetime carcinogenesis bioassay. Included in the evaluations was the thyroid gland. The route of penta entry into the body was oral and the mode of entry was dietary via dosed feed. Following lifetime ingestion of the PCP containing feed at up to 30 mg/kg/day, the thyroid histology was inconspicuous compared to the concurrent control group. This shows that the thyroid is not a particularly sensitive target organ for penta. Indeed, the target organs selected by NTP for further evaluation of penta toxicity were the liver, kidney and bone marrow (p. 15, NTP report) (NTP, 1999).

OEHHA's Selection of the Thyroid Is Based on Flawed Studies

OEHHA's focus on thyroid function is based on a number of animal studies, in particular the work of Rawlings et al. in sheep and mink. But, thyroid parameters in either sheep or mink are not commonly used for human hazard assessment. The proper selection of an animal model is critical, here. In a recent scientific workshop sponsored by the NTP Center for the Evaluation of Risks to Human Reproduction of the NIEHS, the relevance of animal models for predicting human health effects was explored (Jahnke et al., 2004). The conclusion was reached that species differences in thyroid system physiology and differences in adverse effects observed in humans and animals with altered thyroid systems may not be highly predictive of human health effects. The Workshop report further noted that "*...there is a continuing and pressing need to develop and validate animal models and good predictors of human health effects.*" And, finally the Report concluded that the rat is the animal species most commonly used in chemical hazard identification studies. Again, the NTP rat study demonstrates that the thyroid is not particularly sensitive to penta.

Moreover, the two publications by van Raaij cited in the OEHHA draft report are not well suited for development of a chRD. Both studies were designed as mechanistically oriented research projects. The 1991 publication used a single intraperitoneal injection of PCP, and this route of administration is atypical in toxicology testing. The 1994 publication by van Raaij and coworkers studied PCP administration by oral bolus dosing on an intermittent schedule (3 x/ week) for variable durations (2 and 4 weeks). Although, oral bolus dosing is still a commonly used route of delivery of a test chemical in test guideline compliant hazard identification studies, it is now well documented that gavage can profoundly distort the pharmacokinetics/ toxicokinetics of a test chemical. In short, oral bolus dosing may lead to misleading results. In contrast, administration via feed or drinking water containing the test article, such as that performed in the NTP rat study, provides a more realistic protracted daily intake and the resultant pharmacokinetics/ toxicokinetics and pharmacodynamics/ toxicodynamics more closely parallel human exposures than in the case of gavage dosing. This is clear if one considers that humans are not exposed to environmentally-occurring chemicals by oral bolus ingestion.

Jekat et al. (1994) is another reference cited in the OEHHA draft report. But that study was also conducted by oral bolus dosing and suffers from the same shortcomings discussed above. When one compares the dosing regime in the NTP rat bioassay (30 mg/kg/day, dosed feed) with that in Jekat et al. (30 mg/kg/day, oral gavage), it is apparent that the mode of entry of PCP differs profoundly in the two studies. As such, it must be true that the dose of PCP delivered to the target organ thyroid was different. Indeed, the bioavailability of PCP from dosed feed is lower than that resulting from oral bolus dosing (gavage). These discrepancies would explain the NOAEL of 30 mg/kg/day on the thyroid gland in the NTP report as opposed to significant PCP dose-related effects reported by Jekat et. al (1994).

Even If the References Were Valid, the Thyroid Still Would Not Be Appropriate for Penta chRD Development

Uncertainties about animal species differences in thyroid physiology and route and mode of PCP administration make it tenuous to select a critical effect level, i.e., the Point of Departure (POD) for estimation of a reference dose built on the weight of the experimental data evidence.

The deliberations of an international conference on the thyroid gland and brain development may serve to illustrate the difficulties in applying these uncertainties to a chRD. ("Thyroid Hormone and Brain Development: Translating Molecular Mechanisms to Population Risk," held on 23-25 September 2002 at the National Institute of Environmental Health Sciences; cited in Jahnke et al., 2004). A major topic of discussion was the extent to which children are affected by undiagnosed thyroid dysfunction and how to test for it. The conference participants agreed that the effect of thyroid toxicants is not well understood and the relative sensitivities of various end points not well defined.

Penta Developmental Neurotoxicity is Not a Data Gap

The OEHHA draft document derives the chRD for penta by applying a 3-fold uncertainty factor to the 0.001 mg/kg-d Minimum Risk Level (MRL) for penta developed by the Agency for Toxic Substance and Disease Registry (ATSDR) to account for the lack of a developmental neurotoxicity study on penta. As discussed above, the ATSDR MRL is flawed because it is based in its entirety on the mink reproductive toxicity studies conducted by Beard and Rawlings (1998), which itself is flawed. Moreover, Beard and Rawlings (1998) does not support a linkage between penta's purported thyroid hormone effects and neurological development. Indeed, in the study brain weights from penta-exposed mink were determined and were unchanged compared to the concurrent controls. The investigators mention neither any measurements directed towards detecting neurotoxic effects nor do they discuss their data in the context of an association between thyroid perturbation by PCP and neurobehavioral consequences in mink. Given the uncertainties of using mink reproductive toxicity data for extrapolations to human health and child health in particular, this factor needs to be considered and addressed.

Moreover, it is not fair to say that developmental toxicity is a data gap in the penta toxicological database. The U.S. EPA has posted on its website for comment a review of all of the studies commissioned by the PTF in support of penta reregistration. The pertinent section of review entitled, "Toxicology,"available at http://docket.epa.gov (Dkt.Id.OPP-2004-0402;Doc.# OPP-2004-0402-009) is attached hereto, and addresses in Section 6 the data requirements under the Food Quality Protection Act (FQPA) and considerations of special sensitivity to PCP in infants and children. EPA notes that the penta toxicity database was reviewed by the Hazard Identification Science Advisory Committee of the Health Effects Division of the EPA's Office of Prevention, Pesticides and Toxic Substances (EPA, 1997). The Committee used the weight-of-the-evidence determination and recommended that a developmental neurotoxicity study in rats was not needed. The reasoning was that there was only minimal clinical evidence of non-specific neurobehavioral effects in animal testing, such as salivation, ataxia or convulsions. In

contrast the available database revealed no frank, unequivocal neurotoxicity. This included brain weights and occurrence of any histological signs neuropathology in the CNS. Furthermore, the Committee noted, with reference to the NTP studies that, "*The nervous system has not been generally considered a target tissue.*" Additionally, there was "*no evidence of abnormalities in the development of the fetal nervous system in prenatal developmental toxicity studies in either rats or rabbits at maternally toxic doses of up to 30 mg/kg/day.*" Overall, the Committee concluded that the accumulated data from developmental toxicity studies (two species, rats and rabbits) as well as a two-generation reproductive toxicity study in rats were judged acceptable for regulatory purposes. With respect to PCP susceptibility all acceptable studies gave no indication of increased sensitivity among young animals to prenatal and/or postnatal PCP exposure.

It is also noteworthy that ATSDR did not identify developmental neurotoxicity as a priority data need for pentachlorophenol in its most recent Notice on the matter. See 68 Fed. Reg. 22,704 (April 29, 2003). The Task Force considers this point to be significant in light of the reliance placed by OEHHA on the ATSDR MRL for Penta.

* * *

In sum, the Task Force urges that OEHHA reconsider the basis of its proposed chRD for penta and develop an appropriate HGV based on the known liver toxicity of penta to laboratory animals.

Respectfully submitted,

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E. John Wilkinson

References:

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U.S. EPA "TOXICOLOGY " SECTION

TOXICOLOGY

1.0 Hazard Characterization

The acute toxicity of pentachloropehnol is low for dermal toxicity (Toxicity Category IV) and primary dermal irritation (Toxicity Category III) but shows higher toxicity for acute oral toxicity and primary eye irritation (Toxicity Category II). No dermal sensitization was observed with the technical test material. Acceptable acute inhalation toxicity data for pentachlorophenol were not available, but waivers were granted for these data.

In a subchronic dermal toxicity study in rats, the liver appeared to be the target organ for pentachlorophenol toxicity, as shown by increased incidence of hepatocellular degeneration accompanied by chronic inflamation at doses of 500 and 1000 mg/kg/day in both males and females. Significant increases in alanine and aspartate aminotransferase were also observed at these dose levels.

In a chronic toxicity study in dogs, the primary target organ also appeared to be the liver, as demonstrated by increased liver weight, increased incidence of pigmentation, increased activities of alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase at 3.5 and 6.5 mg/kg/day.

Pentachlorophenol has been classified as a B2 (probable human carcinogen) carcinogen by the Health Effects Division Carcinogenicity Science Assessment Review Committee and EPA's Science Advisory Board. The oral cancer risk estimate (q_1*) of 7.0×10^{-2} was calculated based on the incidences of hepatocellular neoplasms, adrenal medullary neoplasms, and hemangiosarcomas that developed in female mice treated with technical grade PCP or Dowicide EC-7 (NTP, 1989). All three tumor types are clearly related to the dose of PCP administered and are considered related to the administration of PCP. Hemangiosarcomas are considered tumors of great concern; the EPA Science Advisory Board (U.S. EPA, 1991) found that "these tumors were related to the administration of the PCP formulations tested, occurring in a dose-response manner in the treated animals, and are morphologically related to known fatal human cancers that are induced by xenobiotics." Hemangiosarcomas were found predominantly in female mice. Use of hemangiosarcoma tumor data focuses on the tumor of greatest concern, while inclusion of liver tumor data in female mice addresses the high spontaneous liver tumor incidence found in male mice of this strain while at the same time acknowledging that the liver tumors are treatment-related.

The slope factor was calculated as the geometric mean of the individual slope factors derived from two data sets: female mouse data for technical grade and Dowicide EC-7 pentachlorophenol. Both PCP preparations were used because the two grades of PCP induced neoplasms at the same anatomical sites. tPCP, however, appeared to be slightly more potent than EC-7, suggesting some enhancing activity due to the impurities. A recently conducted rat

based upon combined incidence of hemangiosarcomas, liver adenomas/carcinomas, and adrenal pheochromocytomas observed in female mice from the 1989 NTP study in mice. This conclusion was supported by both the Hazard Identification Assessment Review Committee and the Mechanism of Toxicity Committee within the Health Effects Division, OPP.

With respect to carcinogenicity of pentachlorophenol, there are experimental studies that suggest a possible mechanism for pentachlorophenol-induced tumorigenesis involving generation of quinone and semiquinone metabolites, oxidative damage to cell membrane components as well as cell DNA, and sustained cell proliferation. These results are corrorborated by the study of Lin et al. (Carcinogenesis 23(2): 365-369, February 2002) , who examined the DNA in tissue samples from rats exposed acutely to pentachlorophenol for 1 or 5 days and in rats from a 27 week interim sacrifice of the 2 year NTP bioassay. A two-fold increase in 8-hydroxy-deoxyguanosine levels were found in the stop-exposure group of rat livers as compared to control. The pentachlorophenol metabolites tetrachloro-1,4-benzoquinone and tetrachloro-1,2-benzosemiquinone were observed to be bound to the liver proteins in male rats in the stop-exposure dose group.

6.0 FQPA Considerations

6.1 Special Sensitivity to Infants and Children

There are no existing food uses for the wood preservative uses of pentachlorophenol. Dietary monitoring data assembled by the Food and Drug Administration indicated the presence of pentachlorophenol in certain food items (i.e. milk, pears, pork, but these data are old (i.e. 1991), and FDA discontinued monitoring for pentachlorophenol residues after 1992 based on lack of detectable residue. However, based on potential residential exposures to pentachlorophenol from treated utility poles, and pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for pentachlorophenol was evaluated by the Hazard Identification Science Advisory Committee of the Health Effects Division, OPP.

Adequacy of data: The data included developmental toxicity studies in the rat and rabbit, as well as a two-generation reproduction toxicity study in rats. All of these studies have been reviewed and judged to be acceptable for regulatory purposes. Based on a weight of the evidence determination, the Committee did not recommend a developmental neurotoxcity study in rats.

Susceptibility issues: In the developmental toxicity studies in rats and rabbits as well as in the two-generation reproductive toxicity study in rats, there was no indication of increased sensitivity of young animals to pre- and/or post-natal exposure to pentachlorophenol. However, contaminants of pentachlorophenol formulations have been demonstrated to be teratogenic agents. Based on this information, labeling was agreed to in Position Document 4, issued July 1984, that all registrants of products containing pentachlorophenol or its salts would incorporate language stating that the U.S. EPA has determined that pentachlorophenol can produce defects in the offspring of laboratory animals, and that exposure to pentachlorophenol during pregnancy should be avoided.

6.2 Recommendation for a developmental neurotoxicity study:

The Health Effects Division Hazard Identification Science Advisory Committee determined that, based on a weight-of-the-evidence review of available data, that a developmental neurotoxicity study is not recommended for pentachlorophenol. The following information was considered in reaching this determination:

1) Evidence in support of requiring a developmental neurotoxicty study:

- Minimal clinical evidence of non-specific neurobehavioral effects such as salivation, ataxia, or convulsions.

2) Evidence against the requirement for a developmental neurotoxicity study:

- Based on the available data, there is no evidence of frank, unequivocal neurotoxicity in the database, including changes in brain weight or incidence of neuropathology in the central nervous system tissues (nonperfused). The nervous system has not been generally considered as a target tissue.

3) No evidence of abnormalities in the development of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats or rabbits at maternally toxic oral doses up to 30 mg/kg/day. Cited incidences of hydrocephaly in the prenatal study in rats were included in only 2 fetuses of 2 litters and were within published historical control ranges.

Summary of Toxicological Endpoints to be used for Risk Assessment of Pentachlorophenol			
Exposure Scenario	**Dose (mg/kg/day)**	**Endpoint**	**Study**
Carcinogenicity (dietary)	q1*= 7.0 X 10 -2	Pentachlorophenol is classified as a B2 (probable human carcinogen) using a linear low-dose extrapolation model for humans.	
Short-term[b]	NOAEL = 30	increased resorptions, reduced fetal weight, skeletal malformations	Developmental - Rat
Intermediate-term[b]	NOAEL = 30	increasd resorptions, reduced fetal weight, and skeletal malformations	Developmental - Rat

Long-term	LOAEL = 1.5	Incr. liver weight and alk. phos. activity; increased incidence of granular cytoplasmic pigment accumulation in the liver	Chronic Toxicity - Dog
Inhalation (any time period)[c]	waivers granted for inhalation studies. Biomonitoring data used for total dose calculation.		

Note: All exposure scenarios are based on absorbed dose from the biological monitoring studies (oral short- and intermediate-term NOAEL and oral long-term LOAEL are used to estimate risks with the Target MOEs of 100 and 300, respectively).

The Health Effects Division Hazard Identification Assessment Review Committee determined that there is no issue with respect to increased sensitivity of infants and children from the available toxicology database.

[b]Although a 90-day dermal toxicity study in rats (MRID # 43182301) was available, it was not considered appropriate for this risk assessment because of the concern for developmental effects that were seen in rats which were not observed in the 90-day dermal toxicity study.

[c]One inhalation toxicity study was available for the technical material in the scientific literature which was considered unacceptable for regulatory purposes, while studies in the toxicology one-liner database with pentachlorophenol formulations were all considered unacceptable by the Agency. Due to the lack of route-specific data, oral endpoints are used for assessment of inhalation risk.

APPENDIX 3: OEHHA Response to External Peer Review Comments

Response to comments on manganese

Francis M. Crinella, Ph.D., Clinical Professor of Pediatrics, Psychiatry & Human Behavior, and Physical Medicine & Rehabilitation; Director, Neuropsychology Laboratory

Comment1: The report is very well done, and Dr. Crinella believes the calculations leading to a recommended chRD of 0.03 mg/kg-day for Mn are thoughtfully derived. The fact that there is a strong agreement on the chRDs based on a human NOAEL (0.03 mg/kg-day) and an average of all other calculated values promotes confidence in the calculations.

Response1: Comment noted.

Comment2: Manganese absorption will be greater in persons with nutritional deficiencies of iron, zinc, and phosphorus.

Response2: OEHHA shares the concern for the increased absorption under these circumstances. As a human variability parameter, it is especially of concern if the size of the dataset is small. The human data came from very large population studies and thus no additional uncertainty factor for human variability is proposed. However, a factor of three has been proposed to account for higher GI absorption in children. In using smaller animal datasets, on the other hand, OEHHA has proposed a factor of 10 for human variability. This proposed factor is intended to also protect persons with such conditions.

Comment3: There is a relatively new body of literature developing on the effects of manganese toxicity on gene expression.

Response3: These types of mechanistic information ranging from increasing the mRNA for nitric oxide synthetase and the production of the highly reactive, potent cell poison, nitric oxide to decreasing the metallothionein (MT-I) mRNA and the decrease in the sequestration of oxidants by metallothionein (MT-I) are helpful in understanding the mode(s) of manganese's toxicities. However, they do not contain quantitative data that can be used in developing the chRD. As such, they have not been incorporated in the text.

Comment4: There is now a primate study that comes up with many of the same findings of our rodent studies.

Response4: The primate study lends further support to the validity of the cited rodent studies. This information has been incorporated in the revision of the report.

Response to comments on pentachlorophenol

David A. Eastmond, Ph.D., Professor, Environmental Toxicology Graduate Program, University of California, Riverside

Comment1: The selection of the thyroid/neurodevelopment endpoint and the use of uncertainty factors are appropriate for derivation of the chRD. However, the use of the three-fold UF for database deficiency is not necessary.

Response1: Dr. Eastmond elaborated that since the neurological effects are a consequence of the alterations in hormone levels, a dose that protects against changes in thyroid hormones should be protective against downstream neurodevelopmental effects. OEHHA agrees with this observation that the estimated NOAEL should also protect the neurodevelopmental endpoint. Accordingly, this additional 3X factor has been removed.

Comment2: Significant portions of the descriptions appeared to come from the ATSDR monograph. The document would benefit from an expanded description of the results of the Beard and Rawlings (1998 and 1999) studies.

Response2: This comment underscores that OEHHA should better define the nature and the scope of this document. Each technical chapter is a concise summary of 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/or 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 is trying not to reiterate basic data that have been adequately covered in the cited baseline documents. This language has been added to the Introduction for clarification.

Comment3: There is minimal discussion of pentachlorophenol metabolism, mode of action and exposure.

Response3: Exposure pathways are usually addressed and discussed in the site-specific risk assessment. OEHHA has not come across any pentachlorophenol metabolism information relevant to childhood sensitivity. Thus, these items were not discussed. In terms of the mode of action, OEHHA, based on available data, has summarized pentachlorophenol's effect on thyroid hormones and discussed its probable impact on the developing brain as a result of this endocrine disruption mechanism.

Comment4: Re-check the bioconcentration factor cited.

Response4: Thank you for the suggestion. The bioconcentration factor has been changed to between 100 and 10,000.

Comment5: The statement that the Department of Toxic Substances Control has detected pentachlorophenol at proposed school sites (mentioned in the response to the Pentachlorophenol Task Force) should be included with an appropriate citation in the "Use and Environmental Fate" section.

Response5: This information was provided in the section "Basis for Selection" right before the "Use and Environmental Fate" section. It seems duplicative to include in the Use and Environmental Fate section.

Comment6: The approach used is standard and the studies of mink and sheep, while not typical for toxicological investigations, seem appropriate for use in deriving the chRD. It should also be noted that altered T4 levels were also seen in cattle administered both analytical and technical grade pentachlorophenol (McConnell et al., 1980, Toxicol. Appl. Pharmacol. 52:468-490). The fact that altered thyroid hormones have been seen following pentachlorophenol administration in four different mammalian species, and that alterations in thyroid hormone levels are associated with neurodevelopmental effects in humans, provides substantial weight for the use of this particular endpoint in deriving the chRD. In addition, the observation that thyroid hormone-altering effects were seen in the minks and the lambs at similar doses also provides strong support for their use in deriving the chRD.

Response6: This assessment reaffirms the use of mink and sheep studies as the basis for the chRD and has been added to the document.

Comment7: Dr. Eastmond found OEHHA's responses to the Pentachlorophenol Task Force to be reasoned and adequately presented. One additional reason for not relying primarily on the NTP bioassay results is that exposure of the test animals begins after much of the prenatal and postnatal development has occurred. As a result, critical developmental effects may have been missed.

Response7: Thank you for the observation of the NTP study.

APPENDIX 4: External Peer Review Comments

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21 JUN 05

Jim Carlisle
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Re: Draft Report on Development of Health Criteria for School site Risk Assessment Pursuant to Health and Safety Code Section 901(g): Proposed chRfDs for School Site Risk Assessment—Manganese and Pentachlorophenol, dated February 2005

Dear Dr. Carlisle:

Thank you for asking me to review the section of the above-captioned document with specific reference to manganese (Mn). The report is very well done, and I believe the calculations leading to a recommended chRD of 0.03 mg/kg-day for Mn are thoughtfully derived. The fact that there is a strong agreement on the chRDs based on a human NOAEL (0.03 mg/kg-day) and an average of all other calculated values, including some animal work with which I was involved, promotes confidence in the calculations.

I have no criticism of the literature selected for the draft report, as it represents the mainstream of manganese research over the past three decades. There are three areas that I might want to touch upon:

1. Mn absorption will be greater in the presence of nutritional deficiencies, especially iron (Fe) (Mena et al, 1967;Mena, 1974), calcium (Ca) (Murphy, Rosenberg, Smith & Rapoport, 1991); zinc (Donaldson, La Bella & Gesser, 1981; Cawte & Florence, 1989); and phosphorus (Wedekind & Baker, 1990; Wedekind, Murphy & Baker, 1991).

   The most work has been done on Fe deficiency. Although Mn retention is normally low after weaning, iron (Fe) deficiency will cause increased Mn absorption in mature individuals. During Fe deficiency, Fe absorption is dramatically up-regulated by homeostatic mechanisms in order to compensate for decreased tissue Fe. Since Mn and Fe share the same transport pathway, Mn absorption substantially increases in situations of impaired Fe status. In fact, the intestine cannot distinguish between Fe and Mn.

(Davidsson, Lonnerdal, Sandstrom, Kunz & Keen, 1989; Rossander-Hulthen, Brune, Sandstrom, Lonnerdal & Hallberg, 1991; Davidsson, Cederblad, Lonnerdal & Sandstrom, 1992; Vayenas, Reanti, Vassilopoulos & Papanastasiou, 1998).The significance of this work has to do with the fact that Fe deficiency is the most prevalent of all nutritional deficiencies, not only in third world countries, but also in areas of socioeconomic disadvantage in the U.S.

Low dietary Ca has also been shown to increase distribution of exogenously-loaded Mn in animal tissues. Animals fed calcium deficient diets showed increased dietary Mn absorption and brain Mn levels Low Ca levels can result in an increased intestinal absorption of Mn, which can accelerate transport of toxic metals to the brain (Murphy, Rosenberg, Smith & Rapoport, 1991; Rosenberg, Murphy, Smith & Rapoport, 1990).

2. There is a relatively new body of literature developing on the effects of Mn toxicity on gene expression, specifically:

Mn can increase the iNOS mRNA and the release of the highly reactive biological messenger molecule and potent cell poison, nitric oxide (NO; Spranger, Schwab, Desiderato, Bonman, Krieger & Fandrey, 1998), stimulating apoptosis (Donaldson, 2001; Boje & Orora, 1992; Chao, Hiu, Molitor, Shaskan & Peterson, 1992).

Decreased glutamate uptake due to Mn exposure in astrocytes is linked to decreased glutamate transporter and glutamate/aspartate transporter (GLAST) mRNA, leading to exaggerated excitotoxic response due to diminished glutamate uptake by astrocytes. Uptake of Mn into astrocytes in the basal ganglia and subsequent mitochondrial accumulation in these cells results in compromised energy metabolism, oxidative damage, impaired astrocytic-neuronal communication, indirect alterations in excitatory and inhibitory influences, and development of secondary glutamate-mediated toxicity. In the basal ganglia, astrocytes may be regionally differentiated functionally and particularly sensitive to manganese (Hazell, 2001; Erikson & Aschner, 2002).

Decreased metallothionein (MT-I) mRNA due to Mn exposure decreases the sequestration of oxidants by metallothionein (MT-I); (Erikson & Aschner, 2002).

Mn, by acting on the iron regulatory protein transferrin in the chorioid plexus, may promote the expression of transferrin receptor, which partly facilitates the influx of iron from blood to CSF, and iron-induced oxidative stress in sensitive brain regions (Zheng, Zhao, Slavkovich, Aschner & Graziano,1999).

3. There is now a primate study, in press, that comes up with many of the same findings of our rodent studies. Since it is in press, I am taking the liberty of attaching the manuscript.

Again, I don't think that your calculations of the chRDs would be appreciably altered by any of this information, but it might help to round out your report.

Thanks for the opportunity to review this work.

Sincerely,

Francis M. Crinella, Ph.D.
Clinical Professor of Pediatrics,
Psychiatry & Human Behavior,
and Physical Medicine & Rehabilitation
Director, Neuropsychology Laboratory

Review of the "Draft Report on Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code Section 901(g): Proposed Child-specific Reference Dose (chRD) for School Site Risk Assessment – Pentachlorophenol".

by

David A. Eastmond, Ph.D.
Environmental Toxicology Graduate Program
University of California, Riverside

Dec. 31, 2005

Overview:
OEHHA has proposed a child-specific reference dose (chRD) for pentachlorophenol of 0.0003 mg/kg-day based on pentachlorophenol-induced alterations in thyroid hormone homeostasis and the potential of these alterations to cause neurodevelopmental effects in children. Pentachlorophenol-induced alterations in thyroid hormone levels have been seen in studies of four species of mammals, including a multi-generational study in mink and a chronic study in young sheep that were selected as the basis for establishing the chRD. Alterations in thyroid homeostasis were seen at the same pentachlorophenol dose (1 mg/kg-day) in both studies. The chRD was based on the LOAEL of 1 mg/kg-day seen in the mink and sheep studies of Beard and Rawlings (1998, 1999) and used an overall uncertainty factor of 3000 to account for inter-human variability (10X), interspecies extrapolation (10X), extrapolation from a LOAEL to an NOAEL (10X), and a factor of three for a database deficiency as adequate developmental neurotoxicity studies were not available. I believe that the selection of the thyroid/neurodevelopment endpoint and the use of uncertainty factors are appropriate for derivation of the chRD. However, I not believe that the use of the three-fold UF for database deficiency is necessary. Responses to the specific questions posed by OEHHA and the rationale for my recommendations are presented below.

Specific questions:
1) Accuracy of the information presented, including data on toxicity, metabolism, mode(s) of action and exposure.

The information presented was largely based upon previous risk assessments of pentachlorophenol that have been conducted by EPA, ATSDR and OEHHA, and the information accurately reflected what was found in documents produced by the various agencies. However, the key sections on "Existing Health Criteria" were not adequately referenced and the references should be in the final chRD documentation. Significant portions of the descriptions appeared to come from the ATSDR monograph. I believe that the document would benefit from an expanded description of the results of the Beard and Rawlings (1998 and 1999) studies.

There is minimal discussion of pentachlorophenol metabolism, mode of action and exposure. While competition by pentachlorophenol for the thyroxin binding site on transthyretin appears to explain a number of the observed alterations, other mechanisms such as a direct effect on the

thyroid or altered thyroid hormone metabolism could also play a role (see Beard and Rawlings, 1999 for additional discussion).

Several sources supported the statement that pentachlorophenol was able to bioaccumulate to moderate levels [bioconcentration factors (BCF) <1000]. However, occasionally BCFs were found that exceeded 1000. For example, in the Hazardous Substances Data Base, it indicated that BCFs of 10,000 to 45,000 had been found for zebra mussels (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB). Similarly, BCF of up to 10,000 in several species was also reported in the Extension Toxicology Network Pesticide Information Profile (http://extoxnet.orst.edu/pips/pentachl.htm). These should be checked for accuracy, and the description modified if necessary.

Also the statement that the Department of Toxic Substances Control has detected pentachlorophenol at proposed school sites (mentioned in the response to the Pentachlorophenol Task Force) should be included with an appropriate citation in the "Use and Environmental Fate" section.

2) The appropriateness of the approach and studies used in developing the proposed chRD, including selection of the data set and supporting information.

The approach used is standard and the studies of mink and sheep, while not typical for toxicological investigations, seem appropriate for use in deriving the chRD. It should also be noted that altered T4 levels were also seen in cattle administered both analytical and technical grade pentachlorophenol (McConnell et al., 1980, Toxicol. Appl. Pharmacol. 52:468-490). The fact that altered thyroid hormones have been seen following pentachlorophenol administration in four different mammalian species, and that alterations in thyroid hormone levels are associated with neurodevelopmental effects in humans, provides substantial weight for the use of this particular endpoint in deriving the chRD. In addition, the observation that thyroid hormone-altering effects were seen in the minks and the lambs at similar doses also provides strong support for their use in deriving the chRD. Alterations in thyroid hormone levels have also been seen for other chlorinated aromatic compounds and this further supports the relationship between thyroid alterations and pentachlorophenol exposure.

3) Other major and critical effect information that should have been considered that might affect the selection of endpoint(s) applicable to the school population as defined.

As indicated in the document, pentachlorophenol induces toxicity affecting a number of organ systems. Pentachlorophenol-induced effects on these other systems have previously been used to establish reference doses (RfD) by the EPA and by OEHHA. Hematologic effects have been seen at doses not-distantly removed from 1 mg/kg-day. The use of anemia as an critical endpoint, as previously performed by OEHHA, results in a RfD that is well within an order of magnitude of that generated by the current approach. I see no compelling reason for choosing these other effects over the thyroid/neurodevelopmental effects. Indeed, basing the chRD on the thyroid effects would appear to be more appropriate for protecting against potential developmental effects in children.

It should be noted that, based on a Medline abstract of an article published in 1998, Rawlings and colleagues [J Toxicol Environ Health 54(1):21-36] reported that alterations in thyroxin levels were seen in ewes administered 2 mg/kg pentachlorophenol two times per week for 43 days. Expressed on a weekly basis, this dose is lower than that seen in the multigenerational mink study and the chronic sheep study that were used to derive the chRD. However, alterations in thyroxin were seen for a variety of pesticides, which suggests that the observed changes may be non-specific types of response.

4) The appropriateness of the uncertainty factors used in the chRD calculation.

Four uncertainty factors were used in deriving the chRD, a 10X factor for inter-human variability, a 10X factor for interspecies extrapolation, a 10X factor for the use of a LOAEL rather than a NOAEL, and a 3X factor for database deficiencies. The first three of these are standard, although a 3X or 5X factor may at times be used for the use of a LOAEL rather than a NOAEL. While the use of a 3X factor for database deficiencies is not uncommon, I do not think that it is necessary in this case. The alterations in thyroid hormone levels represent an intermediate biochemical and physiological alteration that can lead to neurodevelopmental effects. Since the neurological effects are a consequence of the alterations in hormone levels, a dose that protects against changes in thyroid hormones should be protective against downstream neurodevelopmental effects. As a result, the additional 3X uncertainty factor seems unnecessary to me. I would think that a 1000X uncertainty factor applied to studies that included exposure during gestation and lactation as well as over much or all of an animal's lifetime should provide ample protection for children that may be exposed at a school site during only a portion of their childhood.

5) The technical merit of OEHHA's responses to comments of the Pentachlorophenol Task Force.

I found OEHHA's responses to the Pentachlorophenol Task Force to be reasoned and adequately presented. One additional reason for not relying primarily on the NTP bioassay results is that exposure of the test animals begins after much of the prenatal and postnatal development has occurred. As a result, critical developmental effects may have been missed.

APPENDIX 5: OEHHA Response to Pentachlorophenol Task Force Comments on Final Draft

Response to comments of the Pentachlorophenol Task Force

Comment: OEHHA has revised the reported range of bioconcentration factors (BCF) from 100-1000 to 100-10,000 in its final draft report. The Pentachlorophenol Task Force feels that BCF values greater than 1000 were based on studies with inappropriate methodologies. Thus, BCF values up to 1000 are appropriate for use in the risk assessment and this information should be reflected in the final report.

Response: OEHHA provided a BCF in the Use and Environmental Fate Section of the report reported in cited references. This section serves as background information and is not intended for use in school site risk assessment. More importantly, soil contamination is the main issue in school site risk assessment and food is not an exposure pathway in that setting. Thus, BCF will not be a part of the equation in school site risk assessment. In this vein, OEHHA has relied on the reviews of the Agency for Toxic Substances and Disease Registry, and California Department of Pesticide Regulation, making use of their findings in describing the range of BCF. No attempt has been made to review the original studies because this parameter is not relevant in this context. In the final report, however, OEHHA now notes that the Pentachlorophenol Task Force performed an independent review and arrived at a different conclusion regarding BCF.

APPENDIX 6: Pentachlorophenol Task Force Comments on Final Draft

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Manager

May 15, 2006

Mr. Leon Surgeon
Integrated Risk Assessment Section
Office of Environmental Health Hazard Assessment
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Re: Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code Section 901(g): PROPOSED CHILD-SPECIFIC REFERENCE DOSE (chRD) FOR SCHOOL SITE RISK ASSESSMENT, Manganese and Pentachlorophenol

Dear Mr. Surgeon:

These comments are submitted by the Pentachlorophenol Task Force (PTF or the Task Force) in connection with the draft final report entitled "Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code Section 901(g): PROPOSED CHILD-SPECIFIC REFERENCE DOSE (chRD) FOR SCHOOL SITE RISK ASSESSMENT, Manganese and Pentachlorophenol," (Final Draft April 2006), that was posted on the Office of Environmental Health Hazard Assessment (OEHHA) website for comment until May 15, 2006.

The Task Force filed extensive comments on an earlier February 2005 draft of the report that were specifically directed toward use of the thyroid as a critical effect for pentachlorophenol (penta) chRD development. Although the Task Force in large part does not agree with OEHHA's response to its earlier comments, we do agree that OEHHA's decision not to apply a 3X uncertainty factor for database deficiency is appropriate.

These comments are directed to a different issue concerning the discussion of the bioaccumulation potential for penta. In the February 2005 draft, OEHHA correctly reported the bioconcentration factor (BCF) for penta of 100 to 1000. The Final Draft, however, makes the following statement:

> "ATSDR (2001b) indicates that…The compound has been found to bioaccumulate to moderate levels (e.g., bioconcentration factors of 100 to 10,000); however, food chain biomagnification has not been observed." (p. 17)

As explained below, although there are sporadic reports of BCFs for penta in the literature above 1,000, these reports are found only in studies that use methodologies inappropriate for establishing BCFs and therefore are unreliable. The highest bona fide fish whole body BCF value for penta is 770. This value is supported by seven (7) high quality studies (with six species of fish) designed specifically to measure bioconcentration. The range of fish BCFs is 64 (saltwater) to 770. The higher BCF values reported (up to and >10,000) are found in the filter-feeding zebra mussels. However, exposure was for only 6 hours, a time insufficient to establish steady state concentrations and thus not a reliable measure for establishing BCF values. Therefore, only the reported fish BCF values up to 770 (or rounded up to 1,000) are appropriate for use in risk assessments.

This point was understood by the Agency for Toxic Substances and Disease Registry (ATSDR). That is why the first page of the chapter on "Potential for Human Exposure" of the ATSDR Toxicology Profile for Pentachlorophenol (ATSDR 2001) states: "The compound has been found to bioaccumulate to modest levels (e.g., bioconcentration factors of <1,000), but food chain biomagnifications has not been observed." (ATSDR 2001, p.145). The higher end of the BCF as reported in the OEHHA Draft Final report appears much later in the ATSDR profile (page 155) and is thus supplementary information.

The core ATSDR conclusion that the penta BCFs are below 1000 is supported by other expert analysis. For example, the Dutch National Institute for Public Health and the Environment (RIVM) reported in its comprehensive review of penta, in 1991,

> "In aquatic organisms PCP is cumulated to a limited extent. Bioconcentration factors (BCFs) for algae, invertebrates and fishes calculated on the basis of laboratory and field observations are generally in the order of 100 to 1000".
> ... and "biomagnification of PCP does not play a significant role in the aquatic environment" (RIVM 1991)

Similarly, EuroChlor in its comprehensive assessment of penta, EuroClor Risk Assessment for the Marine Environment Pentachlorophenol -- OSPARCOM Region - North Sea, November 1999, summarized the situation as follows:

> "Significant bioaccumulation of pentachlorophenol in aquatic species is unlikely in view of its properties. The octanol-water partition coefficient (Kow) of pentachlorophenol is highly dependent and inversely related to pH. Measured log Kow values range from about 2.7 to 3.7 across the environmentally relevant pH range of 6 to 9 (Montgomery 1996). Chemicals with log Kow values in this range are not expected to have significant bioaccumulation. Log Kow values as high as 5.0 (measured at pH 1-2) have been reported but are inappropriate in environmental assessments considering the speciation of pentachlorophenol under environmental pH conditions (described in Section 4.1).

"In aquatic organisms PCP is cumulated to a limited extent. Bioconcentration factors (BCFs) for algae, invertebrates and fishes calculated on the basis of laboratory and field observations are generally in the order of 100 to 1000" (RIVM 1991). Recent UK and Dutch hazard assessments for PCP include BCF data; for example, the reported BCF for Daphnia magna is 400 (Hobbs et al.., 1993). In addition, "biomagnification of PCP (cumulated within food chains) does not play a significant role in the aquatic environment" (RIVM 1991)."

The limited bioaccumulation has been confirmed in a number of laboratory studies. At least six Reliability Level 1 fish bioconcentration tests have been reported. Test species have included fathead minnow, bluegill, rainbow trout, killifish, and flagfish. The whole body fish bioconcentration factors (BCFs) range from 64 for the saltwater killifish (study conducted at pH 8.3) to 770 for the fathead minnow (pH 7.5) and 771 for the rainbow trout (dechlorinated tap water). The most recent study is a 1993 test with bluegill conducted as part of the pentachlorophenol chemical re-registration under USEPA protocols. The whole body BCF was 490 at a pH of 6.9-7.2. These studies also demonstrated rapid depuration which is accounted for by pentachlorophenol's rapid metabolism in the fish.

The six Reliability Level 1 fish bioconcentration tests are as follows:

Test Species	Whole Body BCF	Reference
fathead minnow	770	Veith et al. (1979)
fathead minnow	174 - 284	Huckins and Petty (1983)
bluegill	490	Dionne (1993)
rainbow trout	91 - 771	Niimi and McFadden (1982)
killifish (saltwater)	64	Trujillo et al. (1982)
flagfish	216	Smith et al. (1990)

Avilable online at http://www.eurochlor.org/upload/documents/document91.pdf. There is thus no question that the correct value of the BCF for penta is less than 1000.

The OEHHA revision of the discussion on penta's BCF values from that presented in the February 2005 draft report appears to have originated from a comment by Dr. David Eastmond of the University of California, Riverside in connection with the external peer review comments to the February 2005 draft. Dr. Eastmond states that while several sources support that pentachlorophenol BCFs were <1,000, reference to higher BCF values could be found in the Hazardous Substances Data Base (HSDB) and the Extension Toxicology Network Pesticide Information Profile (EXTOXNET). However, he cautioned that these values should be checked for accuracy.

As noted above, the OEHHA document quotes the ATSDR Toxicology Profile. Therefore, that document was reviewed, as was the HSDB and EXTOXNET documents, both of which are secondary resources that cite primary research articles. A subset of these original sources of BCF data was reviewed in an effort to evaluate the reliability of the studies that reported the higher BCF values. In addition, the BCF data reported in the USEPA ECOTOX database was reviewed.

As noted above, the ATSDR Toxicology Profile reports BCF values of pentachlorophenol in algae, aquatic invertebrates, and fish to be "up to 10,000." The majority of reported BCFs for fish are below 1,000. The BCF values reported as up to 10,000 and above were observed only in studies with the zebra mussel Dreissena polymorpha (Gossiaux 1996). However, the exposure duration for this study was only 6 hours, far too short for a steady state to be reached, especially for an organism that filters a full liter of water per day[1]. In addition, while the results table lists pentachlorophenol only, the methods indicate that the actual dosing was done with a combination of Benzo(a)pyrene and pentachlorophenol, which adds further uncertainty to the results and makes these BCF values unreliable for risk assessment purposes.

Another high BCF value (3,830) reported in ATSDR was calculated for the pipe worm, a polychaete (Ernst 1979). The Ernst study does not provide much detail regarding the bioaccumulation in the pipe worm, but it does indicate a short exposure period (approximately 2 days) and reports no elimination of PCP following 20 days of post exposure measurements. **Most of the report deals with the mussel and its BCF of 390 and relatively rapid elimination.** Interestingly there is only one other reported study of PCP bioaccumulation in marine pipe worms reported in the literature of which are aware. The report is by Carr and Neff, 1981, and there a BCF of 280 is given. A careful of the Ernst and the Carr and Neff reports indicates that the Carr and Neff work is far more defensible. Carr and Neff used a C-14 labeled penta to enhance the accuracy of their measurement. They also report measurable elimination of penta in the pipe worm once exposure was discontinued. The apparent discrepancy between these two studies is easily explained if one considers to different analytical techniques used by the two researchers. In the 1978 paper Ernst reports a 0.04 parts per trillion (ppt) measurement (determined by GC) in seawater as the basis for calculated BCF values of 2600 - 8500 in pipe worms. This extremely low level of measurement is far below any other being reported in the literature in the 1970s or even since. The BCF estimate is completely dependent upon the accuracy of measurement in the water and in the tissue. If the 0.04 ppt measurement is really 0.4 ppt (which is still the lowest PCP detection reported in the 1 970s), then the BCF value would be 10-times lower and more in line with the other reported BCF values in the literature. Therefore, the calculated BCF of 3,380 is not reliable for risk assessment purposes.

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[1] Filter-feeding bivalves pass large amounts of both biotic and abiotic particulate matter through the organism, assimilating nutrients and then expelling indigestible solids.

The two highest BCF values for fish reported in ATSDR were 1000 for goldfish (whole body; Kobayashi and Akitake 1975) and 1,633 for American flagfish (fish lipid basis; Smith et al. 1990). The goldfish study is inappropriate for use in establishing BCFs because the 5-day exposure was insufficient time to reach steady state. In addition, all fish above the lowest concentration tested died during the study, so any survivors were likely highly stressed and would be unable to efficiently metabolize pentachlorophenol. Similarly, the flagfish data are inappropriate for establishing a BCF because it was calculated on a lipid basis, which would be much higher than the whole body BCF. It is important to note that the whole body BCF from this study was 214.

The HSDB database also cites studies with BCF values mostly below 1,000. For rainbow trout, the range of values is cited as 251-5,370, with the high value apparently the 5,360 reported in a study by Stratham et al. (1976). A closer review of the Stratham study reveals that the exposure lasted only 24 hours, which is insufficient to fully establish steady state concentrations. In addition, the high BCF reflects the ratio of bile to water, so is not appropriate for use in establishing a BCF classification. A second study cited in HSDB reports a BCF range of 380-1,698 for the minnow Oryzias latipes (Tachikawa et al. 1991; also cited in Devillers et al. 1996). A review of this study shows that the exposure was too short and fish were dying by day 4 at all three concentration levels tested. Therefore, steady state would not have been reached and survivors would be too stressed to metabolize pentachlorophenol normally.

EXTOXNET states that "[s]everal species of fish, invertebrates, and algae have had levels of PCP that were significantly higher (up to 10,000 times) than the concentration in the surrounding waters" and cites the draft (1992) version of the ATSDR profile. Therefore, this high value issue has been addressed already in the discussion above in reference to the final (2001) ATSDR profile data.

The USEPA's ECOTOX database was also accessed to determine if additional BCF data were available. While a few additional studies were cited, only one reported a BCF above 1,000. Hickie et al. (1989) reported BCF values ranging from 290 to 1,454 in three studies that varied in the diet provided to rainbow trout. Fish were exposed to pentachlorophenol water concentrations of 50 µg/L for 12 weeks, with no depuration period. The three diets were based on low, intermediate, and high carbohydrate content relative to lipids. Results indicated that the higher BCF values were associated with the low carbohydrate/high lipid diets, confirming that BCF is highly dependent on the lipid content of fish and other organisms. The BCF for the intermediate carbohydrate content diet, which most approximates the normal diet, was 596, well within the range for other fish species.

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In summary, the BCF data for pentachlorophenol cited in the OEHHA Draft Final were reviewed for reliability. While the OEHHA document states that penta has "bioconcentration factors of 100 to 10,000," the data demonstrate that valid fish BCF values are less than 1000. Values above 1,000 for fish are found only in studies that use methodologies inappropriate for establishing BCFs and therefore unreliable. The highest BCF values reported (up to and >10,000) were found in the filter-feeding zebra mussels. However, exposure was for only 6 hours, a time insufficient to establish steady state concentrations and thus not a reliable measure for establishing BCF values. Therefore, BCF values up to 1,000 are appropriate for use in risk assessments and that value should be reflected in the Final Report.

Respectfully submitted,

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