DRAFT

DEVELOPMENT OF GUIDANCE TISSUE LEVELS AND SCREENING VALUES FOR COMMON CONTAMINANTS IN CALIFORNIA SPORT FISH:

CHLORDANE, DDTs, DIELDRIN, METHYLMERCURY, PCBs, SELENIUM, AND TOXAPHENE

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FOREWORD

This report documents the process of developing guidance tissue levels and screening values for the contaminants methylmercury, chlordane, DDTs, dieldrin, PCBs, and toxaphene in California sport fish. Guidance tissue levels are designed to provide a number of recommended fish meals that correspond to the range of contaminant concentrations found in fish and are used to provide meal consumption advice to prevent consumers from being exposed to more than the average daily reference dose for non-carcinogens or to a risk level greater than $1x10^{-4}$ for carcinogens. Screening values are specific guidance tissue levels used to identify situations where contaminant concentrations in fish are of potential health concern and further action (e.g., additional sampling or developing consumption advice) is recommended.

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EXECUTIVE SUMMARY

Chemical contamination of fish is a global problem that has resulted in the issuance of fish consumption advisories in most states, including California. Although mercury contamination is a frequent cause of these advisories, polychlorinated biphenyls (PCBs) and chlorinated pesticides such as chlordane and DDTs are also often implicated. In California, the Office of Environmental Health Hazard Assessment (OEHHA) is the agency responsible for evaluating the potential public health risks of chemical contaminants in sport fish and issuing advisories, when appropriate.

In order to evaluate whether a consumption advisory for a specific fish species in a particular water body is necessary, contaminant levels in those fish must be measured and the predicted exposure compared to toxicity values for each chemical. In this document, cancer and non-cancer health effects were evaluated for seven common contaminants found in California sport fish: chlordane, dichlorodiphenyltrichloroethane and its metabolites (DDTs), dieldrin, mercury (as methylmercury), polychlorinated biphenyls (PCBs), selenium, and toxaphene. For each chemical, the toxicological literature was reviewed to establish an acceptable non-cancer reference dose (an estimate of daily human exposure to a chemical that is likely to be without significant risk of adverse effects during a lifetime) and/or a cancer slope factor (an upper-bound estimate of the probability that an individual will develop cancer over a lifetime as a consequence of exposure to a given dose of a specific carcinogen).

Once critical toxicity values for each chemical were determined, guidance tissue levels (GTLs) were developed to provide a number of recommended fish meals that correspond to the range of contaminant concentrations found in fish. GTLs are used to provide meal consumption advice to prevent consumers from being exposed to more than the average daily reference dose for non-carcinogens or to a risk level greater than 1×10^{-4} for carcinogens. GTLs assume that meal size is a standard 8-ounce (227 g) portion of uncooked fish (approximately six ounces after cooking) for adults who weight 70 kg. These criteria are used by other agencies, including in other fish advisory programs (for example, Georgia and West Virgina).

GTLs also take into account organic contaminant loss during the cooking process. The concentration of PCBs and other organic contaminants in fish are generally reduced by at least 30 percent, depending on cooking method. A cooking reduction factor to account for such loss was including in the GTL equation. Removing the skin from fillets also reduces organic contaminant levels; the GTL calculations assume fish are consumed as skin-off fillets.

GTLs for each chemical were used to establish screening values for California water bodies, i.e., levels of contaminants in fish that are of potential public health concern, for use by OEHHA or other agencies. When screening values are exceeded, it is an indication that additional site-specific monitoring and/or human health risk assessment should be performed.

INTRODUCTION

Fish consumption advisories have been issued in most states and cover approximately 35 and 24 percent of the country's total lake acreage and river miles, respectively (U.S. EPA, 2004). Mercury contamination of fish, in particular, is a national problem that resulted in the issuance of 222 new advisories in 2003 alone (U.S. EPA, 2004). Polychlorinated biphenyls (PCBs) and chlorinated pesticides such as chlordane and DDTs are also a frequent cause of fish consumption advisories throughout the United States (U.S. EPA, 2004). In California, the Office of Environmental Health Hazard Assessment (OEHHA) is the agency responsible for evaluating potential public health risks from chemical contamination of sport fish. This includes issuing advisories, when appropriate, based on mandates in the California Health and Safety Code, Section 59009, to protect public health, and Section 59011, to advise local health authorities, and the California Water Code, Section 13177.5, to issue health advisories. More recently, advisories (which focus primarily on fish whose consumption should be restricted) are being expanded to include "safe eating guidelines," which also inform consumers of fish with low contaminant levels considered safe to eat frequently.

In order to develop advisories or safe eating guidelines, states must first collect and analyze edible fish tissue for selected chemicals. In California, fish contaminant monitoring has historically been conducted by a variety of state programs, which recently have been integrated into the Surface Water Ambient Monitoring Program (SWAMP) of the State Water Resources Control Board (SWRCB). Data may also be collected by federal, county, and non-governmental organizations and provided to OEHHA for evaluation. The choice of chemicals to monitor depends, in part, on the chemical's prevalence, toxicity, bioaccumulation potential in fish tissue, and analytical methods (U.S. EPA, 2000a). Although in some instances only one chemical is tested based on known contamination at a site (e.g., mercury), often a suite of organic and inorganic chemicals are analyzed using screening survey methodology as recommended by U.S. EPA. Screening surveys typically test a limited sample of indicator species to determine whether any chemical contaminants in fish are a potential human health concern in the sampled water body. U.S. EPA recommends using chemical screening values to identify contaminants that are of potential concern and to select water bodies for further intensive monitoring (i.e., analysis of more samples and more species to characterize levels of the chemicals of concern) (U.S. EPA, 2000b). OEHHA is establishing screening values based on the same risk assessment parameters OEHHA uses for fish consumption advisories. This allows potential public health risks associated with fish consumption to be identified and fully characterized so that fish consumption advisories can be developed. The health benefits of fish consumption are also considered.

Once sufficient fish tissue data have been collected and analyzed, contaminant concentrations must be evaluated to ascertain the quantity of a fish species that can be safely consumed. This determination must take into account a chemical's toxicity (cancer and non-cancer) to different population groups. Relevant toxicity studies are examined and a reference dose and/or cancer slope factor is established for each

chemical. These toxicity values are then combined with daily consumption rates corresponding to specific recommended numbers of fish meals to be consumed per unit time (e.g., a meal per month) to establish a series of tissue concentrations for each contaminant, known as guidance tissue levels (GTLs). GTLs are used to provide meal consumption advice to prevent consumers from being exposed to more than the average daily reference dose for non-carcinogens or to a risk level greater than $1x10^{-4}$ for carcinogens.

The simplest GTL, for non-nutrient, non-carcinogens, is derived from the following basic equation:

$$\text{Tissue concentration} = \frac{\text{(Reference dose)(Body weight)}}{\text{Daily consumption rate}}$$

Additional discussion and examples of GTL development can be found in the section "Equations used to calculate GTLs."

Using contaminant concentrations measured in local fish and GTLs established for each chemical, OEHHA advises consumers whether it is safe to eat 12, 8, 4, 1, or no meals of a species per month from a specific site. Other meal frequency categories may be used in fish consumption advisories, if determined to be more appropriate. OEHHA assumes that when exposure is averaged over the maximum consumption interval (a one-month period), the critical dose is not exceeded in a single day.

This report provides critical toxicity values, guidance tissue levels and screening values for seven common contaminants in California sport fish: chlordane, DDTs, dieldrin, methylmercury, PCBs, selenium, and toxaphene. The toxicology of each chemical is reviewed; limited background information on the chemistry, environmental fate, metabolism, and typical exposure routes is also provided. Most fish advisories in the United States are issued for mercury, PCBs, chlordane, dioxins, and DDTs (U.S. EPA, 2005). OEHHA also included toxaphene and selenium in this GTL document because of historic use in the state and natural occurrence, respectively. At this time, OEHHA does not have sufficient analytical data for dioxins in fish throughout the state to support development of a GTL for this chemical. However, GTLs may be developed in the future for dioxins and additional contaminants, as necessary, using the same methodology.

TOXICOLOGY AND CRITICAL TOXICITY VALUES FOR COMMON CONTAMINANTS IN CALIFORNIA SPORT FISH

CHLORDANE

CHLORDANE TOXICOLOGY

Chlordane is a chlorinated cyclodiene insecticide that was used in the United States beginning in 1948 for a variety of agricultural and structural pest control purposes (ATSDR, 1994; Ecobichon, 1991; Matsumura, 1985; U.S. EPA, 1997). Technical chlordane, the commercial mixture, is comprised of approximately 60 percent *cis* and *trans* chlordane isomers and about 40 percent other related compounds (e.g., *cis*-nonachlor, *trans*-nonachlor and oxychlordane) (U.S. EPA, 1997). As a result of their lipophilicity, low volatility and slow degradation rates, chlordane and other organochlorine pesticides are exceptionally persistent in the environment and are able to bioconcentrate and biomagnify throughout the food chain (Ecobichon, 1991). Bioconcentration factors (the quotient of the concentration of a chemical in an organism divided by the concentration of the chemical in the ambient water) for chlordane in various marine and freshwater fish, for example, have been reported as high as 3,000 to 37,800 (ATSDR, 1994; Fisher, 1999). Because of this, as well as concerns over human cancer risk and hazards to wildlife, the use of chlordane was severely restricted in the United States in 1978 and ultimately banned in 1988 (ATSDR, 1994; U.S. EPA, 2000). Chlordane remains a contaminant in many soils and waterways, however, with the most frequent source of human exposure being consumption of contaminated foods, especially fish (ATSDR, 1994). Saltwater and fresh water fish and shellfish, combined, account for approximately 95 percent of the total dietary exposure to chlordane (Dougherty et al., 2000).

Chlordane is readily absorbed by all exposure routes (ATSDR, 1994). Once absorbed, chlordane is rapidly distributed to the liver and kidneys, whereupon it undergoes transformation to a number of metabolites. Chlordane excretion is mainly through bile and breast milk (ATSDR, 1994). Chlordane that is not excreted is deposited in adipose tissue, primarily as the metabolites oxychlordane and heptachlor epoxide (ATSDR, 1994, U.S.EPA, 1997). The elimination half-life of chlordane in humans reported in different studies has ranged from 21-88 days (Aldrich and Holmes, 1969; ATSDR, 1994; Curley and Garrettson, 1969; Olanoff et al., 1983).

ATSDR (1994), U.S. EPA (1997), and Brown (1997) have extensively reviewed the toxicity of chlordane. Following acute oral exposures (14 days or less), chlordane is considered moderately to highly toxic to humans (U.S. EPA, 2000). WHO (1984) estimated the acute human lethal dose to be between 25 and 50 mg/kg body weight. Acute poisoning symptoms include vomiting, diarrhea, seizures, anuria, ataxia, tremors, coma, and respiratory failure (ATSDR, 1994; Curley and Garrettson, 1969; NIOSH, 1981, 2003; Olanoff et al., 1983), and can occur within 45 minutes of exposure (Grutsch and Khasawinah, 1991). The difference between the no-effect and the fatal serum levels in humans is small (approximately 3 to 5 times), indicating a steep dose-response curve

(Grutsch and Khasawinah, 1991). Death is rare following acute oral poisoning, however, because the individual generally vomits, reducing the available dose (Grutsch and Khasawinah, 1991). Apparent recovery in non-fatal cases is rapid (Aldrich and Holmes, 1969; Curley and Garrettson, 1969; Grutsch and Khasawinah, 1991), although chemical hepatitis may develop subsequent to the acute phase (Olanoff et al., 1983). Acute chlordane toxicity in animals also results in neurotoxicity signs such as hyper-excitability, tremors, convulsions, hind limb paralysis and hypothermia (ATSDR, 1994; Grutsch and Khasawinah, 1991). Like other cyclodiene insecticides, the mechanism of neurotoxic action is believed to be inhibition of chloride transport, resulting in only partial repolarization of neurons and uncontrolled central nervous system stimulation (Ecobichon, 2003; Klassen and Watkins, 1999).

Subchronic or chronic chlordane toxicity in humans has been difficult to quantify because of problems with dose determination and confounding exposures. Some humans living in chlordane-treated homes have developed hepatic and neurological signs such as jaundice and grand-mal seizures, respectively. The exact dose-response relationship has not been determined, however (ATSDR, 1994). In their review of the literature, Grutsch and Khasawinah (1991) reported that chronic, low-level chlordane exposure via inhalation, oral, or dermal routes has not been found to elicit signs or symptoms indicative of chlordane toxicity. ATSDR (1994) also noted that adverse health effects resulting from chlordane exposures have not been confirmed in studies of workers engaged in the manufacture of chlordane. More recent epidemiological studies, though, have indicated that chlordane may cause neurotoxicity following chronic exposures in humans (IRIS, 1998). In a cross-sectional study, Kilburn and Thornton (1995) found that neurobehavioral functions such as reaction times, verbal recall, and trail-making were impaired in 216 adults exposed to chlordane via inhalation compared to an unexposed referent population matched by age and educational level. However, effect levels could not be assigned because data on exposure, dose-response or potential co-exposure to other neurotoxicants were not available (U.S. EPA, 1997). In a subsequent study of nine chlordane-exposed patients seen consecutively for effects of chemical exposure, Kilburn (1997) noted that neurobehavioral functions such as balance, reaction times, verbal recall, and color discrimination were also diminished in the exposed group compared to a control population. Exposure dose was unknown and exposure duration ranged from 50 minutes to 18 years. Potential problems associated with experimental design, including selection bias and an inadequately matched control population, severely limit interpretation of this study.

In rodent studies, the liver is clearly the target organ of chronic chlordane toxicity and hepatic necrosis has been deemed the critical effect (U.S. EPA, 1997). Khasawinah and Grutsch (1989a, 1989b) conducted the most extensive rat and mice toxicity studies available for chlordane, at similar doses, which indicated that the mouse is more susceptible to the hepatotoxic effects of chlordane than is the rat (U.S. EPA, 1997). Additional hepatic toxicity signs in mice included increased liver weights and elevated serum aspartate transferase (AST) and alanine transferase (ALT) levels (Khasawinah and Grutsch, 1989b).

Reproductive toxicity has been shown to occur following oral exposure to relatively high levels of chlordane in male mice. Balash et al. (1987) found that mature male mice orally gavaged with chlordane for 30 days had dose-related histological changes in seminiferous tubules. Similarly, Al-Omar et al. (2000) determined that mice gavaged with approximately 20 or 70 percent of the median lethal dose of chlordane suffered damage to testicular tissues, including decreased seminiferous tubule diameter, and reduced numbers of spermatogonia, spermatocytes and spermatids.

Developmental effects have also been reported in response to chlordane exposure in mice and rats (ATSDR, 1994). A series of neurobehavioral tests given to mice offspring following third-trimester fetal exposure to chlordane found depressed avoidance response acquisition and increased seizure threshold and exploratory activity, suggesting an effect on fetal brain (ATSDR, 1994; Al-Hachim and Al-Baken, 1973). Cassidy et al. (1994) showed that male and female rats exposed to low levels of chlordane *in utero* and during the early postnatal period (Day 4 of gestation through Day 21 of lactation) had gender-dependent alterations of sexually dimorphic functions and behaviors such as spatial abilities and auditory startle-evoked responses. Based on these results, the authors suggested that chlordane mimics and/or alters sex steroid concentrations and, thus, has a masculinizing effect on fetal and/or neonatal rats. In their review of the paper, however, U.S. EPA (1997) noted that dose-response relationships were inconsistent, as effects in high-dose animals were often similar to controls. Additionally, testosterone levels in males and females were not systematically related to the observed behavioral changes. U.S. EPA thus questioned the authors' interpretation of the study results and indicated that further research was necessary to confirm a relationship between these behavioral effects and low-dose chlordane exposure.

Immunological studies in mice indicated that *in utero* and neonatal treatment with chlordane suppressed cell-mediated immunity (Barnett et al., 1985a, 1985b; 1990a, 1990b; Blaylock et al., 1990; IRIS, 1998; Menna et al., 1985). Reported effects following such chlordane exposures included decreased fetal hematopoietic activity, delayed-type hypersensitivity-mediated pathology, and mixed lymphocyte reactivity. However, in some experiments, this suppression led to increased survival following influenza virus infection during young adulthood (Barnett et al., 1985a; Blaylock et al., 1990; Menna et al., 1985). More recent research has shown a variety of immunotoxic responses of rats following 28-day oral gavage of *cis*-nonachlor, *trans*-nonachlor and technical chlordane (Tryphonas et al., 2003). In those studies, *cis*- and *trans*-nonachlor were more likely to cause immunotoxic effects than technical chlordane, with these results more pronounced in females.

Oxychlordane, one of the principal metabolites of chlordane, is the second most common chlordane-related residue found in food, following *trans*-nonachlor (Bondy et al., 2003). A series of twenty-eight-day feeding studies in female rats showed that oxychlordane caused weight loss and histopathological changes in the liver, thymus, and thyroid and produced signs of toxicity at doses approximately eight times lower than *cis*- or *trans*-nonachlor (Bondy et al., 2003). The authors suggested that exposure to oxychlordane

may prove to be a more significant human health hazard than exposure to other chlordane compounds found in foods.

Information regarding the potential carcinogenicity of chlordane in humans is conflicting. A few studies have shown an association between chronic chlordane inhalation exposure in humans and the development of various blood dyscrasias, such as leukemia (reported in ATSDR, 1994; U.S. EPA, 1997). In contrast, Brown et al. (1990; 1993) failed to find a relationship between leukemia or multiple myeloma and chlordane inhalation exposure in adult men (U.S. EPA, 1997). A retrospective mortality study of workers in the chlordane manufacturing industry (Brown, 1992) indicated that workers exposed to chlordane and other organochlorines had lower than expected mortality from all causes as well as from all malignant neoplasms (ATSDR, 1994). Yet, in two case-control studies, Cantor et al. (1992) and Woods and Polissar (1989) found that non-Hodgkin's lymphoma patients were more likely to have had previous inhalation exposure to chlordane than healthy controls, although this association was only significant in the Cantor et al. study. U.S.EPA (1997) notes that there is no evidence to support the conclusion that oral exposure to chlordane from food or drinking water causes human carcinogenicity; however, the weight of evidence following high-level, long-term dermal or inhalation exposures does suggest that chlordane is likely a human carcinogen.

The International Agency for Research on Cancer (IARC) has listed chlordane as a possible human carcinogen, based on inadequate evidence in humans and sufficient evidence in experimental animals (IARC, 2001). U.S. EPA has classified chlordane as a likely human carcinogen, based on limited epidemiological evidence in humans, development of hepatocellular carcinomas in multiple strains of mice and liver toxicity in rats, and the structural resemblance of chlordane to other rodent hepatic carcinogens (IRIS, 1998; U.S. EPA, 1997). Chlordane is on the Proposition 65 list of chemicals known to the State of California to cause cancer.

DERIVATION OF A REFERENCE DOSE AND CANCER SLOPE FACTOR FOR CHLORDANE

A chronic reference dose (RfD) is an estimate of daily human exposure to a chemical that is likely to be without significant risk of adverse effects during a lifetime (including to sensitive population subgroups), expressed in units of mg/kg-day (IRIS, 1995). This estimate includes a factor to account for data uncertainty. The underlying assumption of a reference dose is that, unlike most carcinogens, there is a threshold dose below which certain toxic effects will not occur. The reference dose for a particular chemical is derived from review of relevant toxicological and epidemiological studies in animals and/or humans. These studies are used to determine a No-Observed-Adverse-Effect-Level (NOAEL; the highest dose at which no adverse effect is seen), a Lowest-Observed-Adverse-Effect-Level (LOAEL; the lowest dose at which any adverse effect is seen), or a benchmark dose level (BMDL; a statistical lower confidence limit of a dose that produces a certain percent change in the risk of an adverse effect) (IRIS, 1995). Based on these values and the application of uncertainty factors to account for incomplete data and sensitive subgroups of the population, a reference dose is then generated. Exposure to a

level above the RfD does not mean that adverse effects will occur, only that the probability of adverse effects occurring has increased (IRIS, 1993).

Because chlordane dose-response data in humans are inadequate, the U.S. EPA RfD for this chemical was derived from animal data based on hepatic necrosis as the critical effect (IRIS, 1998; U.S. EPA, 1997). Although several studies have indicated that chronic chlordane exposure may also result in neurobehavioral or other neurotoxic effects, reliable dose-response information as well as data to support a plausible mode-of-action are not available for these endpoints (U.S. EPA, 1997). U.S. EPA thus chose Khasawinah and Grutsch (1989b) as the principal study for the RfD because of the clear dose-related incidence of hepatic effects, overall strength of the study, and comparatively low adverse effect level (IRIS, 1998; U.S. EPA, 1997). Newer chlordane toxicity studies published since the RfD was developed do not have sufficient data to determine acceptable exposure values and/or have not shown a lower adverse effect level.

Khasawinah and Grutsch (1989b) fed 80 ICR mice per sex per group 0, 1, 5, or 12.5 parts per million (ppm) dietary chlordane (estimated to be 0, 0.15, 0.75, and 1.875 mg/kg-day, respectively) for 104 weeks. Hepatocellular swelling was seen in both male and female mice at doses of 5 and 12.5 ppm dietary chlordane; incidence of hepatic necrosis was also significantly elevated at those dose levels, but only in male mice. Other hepatic effects, such as increased relative liver weights and alanine transferase activity, were seen at varying dose levels. The NOAEL and LOAEL values for this study were considered to be 1 and 5 ppm, respectively. To the NOAEL, U.S. EPA applied a 300-fold uncertainty factor (10 for interspecies extrapolation, 10 for intraspecies variation, and 3 for lack of a multigenerational reproductive study), leading to an RfD of $5x10^{-4}$ mg/kg-day (IRIS, 1998; U.S. EPA, 1997). This RfD will be used to evaluate chlordane non-cancer risk for OEHHA fish consumption guidelines.

A cancer slope factor (CSF) is an upper-bound estimate of the probability that an individual will develop cancer over a lifetime as a consequence of exposure to a given dose of a specific carcinogen and is expressed as $(mg/kg\text{-}day)^{-1}$ (U.S. EPA, 1989). The higher the CSF, the greater the estimated potency of a carcinogen. As is the case with noncancer endpoints, only animal data are available to quantify the carcinogenic risk of chlordane (U.S. EPA, 1997). In their 1998 cancer assessment, U.S. EPA combined the results of five liver tumor data sets for male and female CD-1 and B6C3F1 mice and male ICR mice orally exposed to chlordane at doses from 5 to 64 ppm for a period of 78 to 104 weeks (IRDC, 1973; NCI, 1977; Khasawinah and Grutsch 1989b; U.S. EPA, 1997; IRIS, 1998). U.S. EPA used $(body\ weight)^{3/4}$ scaling and the linearized multistage model in Global 86 software to determine cancer potency. Individual slope factors for each of the data sets ranged from 0.114 to 0.858 $(mg/kg\text{-}day)^{-1}$; a geometric mean of these values was then calculated to derive an oral cancer slope factor for chlordane of 0.35 $(mg/kg\text{-}day)^{-1}$ (IRIS, 1998). At the time of completion of this cancer risk assessment, however, the 1996 Guidelines for Carcinogenic Risk Assessment were still in draft form (U.S. EPA, 1996). U.S. EPA noted that using the LED_{10} alternate method of low-dose extrapolation from the newer guidelines to calculate cancer potency would lead

to a slope factor of 0.567 $(mg/kg\text{-}day)^{-1}$ (IRIS, 1998). These guidelines have since been finalized by U.S. EPA (U.S. EPA, 2005).

In the Public Health Goal for chlordane in drinking water developed by OEHHA, only the male and female CD-1 and B6C3F1 mice studies (IRDC, 1973; NCI, 1977) were used to determine a cancer slope factor; the male ICR mice study (Khasawinah and Grutsch,1989b) included in the U.S. EPA assessment (IRIS, 1998) was not used (Brown, 1997). An intercurrent mortality correction of approximately 2.4 was used to correct for less than lifetime duration of these four studies. OEHHA employed the methodology from the 1996 Guidelines for Carcinogenic Risk Assessment (U.S. EPA, 1996) to calculate cancer slope factors for these studies. OEHHA's estimates were based on $(body\ weight)^{3/4}$ scaling and used Tox_Risk software to calculated the LED_{10} because, according to the author, this software had a greater ability to calculate lower bounds on doses in the observed range in the evaluated studies (Brown, 1997). OEHHA then calculated the geometric mean of the best fitting four data sets to determine a cancer slope factor of 1.3 $(mg/kg\text{-}day)^{-1}$. This cancer slope factor will be used to evaluate chlordane cancer risk for OEHHA fish consumption guidelines.

In summary, the non-cancer and cancer critical values used to evaluate chlordane in fish for the development of consumption guidelines will be **$5x10^{-4}$ mg/kg-day and 1.3 $(mg/kg\text{-}day)^{-1}$**, respectively.

DICHLORODIPHENYLTRICHLOROETHANE AND ITS METABOLITES (DDTs)

DDTs TOXICOLOGY

Dichlorodiphenyltrichloroethane (DDT) is a synthetic organochlorine insecticide once used throughout the world to control insects that transmit malaria, typhus, and other significant diseases (Crosby, 1998). First used in the United States in 1942, its registration was cancelled by USEPA in 1973 after discovery of its environmental persistence, bioaccumulative properties, and induction of eggshell thinning in predatory species of birds (Hodgson et al., 1998). DDT is still used in some developing countries, however, because it is an effective and inexpensive method of vector control (ATSDR, 1994; Ecobichon, 1991). Humans are typically exposed to a mixture of DDT and its principal metabolites, DDD (tetrachlorodiphenylethane) and DDE (dichlorodiphenyl-dichloroethylene) (USEPA, 2000), which are referred to collectively as total DDTs. USEPA recommends that fish consumption limits be based on the sum of DDT, DDD, and DDE (i.e., total DDTs) (USEPA, 2000).

DDTs are very lipid soluble and water insoluble, have relatively low volatility, and are chemically and biologically stable, which leads to their persistence in the environment and biomagnification by organisms (Ecobichon, 1991; Menzer, 1991; WHO, 1989). Bioconcentration factors as high as $1x10^6$ have been reported for DDTs in aquatic species (reported in Ecobichon, 1991). Because of their historical widespread use and chemical properties, DDTs are pervasive environmental contaminants (ATSDR, 2002).

Exposure of humans to DDTs occurs most commonly from food consumption, particularly meat, dairy products, poultry, and fish (ATSDR, 2002). Freshwater and saltwater fish, in fact, typically account for approximately 75 percent and 5 percent of the total dietary exposure to DDTs, respectively (Dougherty et al., 2000). DDTs are absorbed in direct proportion to dietary consumption (IRIS, 1996) and then distributed widely by the lymphatic system and blood before being stored primarily in high-lipid tissues such as fat, liver, kidney, and brain (ATSDR, 1994; 2002; USEPA, 2000). Adipose storage of DDTs is considered protective as it lowers the concentration at the target organ (i.e., the brain) (Klaassen, 2001). DDTs are transferred across the placenta to the fetus (Saxena et al., 1981; Waliszewski et al., 2000; 2001) and easily cross the blood-brain barrier (ATSDR, 1994). Although the primary route of DDT excretion is urinary, lesser amounts are also excreted through feces and breast milk (ATSDR, 1994; 2002). Lactation is a significant means of maternal DDT decontamination (Waliszewski et al., 2001). The half-life of DDT in the body is 10-20 years (IRIS, 1996).

ATSDR (1994; 2002) has extensively reviewed the toxicity of DDT and related compounds. DDT has low acute toxicity with no confirmed human deaths reported solely from DDT exposure (ATSDR, 1994). Acute oral exposures to high levels of DDT primarily affect the nervous system in humans. DDT elicits adverse neurological effects by inhibiting ion movement through neuronal membranes (ATSDR, 1994; 2002) and reducing the rate of depolarization, thereby intensifying the sensitivity of neurons to

stimuli (Ecobichon, 2003). Symptoms have been reported to occur at doses of 5-10 mg/kg and above and include paresthesia, anxiety, irritability, vertigo, tremor, and convulsions, (ATSDR, 2002; Ecobichon, 1991; USEPA, 2000). During an acute poisoning episode, tactile or auditory stimuli may induce repetitive tremors and seizures (Ecobichon, 2003).

Chronic oral exposures to moderate DDT levels have been reported to lead to anorexia and weight loss, anemia, tremors, muscular weakness, EEG changes, and anxiety in humans (Ecobichon, 1991). Similar to acute toxicity, the nervous system is considered a principal target following chronic exposure to this chemical (ATSDR, 2002). Subtle neurological deficits have been reported in humans following long-term chronic DDT exposure (van Wendel de Joode et al., 2001). Twenty-seven retired men, aged 55-70, with a history of occupational DDT exposure during the previous 41 years had exposure duration-related reduced neurobehavioral functioning and increased neuropsychological and psychiatric symptoms compared to a reference group. Performance on tests of verbal attention and visuomotor speed and sequencing were the most pronounced differences between groups. Exposure levels were not available.

A few studies have reported an association between plasma DDE levels and altered immune function in humans including lowered mitogen-induced lymphoproliferative activity, increased total lymphocytes, and either increased or decreased immunoglobulins (Vine et al., 2000, 2001; Cooper et al., 2004). Reproductive and developmental effects in humans such as alterations in the duration of lactation, maintenance of pregnancy, fertility, and length of gestation have also been associated with high levels of DDTs in blood and other body tissues (ATSDR, 2002; see, e.g., Gladen and Rogan, 1995; Longecker et al., 2001).

While human epidemiological studies can only suggest a possible causal relationship between a chemical exposure and an adverse effect, animal studies using controlled exposures do demonstrate numerous toxic effects of DDT exposure. Similar to acute high-level DDT exposures in humans, relatively high long-term DDT exposure has been shown to lead to significant neurological signs in non-human primates. Six of 24 cynomolgus and rhesus monkeys given 20 mg/kg DDT for 130 months developed severe irreversible tremors requiring euthanasia during the first seven years of the study. Histological evidence of neurotoxicity was noted on necropsy (Takayama et al., 1999). Neurodevelopmental effects, most notably altered motor behavior in adult mice exposed prenatally, have also been reported in animals exposed to DDT (ATSDR, 2002; Eriksson et al., 1990a,b, 1992).

Although there is no conclusive evidence that DDTs cause hepatic effects in humans (ATSDR, 2002), liver lesions have been shown to be the critical effect following chronic DDT exposure in rodent studies (IRIS, 1996). Laug et al. (1950), for example, found that weanling rats showed dose-related hepatic morphological changes at DDT doses of 5 ppm and above. DDT-induced hepatic effects have also been shown in hamsters, mice and dogs (IRIS, 1996). Fatty liver and histological signs of hepatotoxicity, including toxic hepatitis, coagulation necrosis, and focal liver necrosis, were seen in cynomolgus

and rhesus monkeys dosed with 20 mg/kg DDT for 130 months and then followed for 25 years (Takayama et al., 1999).

Rodent studies have shown that DDTs in comparatively high doses have estrogenic properties that result in increased uterine weights and delayed vaginal opening (Clement and Okey, 1972), as well as antiandrogenic activity such as altered reproductive organ development and delayed puberty (Diel et al., 2000) (reported in ASTDR, 2002). Many animal studies have shown that DDTs are reproductive and developmental toxins. However, human studies have shown no clear link between exposure to environmental levels of DDTs and such effects. Intake of other estrogenic substances (as estrogen equivalents) from dietary bioflavonoids, for example, is estimated to be $4x10^7$ times higher than that from estrogenic pesticides (ATSDR, 2002; Safe, 1995).

Numerous epidemiological studies have attempted to determine whether DDTs cause cancer in humans, particularly those of the breast, pancreas, lymph system, prostate, and endometrium (reported in ATSDR, 2002). To date, these studies have not been sufficient to support a causal relationship between DDT exposure and the development of cancer in humans (ATSDR, 2002). However, the International Agency for Research on Cancer (IARC) has listed DDT as a possible human carcinogen, based on inadequate evidence of carcinogenicity in humans and sufficient evidence in experimental animals (development of liver tumors in several mouse and rat studies) (IARC, 1991). U.S. EPA classifies DDT as a probable human carcinogen, based on development of liver tumors in mice and rats (IRIS, 1996). OEHHA has administratively listed DDTs on the Proposition 65 list of chemicals known to the State of California to cause cancer.

DERIVATION OF A REFERENCE DOSE AND CANCER SLOPE FACTOR FOR DDTs

Because DDT dose-response data in humans are inadequate, the U.S.EPA RfD for this chemical was derived from animal data based on hepatic lesions as the critical effect (IRIS, 1996). U.S.EPA chose Laug et al., (1950) as the principal study for the RfD calculation because it had sufficient exposure duration, established the male rat as the most sensitive animal to DDT toxicity, used doses over the range of the dose-response curve, and provided both a NOAEL and LOAEL, including the smallest LOAEL determined for this chemical (IRIS, 1996).

Laug et al. (1950) fed male and female weanling rats diets containing 0, 1, 5, 10 or 50 ppm commercial DDT for 15-27 weeks. No gross signs of toxicity were apparent. Histological evaluation of liver and kidneys showed centrilobular hepatic cell enlargement at doses of 5 ppm and above, particularly in male rats. The authors concluded that "the difference observed between the control and 5 ppm animals represents the smallest detectable morphologic effects of DDT, based on extensive observations of rat liver as affected by a variety of chemicals" (Laug et al., 1950; IRIS; 1996). The NOAEL and LOAEL values for this study were considered to be 1 and 5 ppm dietary DDT, respectively (IRIS, 1996). To the NOAEL (corresponding to 0.05

mg/kg-day), U.S.EPA applied a 100-fold uncertainty factor (10 for interspecies conversion and 10 to protect sensitive human subpopulations), leading to an RfD of $5x10^{-4}$ mg/kg-day (IRIS, 1996).

ATSDR has developed a minimal risk level (MRL) for DDTs based on neurodevelopmental effects in mice reported by Eriksson and colleagues (ATSDR, 2002; Eriksson and Nordberg, 1986; Eriksson et al., 1990a, 1990b, 1993; Johansson et al., 1995; 1996; Talts et al., 1998). Male suckling mice given a single oral dose of 0.5 mg/kg body weight DDT during the peak period of rapid brain growth (10 days of age) showed increased spontaneous motor activity when subjected to behavioral testing as 4-month old adults, indicating a disruption of habituation (Ericksson et al., 1990 a,b; 1992). Similar effects were not seen when exposures occurred either before (3 days of age) or after (19 days of age) this period (Ericksson et al., 1992). These studies identified a LOAEL of 0.5 mg/kg-day, to which ATSDR applied a 1000-fold uncertainty factor (10 for use of a LOAEL, and 10 each for animal to human extrapolation and intrahuman variability, respectively). The resulting MRL is identical to the U.S.EPA RfD based on hepatic effects ($5x10^{-4}$ mg/kg-day), which will be used to evaluate DDT non-cancer risk for OEHHA fish consumption guidelines.

Although studies to assess carcinogenicity in humans have been inadequate and conflicting, DDT has been shown to cause benign and malignant tumors in multiple animal studies and is structurally related to other known animal carcinogens such as DDD, DDE, dicofol, and chlorobenzilate (IRIS, 1996). In their 1991 cancer assessment, U.S.EPA combined the results of six liver tumor data sets for male and female CF-1 mice, male BABL/C mice, male MRC Porton rats, and male and female Wistar rats (Turusov et al., 1973; Terracini et al., 1973; Thorpe and Walker, 1973; Tomatis and Turusov, 1975; Cabral et al., 1982; and Rossi et al., 1977) given doses from 2 to 500 ppm in lifetime feeding studies. Individual slope factors from each of the data sets ranged from 0.082 to 1.04 $(mg/kg\text{-}day)^{-1}$; a geometric mean of these values was then calculated to derive an oral cancer slope factor for DDT of 0.34 $(mg/kg\text{-}day)^{-1}$. This oral slope factor will be used to evaluate DDT cancer risk for OEHHA fish consumption guidelines.

In summary, the non-cancer and cancer critical values used to evaluate DDT in fish for the development of consumption guidelines will be **$5x10^{-4}$ mg/kg-day and 0.34 $(mg/kg\text{-}day)^{-1}$**, respectively.

DIELDRIN

DIELDRIN TOXICOLOGY

Dieldrin is a chlorinated cyclodiene insecticide widely used in the United States from the 1950s to 1970 on crops such as corn and cotton and as a termiticide in subsequent years, until its registration was canceled by U.S.EPA in 1989 (ATSDR, 2002; Stevenson et al., 1999; WHO, 1989). As a result of their low volatility, slow degradation rates and lipophilicity, dieldrin and other organochlorine pesticides resist degradation in the environment and are able to bioconcentrate and biomagnify throughout the terrestrial and aquatic food chain (ATSDR, 2002; Ecobichon, 1991). For example, bioconcentration factors of 12,500 and 13,300 have been found for dieldrin in guppies and sculpins, respectively (Fisher, 1999). Dieldrin is extremely persistent (Matsumura, 1985) and, as such, is still found in the environment, particularly in soil, sediment, and animal fat (ATSDR, 2002).

Diet is the main source of dieldrin exposure in most individuals, with foods such as dairy and meat products, fish, garden fruits, and root vegetables providing the largest dietary contribution (ATSDR, 2002; WHO, 1989). Currently, approximately 90 percent of dietary dieldrin exposure is derived from saltwater and freshwater fish, combined (Dougherty et al., 2000). Dieldrin levels in fish are most commonly associated with areas of corn production (ATSDR, 2002). Following oral exposure, dieldrin is absorbed from the gastrointestinal tract and rapidly distributed through the lymphatic system to various body tissues before being stored largely in adipose tissue and bone marrow (ATSDR, 2002; de Vlieger et al., 1968; Morgan and Roan, 1970; Scheele, 1998). Body burdens are positively correlated with total body fat (ATSDR, 2002; Hunter and Robinson, 1967; 1968). Dieldrin is transferred across the placenta to the fetus where it is widely distributed to fetal organs (Curley et al., 1969). During labor, levels in extracted lipids of fetal blood are higher than in maternal blood (ATSDR, 2002; Polishuk et al., 1977; WHO, 1989). Dieldrin also crosses the blood brain barrier (WHO, 1989). The primary route of dieldrin excretion is through feces via the bile (ATSDR, 2002; Richardson and Robinson, 1971; WHO, 1989), although dieldrin is also excreted in breast milk (ATSDR, 2002; Schecter et al., 1989; Stevens et al., 1993). Breast milk dieldrin levels have been reported to be significantly lower in vegetarians whose diets do not contain animal products compared to U.S. population means, even though breast milk lipid levels were similar between groups (Hergenrather et al., 1981). The biological half-life of dieldrin is approximately one year (WHO, 1989).

ATSDR (2002) and WHO (1989) have extensively reviewed the toxicity of dieldrin. Similar to other chlorinated cyclodienes, dieldrin has relatively high acute toxicity following oral or inhalation exposures compared to most organochlorine pesticides with signs and symptoms including dizziness, vomiting, motor hyperexcitability, and convulsions that generally appear within 20 minutes to 24 hours post-exposure (Ecobichon, 1991; 2003; Klassen and Watkins, 1999; WHO, 1989). The nervous system is the most sensitive target organ following acute and chronic oral exposures in humans (ATSDR, 2002); adverse neurological effects, including electroencephalographic

abnormalities, have been reported in workers occupationally exposed to dieldrin (Hoogendam et al., 1962; 1965). The mechanism of neurotoxic action is believed to be inhibition of chloride transport, resulting in only partial repolarization of neurons and uncontrolled central nervous system stimulation (Ecobichon, 2003; Klassen and Watkins, 1999). In animals, initial signs of single-dose dieldrin intoxication are irritability and tremor prior to tonic-clonic convulsions; these may occur as little as one hour after exposure (WHO, 1989). The adult human lethal dose is estimated to be five g (WHO, 1989). The single dose oral LD_{50} for dieldrin in the rat is approximately 37 to 46 mg/kg (ATSDR, 2002). Interspecies variation in susceptibility to acute dieldrin toxicity is significant, with toxicity inversely correlated with species total body fat content (Geyer et al., 1993).

Dieldrin may affect the endocrine system in humans. An epidemiological study of blood organochlorine levels found that dieldrin concentrations were inversely correlated with T4 levels in hypothyroid women (Rathore et al., 2002). Correlational studies such as this, however, cannot prove a causal relationship between exposure and adverse effect.

There is no clear evidence that dieldrin causes hepatotoxicity in humans; however, in rodent studies, the liver is the target organ of chronic dieldrin toxicity and liver lesions are considered to be the critical effect (IRIS, 1990). Liver histopathological changes in rats and increased liver weights and liver-to-body weight ratios in rats and dogs were found in response to varying levels of dieldrin exposure for two years (Walker et al., 1969). Hepatomegaly and histopathological evidence of liver damage were also seen in a mice exposed to 10 ppm dietary dieldrin for two years (Thorpe and Walker, 1973). Kitselman (1953) showed that dieldrin-induced gross and histopathological liver changes in dogs were reversible after dieldrin was removed from the diet. In a six-year study of monkeys fed 0.01 to 5.0 ppm dietary dieldrin, hepatic microsomal cytochrome P-450 levels were significantly increased in a dose-dependent fashion at doses of 0.1 ppm and above (approximately 25 to 30 µg/kg body weight per day or greater). Other hepatic variables such as liver weights and alkaline phosphatase, glucose-6-phosphatase, and succinic dehydrogenase activities were not affected by treatment, with the exception of slightly increased microsomal protein contents at the highest doses (Wright et al., 1978).

Several studies have indicated that fertility, litter size, and maternal behavior may be adversely affected following dieldrin exposure in rodents (Harr et al., 1970; Good and Ware, 1969; Virgo and Bellward, 1975; Treon and Cleveland, 1955). A small reproductive study in male and female dogs found delayed estrus, decreased libido, lack of mammary function, and increased stillbirths in animals exposed to 0.15 or 0.30 mg/kg-day dieldrin (Deichmann et al., 1971; reported in ATSDR, 2002). Teratogenesis was not observed in offspring of rats and mice fed graded doses of dieldrin during the period of organogenesis; however, fetotoxicity, as evidenced by an increase in the number of supernumerary ribs and decreased numbers of caudal ossification centers, was seen in doses that also caused signs of maternal toxicity (Chernoff et al., 1975).

Dieldrin has been shown to exert neurobehavioral effects in animals. Following a low dose (0.5, 1.5, or 4.5 mg/kg) acute exposure, a dose-related decrement in adaptive

capacity to an uncontrollable stressor was seen in adult mice (Carlson and Rosellini, 1987). In a small study, 0.1 mg/kg-day dieldrin for 55 days impaired learning acquisition in monkeys while 0.01 mg/kg-day did not (Smith et al., 1976). Neurodevelopmental changes such as cerebral edema, internal and external hydrocephalus, and focal neuronal degeneration were seen in rat pups whose dams were exposed to 0.004-0.008 mg/kg-day dieldrin during gestation (ATSDR, 2002; Harr et al., 1970). However, inadequacies of study design and statistical analyses limit interpretation of these results (ATSDR, 2002).

Mouse studies have shown that dieldrin may cause immunosuppression, as evidenced by increased lethality of various viruses (ATSDR, 2002). For example, Krzystyniak et al. (1985) found that a single oral dose of 18 or 30 mg/kg dieldrin in mice significantly reduced the mean day of death following exposure to a lethal dose of mouse hepatitis virus 3 (MHV3). Mice fed 1 or 5 ppm dietary dieldrin for 10 weeks (corresponding to doses as low as 0.13 mg/kg/day; ATSDR, 2002) had reduced survival times when infected with *Plasmodium berghei* or *Leishmania tropica* (Loose, 1982).

Whether dieldrin can cause cancer in human populations is controversial. Several long-term epidemiological studies of workers in pesticide manufacturing plants have not found higher cancer mortality rates related to occupational dieldrin exposure in workers compared to controls (Amoateng-Adjepong et al., 1995; Ribbens, 1985; Swaen et al., 2002). Although Quintana et al. (2004) found that cadaver adipose tissue dieldrin levels were positively associated with risk of non-Hodgkin's lymphoma, according to the authors, lack of data on confounding variables in cases and controls or exposure level or duration hamper interpretation of these results. On the other hand, Cantor et al. (2003) did not see an association between pre-diagnostic serum dieldrin levels and risk of non-Hodgkin's lymphoma in matched controls. The International Agency for Research on Cancer (IARC) has listed dieldrin as not classifiable as to its carcinogenicity, based on inadequate evidence of carcinogenicity in humans and limited evidence of carcinogenicity in animals (IARC, 1987). In contrast, U.S.EPA lists dieldrin as a probable human carcinogen, based on development of benign liver tumors and hepatocarcinomas in multiple strains of mice (IRIS, 1993) and OEHHA has administratively listed dieldrin on the Proposition 65 list of chemicals known to the State of California to cause cancer.

DERIVATION OF A REFERENCE DOSE AND CANCER SLOPE FACTOR FOR DIELDRIN

Data for determining NOAEL or LOAEL values for dieldrin in humans are inadequate; thus, U.S.EPA derived an RfD for this chemical based on animal studies. In contrast to humans, where neurotoxicity appears to be the most sensitive endpoint for acute and chronic toxicity, hepatic lesions are the chronic critical effect reported in animals (IRIS, 1990). U.S.EPA chose Walker et al. (1969) as the principal study for the RfD because it supported the critical effect and was a comparatively comprehensive chronic toxicity assessment (IRIS, 1990). Although minimal neurotoxic effects were also seen in this study, they occurred at a 10-fold higher dose level than did the hepatotoxic effects (ATSDR, 2002) and were thus not used in deriving a reference dose.

Walker et al. (1969) fed five-week-old male and female CFE rats diets containing 0, 0.1, 1.0, and 10.0 ppm dieldrin for two years. Body weights, feed intake, hematology, clinical chemistry, and mortality were unaffected by treatment. High-dose animals showed irritability and occasional tremors and convulsions during the course of the study. One- and 10 ppm-treated female rats had increased absolute and relative liver weights compared to controls. Hepatic parenchymal cell changes indicative of organochlorine exposure were found in some 10 ppm-treated male and female rats. U.S.EPA identified 0.1 and 1.0 ppm, respectively, as the NOAEL and LOAEL values for this study (IRIS, 1990). To the NOAEL (corresponding to 0.005 mg/kg-day), U.S.EPA applied a 100-fold uncertainty factor (10 for interspecies conversion and 10 to protect sensitive humans), leading to an RfD of $5x10^{-5}$ mg/kg-day (IRIS, 1990). ATSDR (2002) has developed a chronic oral minimum risk level (MRL) of $5x10^{-5}$ mg/kg-day, also based on the Walker et al. (1969) study, which is identical to the U.S.EPA RfD. This RfD will be used to evaluate dieldrin non-cancer risk for OEHHA fish consumption guidelines.

Studies to assess the carcinogenicity of dieldrin in humans are inadequate; however, dieldrin has been shown to cause cancer in multiple mouse strains (see caveats noted above) and is structurally related to other known rodent carcinogens (e.g., aldrin, chlordane, heptachlor, and heptachlor epoxide) (IRIS, 1993). U.S.EPA combined the results of 13 liver carcinoma data sets for male and female C3H and CF1 mice, and male B63F1, C57B1/6J, and C3H/H3 mice to determine carcinogenicity for this chemical. Individual slope factors for each of the data sets ranged from 7.1 to 55 $(mg/kg\text{-}day)^{-1}$. A geometric mean of those values was used to set an oral slope factor for dieldrin of 16 $(mg/kg\text{-}day)^{-1}$ (IRIS, 1993). This oral slope factor will be used to evaluate dieldrin cancer risk for OEHHA fish consumption guidelines.

In summary, the non-cancer and cancer critical values used to evaluate dieldrin in fish for the development of consumption guidelines will be **$5x10^{-5}$ mg/kg-day and 16 $(mg/kg\text{-}day)^{-1}$**, respectively.

METHYLMERCURY

METHYLMERCURY TOXICOLOGY

Mercury is a metal found naturally in rocks, soil, air, and water that can be concentrated to high levels in the aquatic food chain by a combination of natural processes and human activities (ATSDR, 1999). The toxicity of mercury to humans is greatly dependent on its chemical form (elemental, inorganic, or organic) and route of exposure (oral, dermal, or inhalation). Methylmercury (an organic form) is highly toxic and can pose a variety of human health risks (NAS/NRC, 2000). Of the total amount of mercury found in fish muscle tissue, methylmercury comprises more than 95 percent (ATSDR, 1999; Bloom, 1992). Because analysis of total mercury is less expensive than that for methylmercury, total mercury is usually analyzed for most fish studies and assumed to be 100 percent methylmercury for the purposes of risk assessment.

In general, mercury concentrations in fish and other biota are dependent on the mercury level of the environment in which they reside. However, there are many factors that affect the accumulation of mercury in fish tissue. Fish species and age (as inferred from length) are known to be important determinants of tissue mercury concentration (WHO, 1989; 1990). Fish at the highest trophic levels (i.e., predatory fish) generally have the highest levels of mercury. Additionally, because the biological half-life of methylmercury in fish is much longer (approximately 2 years) than it is in mammals, tissue concentrations increase with increased duration of exposure (Krehl, 1972; Stopford and Goldwater, 1975; Tollefson and Cordle, 1986). Thus, within a given species, tissue methylmercury concentrations are expected to increase with increasing age and length. The accumulation of mercury in fish is also dependent on environmental factors such as pH, redox potential, temperature, alkalinity, buffering capacity, suspended sediment load, and geomorphology in individual water bodies (Andren and Nriagu, 1979; Berlin, 1986; WHO, 1989).

Fish consumption is the major route of exposure to methylmercury in the United States (ATSDR, 1999). As noted above, almost all fish contain detectable levels of methylmercury, which, when ingested, is almost completely absorbed from the gastrointestinal tract (Aberg et al., 1969; Myers et al., 2000). Once absorbed, methylmercury is distributed throughout the body, reaching the largest concentration in kidneys. Its ability to cross the placenta as well as the blood-brain barrier allows methylmercury to accumulate in the brain and fetus, which are known to be especially sensitive to the toxic effects of this chemical (ATSDR, 1999). In the body, methylmercury is slowly converted to inorganic mercury and excreted predominantly by the fecal (biliary) pathway. Methylmercury is also excreted in breast milk (ATSDR, 1999). The biological half-life of methylmercury is approximately 44-74 days in humans (Aberg, 1969; Smith et al., 1994), meaning that it takes approximately 44-74 days for one-half of a single ingested dose of methylmercury to be eliminated from the body.

Human toxicity of methylmercury has been well studied following several epidemics of human poisoning resulting from consumption of highly contaminated fish (Japan) or seed

grain (Iraq, Guatemala, and Pakistan) (Elhassani, 1982-83). The first recorded mass methylmercury poisoning occurred in the 1950s and 1960s in Minamata, Japan, following the consumption of fish contaminated by industrial pollution (Marsh, 1987). The resulting illness was manifested largely by neurological signs and symptoms such as loss of sensation in the hands and feet, loss of gait coordination, slurred speech, sensory deficits including blindness, and mental disturbances (Bakir et al., 1973; Marsh, 1987). This syndrome was subsequently named Minamata Disease. A second outbreak of methylmercury poisoning occurred in Niigata, Japan, in the mid-1960s. In that case, contaminated fish were also the source of illness (Marsh, 1987). In all, more than 2,000 cases of methylmercury poisoning were reported in Japan, including more than 900 deaths (Mishima, 1992).

The largest outbreak of methylmercury poisoning occurred in Iraq in 1971-1972 and resulted from consumption of bread made from seed grain treated with a methylmercury fungicide (Bakir et al., 1973). This epidemic occurred over a relatively short term (several months) compared to the Japanese outbreak. The mean methylmercury concentration of wheat flour samples was found to be 9.1 micrograms per gram (μg/g). Over 6,500 people were hospitalized, with 459 fatalities. Signs and symptoms of methylmercury toxicity were similar to those reported in the Japanese epidemic. Review of data collected during and subsequent to the Japan and Iraq outbreaks identified the critical target of methylmercury as the nervous system and the most sensitive subpopulation as the developing organism (U.S. EPA, 1997). During critical periods of prenatal and postnatal structural and functional development, the fetus and children are especially susceptible to the toxic effects of methylmercury (ATSDR, 1999; IRIS, 1995). When maternal methylmercury consumption is very high, as happened in Japan and Iraq, significant methylmercury toxicity can occur to the fetus during pregnancy, with only very mild or even in the absence of symptoms in the mother. In those cases, symptoms in children are often not recognized until development of cerebral palsy and/or mental retardation many months after birth (Harada, 1978; Marsh et al., 1980; Marsh et al., 1987; Matsumoto et al., 1964; Snyder, 1971).

The International Agency for Research on Cancer (IARC) has listed methylmercury compounds as possible human carcinogens, based on inadequate data in humans and limited evidence in experimental animals (increased incidence of tumors in mice exposed to methylmercury chloride) (IARC, 1993). U.S. EPA has also listed methylmercury as a possible human carcinogen (IRIS, 2001). OEHHA has administratively listed methylmercury compounds on the Proposition 65 list of chemicals known to the State of California to cause cancer. No estimate of the increased cancer risk from lifetime exposure to a chemical has been developed for methylmercury.

DERIVATION OF REFERENCE DOSES FOR METHYLMERCURY

The first U.S. EPA RfD for methylmercury was developed in 1985 and set at $3x10^{-4}$ mg/kg-day (U.S. EPA, 1997). This RfD was based, in part, on a World Health Organization (WHO) report summarizing data obtained from several early epidemiological studies on the Iraqi and Japanese methylmercury poisoning outbreaks

(WHO, 1976). WHO found that the earliest symptoms of methylmercury intoxication (paresthesias) were reported at blood and hair concentrations ranging from 200-500 µg/L and 50-125 µg/g, respectively, in adults. In cases where ingested mercury dose could be estimated (based, for example, on mercury concentration in contaminated bread and number of loaves consumed daily), an empirical correlation between blood and/or hair mercury concentrations and onset of symptoms was obtained. From these studies, WHO determined that methylmercury exposure equivalent to long-term daily intake of 3-7 µg/kg body weight in adults was associated with an approximately 5 percent prevalence of paresthesias (WHO, 1976). U.S. EPA further cited a study by Clarkson et al. (1976) to support the range of blood mercury concentrations at which paresthesias were first observed in sensitive members of the adult population. This study found that a small percentage of Iraqi adults exposed to methylmercury-treated seed grain developed paresthesias at blood levels ranging from 240 to 480 µg/L. The low end of this range was considered to be a LOAEL and was estimated to be equivalent to a dosage of 3 µg/kg-day. U.S. EPA applied a 10-fold uncertainty factor to the LOAEL to reach what was expected to be the NOAEL. Because the LOAEL was observed in sensitive individuals in the population after chronic exposure, additional uncertainty factors were not considered necessary for exposed adults (U.S. EPA, 1997).

Although this RfD was derived based on effects in adults, even at that time researchers were aware that the fetus might be more sensitive to methylmercury (WHO, 1976). It was not until 1995, however, that U.S. EPA had sufficient data from Marsh et al. (1987) and Seafood Safety (1991) to develop an oral RfD based on methylmercury exposures during the prenatal stage of development (IRIS, 1995). Marsh et al. (1987) collected and summarized data from 81 mother and child pairs where the child had been exposed to methylmercury *in utero* during the Iraqi epidemic. Maximum mercury concentrations in maternal hair during gestation were correlated with clinical signs in the offspring such as cerebral palsy, altered muscle tone and deep tendon reflexes, and delayed developmental milestones that were observed over a period of several years after the poisoning. Clinical effects incidence tables included in the critique of the risk assessment for methylmercury conducted by U.S. FDA (Seafood Safety, 1991) provided dose-response data for a benchmark dose approach to the RfD, rather than the previously used NOAEL/LOAEL method. The BMDL was based on a maternal hair mercury concentration of 11 ppm. From that, an average blood mercury concentration of 44 µg/L was estimated based on a hair: blood concentration ratio of 250:1. Blood mercury concentration was, in turn, used to calculate a daily oral dose of 1.1 µg/kg-day, using an equation that assumed steady-state conditions and first-order kinetics for mercury. An uncertainty factor of 10 was applied to this dose to account for variability in the biological half-life of methylmercury, the lack of a two-generation reproductive study and insufficient data on the effects of exposure duration on developmental neurotoxicity and adult paresthesia. The oral RfD was then calculated to be 1×10^{-4} mg/kg-day, to protect against developmental neurological abnormalities in infants (IRIS, 1995). This fetal RfD was deemed protective of infants and sensitive adults.

The two previous RfDs for methylmercury were developed using data from high-dose poisoning events. Recently, the National Academy of Sciences was directed to provide

scientific guidance to U.S. EPA on the development of a new RfD for methylmercury (NAS/NRC, 2000). Three large prospective epidemiological studies were evaluated in an attempt to provide more precise dose-response estimates for methylmercury at chronic low-dose exposures, such as might be expected to occur in the United States. The three studies were conducted in the Seychelles Islands (Davidson et al., 1995, 1998), the Faroe Islands (Grandjean et al., 1997, 1998, 1999), and New Zealand (Kjellstrom et al., 1986, 1989). The residents of these areas were selected for study because their diets rely heavily on consumption of fish and marine mammals, which provide a continual source of methylmercury exposure (NAS/NRC, 2000).

Although estimated prenatal methylmercury exposures were similar among the three studies, subtle neurobehavioral effects in children, such as problems with attention, fine-motor function, and verbal memory, were found to be associated with maternal methylmercury dose in the Faroe Islands and New Zealand studies, but not in the Seychelle Islands study. The reasons for this discrepancy were unclear; however, it may have resulted from differences in sources of exposure (marine mammals and/or fish), differences in exposure pattern, differences in neurobehavioral tests administered and age at testing, the effects of confounding variables, or issues of statistical analysis (NRC/NAS, 2000). The National Academy of Sciences report supported the current U.S. EPA RfD of $1x10^{-4}$ mg/kg-day for fetuses, but suggested that it should be based on the Faroe Islands study rather than Iraqi data.

U.S. EPA recently published a new RfD document that arrives at the same numerical RfD as the previous fetal RfD, using data from all three recent epidemiological studies while placing emphasis on the Faroe Island data (IRIS, 2001). In order to develop an RfD, U.S. EPA used several test scores from the Faroes data, rather than a single measure for the critical endpoint as is customary (IRIS, 2001). U.S. EPA developed BMDLs utilizing test scores for several different neuropsychological effects mentioned above with cord blood as the biomarker for mercury exposure. The BMDLs for different neuropsychological effects in the Faroes study ranged from 46-79 µg mercury/liter blood. U.S. EPA then chose a one-compartment model for conversion of cord blood to ingested maternal dose, which resulted in estimated maternal mercury exposures of 0.857-1.472 µg/kg-day (IRIS, 2001). An uncertainty factor of ten was applied to the oral doses corresponding to the range of BMDLs to account for interindividual toxicokinetic variability in ingested dose estimation from cord-blood mercury levels and pharmacodynamic variability and uncertainty, leading to an RfD of $1x10^{-4}$ mg/kg-day (IRIS, 2001). In support of this RfD, U.S. EPA found that benchmark dose analysis of several neuropsychological endpoints from the Faroe Island and New Zealand studies, as well as an integrative analysis of all three epidemiological studies, converged on an RfD of $1x10^{-4}$ mg/kg-day (IRIS, 2001). U.S. EPA (IRIS, 2001) now considers this RfD to be protective for all populations. However, in their joint Federal Advisory for Mercury in Fish, U.S. EPA and U.S. FDA only apply this RfD to women who are pregnant or might become pregnant, nursing mothers, and young children (U.S. EPA, 2004).

OEHHA finds that there is convincing evidence that the fetus is more sensitive than adults to the neurotoxic and subtle neuropsychological effects of methylmercury. As

noted previously, during the Japanese and Iraqi methylmercury poisoning outbreaks, significant neurological toxicity occurred to the fetus even in the absence of symptoms in the mother. In later epidemiological studies at lower exposure levels (e.g., in the Faroe Islands), these differences in maternal and fetal susceptibility to methylmercury toxicity were also observed. Recent evidence has shown that the nervous system continues to develop through adolescence (see, for example, Giedd et al., 1999; Paus et al., 1999; Rice and Barone, 2000). As such, it is likely that exposure to a neurotoxic agent during this time may damage neural structure and function (Adams et al., 2000), which may not become evident for many years (Rice and Barone, 2000). Thus, OEHHA considers the RfD based on subtle neuropsychological effects following fetal exposure to be the best estimate of a protective daily exposure level for pregnant or nursing women and children aged 17 years and younger.

OEHHA also recognizes that fish can play an important role in a healthy diet, particularly when it replaces other, higher fat sources of protein. Numerous human and animal studies have shown that fish oils have beneficial cardiovascular and neurological effects (see, for example, Harris and Isley, 2001; Iso et al., 2001; Cheruka et al., 2002; Mori and Beilin et al., 2001; Daviglus et al., 1997; von Schacky et al., 1999; Valagussa et al., 1999; Moriguchi et al., 2000; Lim and Suzuki, 2000). Nonetheless, the hazards of methylmercury that may be present in fish, particularly to developing fetuses and children, cannot be overlooked. When contaminants are present in a specific food that can be differentially avoided, it is not necessary to treat all populations in the most conservative manner to protect the most sensitive population. Sport fish consumption advisories are such a case. Exposure advice can be tailored to specific risks and benefits for populations with different susceptibilities so that each population is protected without undue burden to the other. Fish consumption advisories utilize the best scientific data available to provide the most relevant advice and protection for all potential consumers.

In an effort to address the risks of methylmercury contamination in different populations as well as the cardiovascular and neurological benefits of fish consumption, two separate RfDs will be used to assess risk for different population groups. OEHHA has formerly used separate methylmercury RfDs for adults and pregnant women to formulate advisories for methylmercury contamination of sport fish (Stratton et al., 1987). Additionally, the majority of states issues separate consumption advice for sensitive (e.g., children) and general population groups. OEHHA chooses to use both the current and previous U.S. EPA references doses to evaluate methylmercury non-cancer risk for fish consumption guidelines for two distinct population groups. In OEHHA advisories, the current RfD of $1x10^{-4}$ mg/kg-day, based on effects in infants, will be used for women of childbearing age and children aged 17 and younger. The previous RfD of $3x10^{-4}$ mg/kg-day, based on effects in adults, will be used for women beyond their childbearing years and men.

In summary, the non-cancer critical values used to evaluate methylmercury in fish for development of consumption guidelines will be **$1x10^{-4}$ mg/kg-day** for women of childbearing age and children age 17 and under and **$3x10^{-4}$ mg/kg-day**, for women beyond childbearing age and men.

POLYCHLORINATED BIPHENYLS (PCBs)

PCBs TOXICOLOGY

Polychlorinated biphenyls (PCBs) are a class of synthetic persistent lipophilic organic chemicals containing complex mixtures of biphenyls that are chlorinated to varying degrees (ATSDR, 2000; USEPA, 2000a). The chemical formula for PCBs is $C_{12}H_{10-n}Cl_n$, where n equals the number of chlorine atoms ranging from one to ten (WHO, 1993). PCBs were manufactured in the United States from about 1930 to 1977 for use as coolants in electrical transformers and capacitors, and as hydraulic fluids, lubricating and cutting oils, and plasticizers (ATSDR, 2000; Erickson, 2001). Although there are 209 possible individual chlorinated biphenyl compounds (known as congeners), only approximately 130 are found in commercial products (USEPA, 2000a; WHO, 1993). In the United States, PCBs were generally sold as mixtures of congeners under the trade name Aroclor (ATSDR, 2000; Nessel and Gallo, 1992).

PCBs primarily enter the environment as a result of accidental spills and leaks from products containing Aroclor mixtures and are redistributed among environmental compartments by volatilization and runoff (ATSDR, 2000). Because of their lipophilicity and slow degradation rates, PCBs are very resistant to degradation in the environment (ATSDR, 2000). PCBs are found chiefly in soil, sediment, and fatty biological tissue, where they accumulate and biomagnify in the food chain (Dekoning and Karmaus, 2000; Menzer, 1991; Moser and McLachlan, 2001). Bioconcentration factors of some congeners are reported to reach as high as $1x10^7$ in fish (Erickson, 2001). PCB residue levels in fish are affected by sediment characteristics (e.g., organic carbon content), fish species and lipid content, and trophic structure of the food chain (Eisler, 1996).

The composition of Aroclor mixtures in the environment will change over time as individual PCB congeners undergo differential partitioning, degradation, and biotransformation. This process, referred to as "weathering," results in differential persistence and bioaccumulation, which changes the PCB pattern found in environmental samples from the original pattern in technical Aroclor mixtures (Erickson, 2001). As a rule, the environmental persistence of PCBs increases with the degree of chlorination (Menzer, 1991). As a result of improved methods and equipment, PCBs in environmental samples can be quantified as congeners and congener patterns can be related to the technical Aroclor mixture they most closely resemble (Newman, et al., 1998). This is useful to relate the concentrations in environmental samples to the technical Aroclor mixtures on which most toxicity values are based.

Saltwater and fresh water fish and shellfish, combined, account for a significant portion of the total dietary exposure to PCBs (Dougherty et al, 2000). In a study comparing frequent and infrequent Great Lakes sport fish consumers, lifetime sport fish consumption was found to be the best predictor of PCB body burdens (Hanrahan et al., 1999). Fishers who consume fish from PCB-contaminated waters have been found to have serum PCB levels several times those of the general population and similar to individuals occupationally exposed to PCBs (Kreiss, 1985).

Absorption of PCBs following oral exposure occurs via passive diffusion and ranges from approximately 75 percent to more than 90 percent (USEPA, 2000a), depending on congener and the diffusion gradient between PCB concentration in the gut contents and serum lipids (Juan et al., 2002; ATSDR, 2000). Once absorbed, PCBs are distributed throughout the body, accumulating primarily in lipid-rich tissues such as liver, adipose tissue, skin, and breast milk (USEPA, 2000a). More than 95 percent of most PCB congeners are absorbed from breast milk (Dahl et al., 1995; McLachlan, 1993). PCBs are also transferred across the placenta to the fetus (ATSDR, 2000; DeKoning and Karmaus, 2000). Excretion of PCBs occurs primarily through the feces and urine as well as breast milk of lactating women (ATSDR, 2000; Moser and McLachlan, 2001). Net absorption (absorption from the gastrointestinal tract minus excretion) is significantly influenced by blood lipid levels, congener body burden (ATSDR, 2000; Schlummer et al., 1998), and body mass index (Juan et al., 2002). Although various studies have shown substantial disparities in estimated half-lives of PCBs (less than one year to greater than 10 years), the best evidence suggests that the majority of PCB congeners found in an occupational setting have half-lives in the human body from one to six years (Shirai and Kissel, 1996; Wolff et al., 1982).

The toxicity of PCBs following occupational exposure has been known since 1936 when the development of chloracne (a severe form of acne) in PCB-exposed workers resulted in the setting of a workplace threshold limit value for these compounds (Erickson, 2001). Occupational exposure has also been reported to result in ocular effects such as Meibomian gland hypersecretion, swollen eyelids, and abnormal conjunctival pigmentation (ATSDR, 2000). Incidents of purported widespread PCB poisonings occurred in Japan in 1968 ("Yusho") and Taiwan in 1979 ("Yu-Cheng") following consumption of PCB-contaminated rice oil (WHO, 1993). Signs and symptoms in affected persons were primarily ocular and dermatological; edema, alterations in blood chemistry values, and various respiratory, immunological, reproductive, developmental, and neurological disturbances were also seen (ATSDR, 2000; WHO, 1993). Although the clinical syndrome was originally thought to have resulted solely from PCB toxicity, ensuing investigations determined that the co-contaminants polychlorinated dibenzofurans (PCDFs) were the primary causal factors in Yusho and Yu-Cheng diseases (Ikeda, 1996; Kunita et al., 1984; Schantz, 1996; Wilson, 1987; Yao et al., 2002). In a sample of Yusho rice oil, for example, 2,3,4,7,8-pentaCDF was found to contribute the majority (58 percent) of the total TEQ, while PCB-126 was the second most abundant contributor to total TEQ (16 percent) (Yao et al., 2002). It is possible, however, that some signs and symptoms in the Yusho and Yu-Cheng poisonings resulted from non-*Ah* receptor mediated mechanisms of PCB toxicity.

Numerous epidemiological studies since that time have attempted to determine whether PCBs pose a human health risk at levels currently found in the environment. Many authors have subsequently reported an association between oral environmental PCB exposures and cancer as well as various adverse neurological, reproductive, and developmental effects (ATSDR, 2000). In particular, several observational cohort studies have found one or more neurodevelopmental deficits in children exposed to PCBs *in utero* and/or postnatally (see descriptions in Winneke et al., 1998; 2002); however,

results have differed with respect to the type and persistence of effects as well as the matrix (e.g., cord blood or breast milk) used to indicate exposure (Winneke et al., 1998). For example, Jacobson et al. (1992) and Jacobson and Jacobson (1996) noted that children exposed to PCBs prenatally through maternal consumption of contaminated Great Lakes fish had poorer performance on cognitive tests for visual, verbal and memory abilities at four years of age, and lowered verbal and full-scale IQ at age eleven compared to children with lower intrauterine PCB exposures. In similarly exposed infants, Gladen et al. (1988) found decreases in psychomotor scores at twelve months as well as delays in motor maturation up to 24 months (Rogan and Gladen, 1991), but no changes in mental scores. These effects were no longer observed at 3-5 years of age (Gladen and Rogan, 1991). Schantz et al. (1999) found no effect on visual-motor coordination or hand steadiness in a population of adults over 50 years of age exposed to PCBs and other contaminants through long-term consumption of Great Lakes fish. However, the same population showed a decrease in verbal memory in one of two standardized tests of memory and learning (Schantz et al., 2001). No effects were seen on executive or visual-spatial function. In a study comparing women who had consumed more than 40 pounds of Great Lakes fish with women who had never consumed Great Lakes fish, Stewart et al., (2000) found a significant linear relationship between highly chlorinated (C17-C19) PCB congeners in cord blood and decreased habituation and autonomic scores in the Neonatal Behavioral Assessment Scale. In a European cohort, Winneke et al. (1998) found the sum of PCBs 138, 153, and 180 in breast milk to be negatively associated with cognitive development, but not motor development or recognition memory in seven-month-old infants. These outcomes were not related to cord plasma PCBs. Neurological effects have also been observed in infants, children, and adults following PCB poisonings (ATSDR, 2000).

Recent data indicate that typical environmental levels of PCBs might affect the developing immune system in humans (Weisglas-Kuperus et al., 2000). Prenatal PCB exposure was positively associated with number of lymphocytes, T cells, and $CD3^+CD8^+$ (cytotoxic), $CD4^+$ $CD45RO^+$ (memory), $TcR\alpha\beta^+$, and $CD3^+$HLA-DR^+ (activated) T cells and negatively associated with antibody levels to mumps and rubella in 42 month-old children. Current plasma PCB levels were positively associated with prevalence of chicken pox and recurrent middle ear infections, while negatively associated with prevalence of allergic reactions. Increased duration of breast feeding counteracted the negative effects of postnatal PCB exposure (Weisglas-Kuperus et al., 2000).

Human studies have shown inconsistent results with respect to adverse reproductive effects following PCB exposures (ATSDR, 2000). Menstrual cycles were slightly shorter and female fecundity was reduced in women consuming PCB-contaminated Great Lakes fish (Buck et al. 2000; Mendola et al. 1997). However, other studies have shown no adverse reproductive effects in women consuming high-PCB fish when examining endpoints such as increased time-to-pregnancy or risk of spontaneous fetal death (Buck et al., 1997; Courval et al., 1999; Mendola et al., 1995), although there was a small association between sport-caught fish consumption and conception delay in men (Courval et al., 1999). Results of human studies on potential developmental effects of PCB exposure have also been mixed (ATSDR, 2000). Maternal PCB exposure via fish

consumption has been reported to have a negative, positive, or no association with birth weight, head circumference, or gestation age (see, for example, Buck et al., 2003; Dar et al., 1992; Jacobson et al. 1990a,b; Lonky et al., 1996; Rylander et al., 1995; Smith, 1984; ATSDR, 2000).

Most human epidemiological studies examining adverse effects of PCB exposure have been confounded by concomitant exposure to the trace contaminants PCDFs or other workplace chemicals such as solvents, benzene, and lead (Erickson, 2001; Persky, 2001), or have had other serious design or reporting flaws (Swanson et al., 1995). In fact, in a systematic critical evaluation of 72 occupational or environmental PCB exposure studies conducted prior to 1995, Swanson et al. (1995) found that only five of the occupational studies and none of the environmental studies provided either positive or suggestive evidence of a causal relationship between PCB exposure and adverse effects in humans. Most studies were deemed inconclusive. This is particularly true in studies of fish-eating populations as fish are often contaminated with multiple organochlorines and other neuro-, developmental or reproductive toxins (Seegal, 1996; 1999). Although human epidemiological studies are quite limited in their ability to prove a causal relationship between PCB exposure and disease (Seegal, 1996), animal studies using controlled exposures to specific Aroclor mixtures do clearly demonstrate adverse effects on the hepatic, hematological, gastrointestinal, immunological, neurological, endocrine, and reproductive systems following oral PCB exposure (ATSDR, 2000). To date, the most sensitive effects of PCB toxicity have been identified in monkeys, including clinical signs showing developmental effects such as ocular exudate, inflamed Meibomian glands, and distorted growth of finger and toenails, as well as immunological effects such as decreased antibody response to sheep erythrocytes (IRIS, 1996). Studies showing specific effects are discussed in more detail below.

As has been the case with various non-cancer endpoints, epidemiological research in humans has also found an association between exposure to PCBs and mortality rates from cancers of the liver, gall bladder, biliary tract, and brain, as well as non-Hodgkin's lymphoma and malignant melanoma (see Cogliano, 1998 and ATDSR, 2000, for discussion). Additionally, male Yusho victims were noted to have an increase in mortality from liver cancer when compared to national death rates (Kuratsune et al., 1987); however, this may have resulted from PCDF contamination (Cogliano, 2001). While epidemiological studies cannot prove a causal relationship between exposure and health effects as noted above, numerous experimental investigations in rodents have clearly shown the ability of various commercial Aroclor mixtures to cause cancerous or pre-cancerous hepatic and gastrointestinal lesions (see Cogliano et al., 1998 and ATSDR, 2000, for discussion). The International Agency for Research on Cancer (IARC) has listed PCBs as probable human carcinogens, based on limited evidence of hepatobiliary cancer in humans and sufficient evidence of malignant liver neoplasms in rodents (IARC, 1987). U.S. EPA also designates PCBs as probable human carcinogens based on tumors found in female mice exposed to Aroclors 1260, 1254, 1242, and 1016 and also in male rats exposed to Aroclor 1260 (IRIS, 1997). Based on these actions, OEHHA has administratively listed PCBs on the Proposition 65 list of chemicals known to the State of California to cause cancer.

DERIVATION OF A REFERENCE DOSE AND CANCER SLOPE FACTOR FOR PCBs

Studies to identify an RfD or cancer slope factor for PCBs have been conducted with the specific Aroclor mixtures that were prevalent as commercial products during the period that Aroclors were actively manufactured and used. However, as noted above, PCBs found in fish or other environmental media have undergone weathering that can selectively increase or decrease individual congeners, possibly increasing the overall toxicity of the mixture (Cogliano, 2001). U. S. EPA has adopted an approach that matches the expected environmental persistence and toxicity of congeners to the congener profile and toxicity of different Aroclors (Cogliano, 2001). Fish consumption is considered an exposure of high risk and persistence, so recommended health effects values are based on the cancer and non-cancer toxicities of Aroclors 1260 and 1254, which show the greatest toxicity and content of environmentally persistent chlorines (U. S. EPA, 1996).

Because PCB dose-response data for non-cancer endpoints in humans are inadequate, the U.S. EPA RfD for these compounds has been derived from animal data. The RfD for Aroclor 1254 is $2x10^{-5}$ mg/kg-day (IRIS, 1996), based on a series of studies in adult female Rhesus monkeys (Arnold et al., 1993a,b; Tryphonas et al., 1989; 1991a,b) that were treated for 23 to 55 months. The critical effects noted in treated adults were ocular exudate, inflamed Meibomian (tarsal) glands, distorted finger and toenail growth, as well as a decreased antibody response to sheep erythrocytes, all of which occurred at the lowest tested dose of 0.005 mg/kg-day (IRIS, 1996). To this LOAEL, an uncertainty factor of three hundred (ten for sensitive individuals, three for extrapolation from rhesus monkey to humans, a partial factor for the use of a minimal LOAEL [i.e., the effects were not severe], and three to convert from subchronic to chronic) was applied to develop the RfD (IRIS, 1996). OEHHA also used the LOAEL from Arnold et al. (1993a,b) and a three hundred-fold uncertainty factor (ten for interindividual variability, ten for interspecies variation and three for mild and reversible effects at the LOAEL) to account for immunological effects of PCBs to derive a Public Health Goal (the concentration of a chemical in drinking water determined to present no significant risk to human health when consumed over a lifetime) (Avalos and Brodberg, 2004). Results of continuing studies in which these treated females were mated to untreated males have been published (Arnold et al. 1995; 1997) since the U.S. EPA derived its RfD. These studies present findings on effects on female reproduction and developmental effects in infants following intrauterine and post parturition exposures (22 weeks via breast milk). Arnold et al. (1995) showed decreased conception rates at 0.02 mg/kg-day and above, but not at 0.005 mg/kg-day. Developmental effects such as inflammation or enlargement of the Meibomian (tarsal) glands, nail lesions and gum recession, as well as a decrease in titers to IgM sheep red blood cells and a dose-related decrease in head circumference were seen in infant rhesus monkeys whose mothers were exposed to 0.005 mg/kg-day Aroclor 1254. Studies with other Aroclor compounds (e.g., Aroclor 1016) have shown developmental and neurological effects in monkeys at slightly higher doses with minor morphological effects occurring at levels where no or minimal neurobehavioral effects were manifested (e.g., Shantz et al., 1989). Although the current RfD is derived from a LOAEL from a

study in adult monkeys, similar morphological effects in offspring were reported at the same exposure level. Since morphological effects have been found to occur at or below the exposure levels causing developmental neurobehavioral effects (Schantz et al., 1989), the RfD is also expected to be protective of the developing fetus. This RfD of $2x10^{-5}$ mg/kg-day will be used to evaluate PCB non-cancer risk for OEHHA fish consumption guidelines.

Human cancer dose-response data for PCBs are also inadequate and, thus, the PCB cancer slope factor has been generated based on animal studies. Because of the differential ability of different PCB mixtures to cause cancer, U.S. EPA developed a range of cancer slope factors based on Aroclors 1016, 1242, 1254, and 1260. These include the range of typical congeners found in various environmental media such as water and fish (IRIS, 1997). For food chain exposure, such as fish consumption, where environmental processes increase risk, a "high risk" cancer slope factor of 2.0 $(mg/kg-day)^{-1}$ is used based on the carcinogenic potential of Aroclors 1254 and 1260 (U.S. EPA, 1996). This value was derived from a study of male and female rats (Brunner et al., 1996; Norback and Weltman, 1985). A significant, dose-related increase in the number of liver adenomas or carcinomas was found in female rats exposed to all Aroclors and in male rats exposed to Aroclor 1260 (IRIS, 1997). Aroclors 1254 and 1260 are the most frequently detected Aroclors sampled in California fish (Brodberg and Pollock, 1999; LACSD, 2000). The cancer slope factor of 2.0 $(mg/kg-day)^{-1}$ will be used to evaluate PCB cancer risk for OEHHA fish consumption guidelines.

For fish consumption advisories, cancer and non-cancer health effects values are applied to the sum of detected Aroclors (generally 1248, 1254, and 1260) in fish tissue, as recommended by U.S. EPA (U. S. EPA, 2000b).

In summary, the non-cancer and cancer critical values used to evaluate PCBs in fish for the development of consumption guidelines will be **$2x10^{-5}$ mg/kg-day and 2.0 $(mg/kg-day)^{-1}$**, respectively.

SELENIUM

SELENIUM TOXICOLOGY

Selenium is a metalloid found naturally, but highly variably, throughout the environment (ATSDR, 1999; Reilly, 1996). Although toxic at relatively low levels, selenium is also a required nutrient that functions to protect against oxidative stress, regulate thyroid hormones, and in vitamin C metabolism (IOM, 2000). The current Recommended Dietary Allowance (RDA) for selenium is 55 µg/day for the general adult population, 60 µg/day for pregnant women, and 70 µg/day during lactation (IOM, 2000). Selenium is found in a variety of inorganic and organic forms (Haygarth, 1994); however, in animal tissues, most selenium occurs as the amino acids selenomethionine or selenocysteine (IOM, 2000). Fish and other food samples are analyzed for total selenium content, as nutritional and toxicity values have not been developed for specific chemical forms of the element.

Selenium is dispersed naturally in the environment by weathering of selenium-containing rocks and volcanic eruptions (ATSDR, 2003). Human activities can significantly redistribute environmental selenium; fossil fuel processing and combustion as well as irrigation of seleniferous soils are important origins of localized selenium contamination (Lemly, 1997). Because of the inherent variability in soil selenium concentrations, human and animal selenium exposures can fluctuate quite dramatically by geographic locale. Human selenium intakes in different regions of China known for endemic deficiency and toxicosis, for example, have been shown to range from seven to 38,000 µg/day, respectively (Levander, 1987).

Environmental conditions (e.g., pH and oxidation-reduction potential) dictate the chemical form in which selenium will be found, which, in turn, determines the biological fate of the element (ATSDR, 2003). Water and air selenium levels are generally low except in isolated areas; humans are exposed to selenium primarily through food. Cereals, grains, and forage crops are the largest contributors of selenium to the diet (ATSDR, 2003), although fish also can be a relatively rich source of the element (USDA, 2004). Freshwater fish in the United States have been found to contain a mean concentration of 0.56 ppm selenium, wet weight (May, 1981); however, in areas of California where high-selenium irrigation drainage water contaminated nearby waterways, selenium concentrations in whole body carp were reported up to 60 ppm (Fan, 1988). Brazil nuts, on average, contain the highest selenium concentration of any common food, ranging from 0.03 to 512 ppm, wet weight, depending on geographic location (Chang et al., 1995). Six to eight nuts (one ounce) typically supply approximately ten times (544 µg) the recommended dietary allowance (RDA) for this nutrient (USDA, 2004).

Following ingestion, most forms of dietary selenium are well absorbed from the gastrointestinal tract (ATSDR, 2003; Barceloux, 1999; Thomson, 1998). Once absorbed, selenium is distributed to many tissues, reaching the highest concentrations in liver and kidney; selenium also crosses the placenta and is found in breast milk (ASTDR, 2003).

Excretion occurs primarily through urine and, to a lesser extent, feces. In cases of excess consumption, selenium is excreted in the breath and sweat as garlic-odored dimethylselenide (IOM, 2000; Klaassen and Watkins, 1999). The half-life of selenomethionine in the human body is 234 days (Klaassen and Watkins, 1999).

The toxicity of selenium was recognized many years before its role as an essential nutrient was discovered in the 1950s by Schwarz and Foltz (1957). Franke and Potter (1935) were the first to prove that selenium was the plant constituent responsible for signs of toxicosis such as hair and hoof loss reported in livestock grazing on the plains of Nebraska and South Dakota (Combs and Combs, 1986). Since that time, selenium toxicity has been well reviewed by many authors (e.g., ATSDR, 2003; Combs and Combs, 1986; Reilly, 1996; Barceloux, 1999; Schrauzer, 2000; Schrauzer, 2003) and is dependent on chemical form and solubility (Klaassen and Watkins, 1999).

Acute, sometimes fatal, selenium toxicity only rarely has been reported in humans and has generally been the result of self-medication, accidental, suicidal, or occupational exposures (Civil and McDonald, 1978; Sioris et al., 1980; Gasmi et al., 1997; Schellmann et al., 1986). Gastrointestinal and neurological signs and symptoms, as well as hair and nail loss, predominate the clinical presentation (Combs and Combs, 1986). At least one case of acute selenium intoxication from a natural source has been noted in the literature. A 54-year-old Venezuelan man suffered anxiety, chills, diarrhea, fever, anorexia, and weakness after consuming 70 to 80 "Coco de Mono" (*Lecythis ollaria*) almonds. Eight days after consuming the nuts, he suffered extensive loss of scalp and body hair (Kerdel-Vegal, 1964). Subsequent studies identified the pharmacologically active agent as selenocystathionine (Aronow and Kerdel-Vegas, 1965; Kerdel-Vegas et al., 1965). Acute selenium poisoning was also reported in five individuals who consumed sodium selenate intended for use as a turkey diet supplement (dose not provided). Symptoms and signs, which resolved within 24 hours, included nausea, vomiting, diarrhea, abdominal pain, chills, and tremors (Sioris et al., 1980). Acute to sub-acute selenium toxicosis occurred in 13 individuals who consumed an improperly formulated over-the-counter selenium supplement (FDA Drug Bulletin, 1984; Jensen et al., 1984; Helzlsouer et al., 1984). Analysis of several tablets revealed that the selenium content was 182 times higher than labeled (approximately 27-30 mg per tablet, in the form of sodium selenate and elemental selenium). Estimates of ingested selenium dose ranged from 27 to 2310 mg (from a single tablet to 77 tablets taken over a 2 ½ month period). Signs and symptoms of toxicity included nausea, abdominal cramps, nail and hair changes (including total hair loss), peripheral neuropathy, garlic breath odor, fatigue, and irritability.

Chronic selenium toxicosis in humans has been well characterized as a result of endemic disease occurring in a seleniferous region of China (Yang et al., 1983; 1989a,b). Excessive selenium intakes (a mean of 4,990 µg per day, versus 116 µg/day in a selenium adequate area) resulted from consumption of high-selenium corn and vegetables during a drought period. Affected individuals suffered nail and hair loss, dermal swelling, erythema and ulcerations, as well as paresthesias. Hair selenium levels were approximately 100 times higher than those found in selenium adequate areas (Yang et al., 1983). Chronic human selenium toxicity as a consequence of environmental exposures

has not been reported in the United States, although ranchers in a seleniferous area of South Dakota were found to consume as much as 724 µg selenium per day (Longnecker et al., 1991).

Although high levels of selenium have been shown to be teratogenic in avians (Ohlendorf, 1986; 1988), there is no evidence that selenium induces terata in humans or other mammals (ATSDR, 2003).

The International Agency for Research on Cancer (IARC) and U.S. EPA have listed selenium compounds as not classifiable as to their carcinogenicity in humans because of inadequate evidence of carcinogenicity in humans or animals (IARC, 1975; IRIS, 1993). Selenium sulfide, an industrial chemical not present in food, is considered a probable human carcinogen by U.S. EPA (IRIS, 1993) and is listed by OEHHA on the Proposition 65 list of carcinogens.

DERIVATION OF A REFERENCE DOSE FOR SELENIUM

The current U.S. EPA RfD for selenium and selenium compounds was developed in 1991 and set at $5x10^{-3}$ mg/kg-day (IRIS, 1991). This RfD was based on an epidemiological study of approximately 400 people residing in a seleniferous region of China noted above. Overt signs of clinical selenosis (e.g., garlic breath odor, nail changes, hair and nail loss, decreased hemoglobin, skin lesions, mottled teeth, and central nervous system effects) were reported at whole blood concentrations of 1.35 mg/L, corresponding to a daily selenium intake of 1.261 mg (Yang et al., 1989b; IRIS, 1991). A blood selenium level of 1.0 mg/L (equivalent to an intake of 0.853 mg selenium/day) did not elicit signs of selenium toxicity. Thus, a chronic oral NOAEL and LOAEL of 0.853 and 1.261 mg/day, respectively, were determined from this study and converted to a body weight basis using the average Chinese adult body weight of 55 kg (IRIS, 1991). U.S. EPA also cited a year-long study of individuals from high-selenium areas of South Dakota and Wyoming in support of the RfD (see above, Longnecker et al. 1991). Individuals consuming as much as 0.724 mg Se/day in these regions did not show signs or symptoms associated with selenium toxicity, thus confirming the NOAEL from the Yang et al. (1989b) study. To account for sensitive individuals, U.S. EPA applied a three-fold uncertainty factor to the NOAEL (0.015 mg/kg-day) to derive an RfD of $5x10^{-3}$ mg/kg-day. Because a similar NOAEL was observed in two moderate-sized populations exposed over a lifetime, a full 10-fold uncertainty factor was not considered necessary (IRIS, 1991). ATSDR (2003) also has developed a chronic oral minimum risk level (MRL) of $5x10^{-3}$ mg/kg-day, based on a follow-up study by Yang and Zhou (1994) that reexamined five individuals included in the original Yang et al. (1989b) paper. This study confirmed the original NOAEL used by U.S. EPA to set the RfD. OEHHA will use this RfD to evaluate selenium non-cancer risk for fish consumption guidelines.

In summary, the non-cancer critical value used to evaluate selenium in fish for the development of consumption guidelines will be **$5x10^{-3}$ mg/kg-day**.

TOXAPHENE

TOXAPHENE TOXICOLOGY

Toxaphene (camphechlor) is an organochlorine insecticide consisting of a mixture of over 670 chlorinated terpenes (ATSDR, 1996; U.S. EPA, 2000). The average chemical formula for toxaphene and related toxaphene-like pesticides is $C_{10}H_{10}Cl_8$ (WHO, 1984; ATSDR, 1996; de Geus, 1999). Toxaphene was first produced in 1945, primarily as an insecticidal agent for cotton, but also for parasite control in livestock and to kill unwanted fish species in various water bodies (DHHS, 2002; de Geus, 1999). Once the most heavily used pesticide in the United States (Ribick et al., 1982), U.S. EPA restricted most applications of toxaphene in 1982 and banned it completely in 1990 (DHHS, 2002).

Because of its extensive use, volatility, and resistance to degradation, toxaphene is distributed throughout various environmental matrices worldwide, particularly in freshwater and marine fish (Alder, 1997; ATSDR, 1996; de Geus, 1999). Bioconcentration factors of persistent toxaphene congeners in fish and shellfish have been reported to reach as high as 3.5 million (Geyer et al., 1999). Biomagnification also occurs in the aquatic food chain (ATSDR, 1996). Fish toxaphene levels have been shown to be positively correlated with fish age and fat content (Alder, 1997). Similar to the case with PCBs, the composition of the toxaphene "technical" mixture is altered in the environment as a result of differential degradation of individual congeners (Stern et al., 1992). The number of congeners decreases with increasing trophic level; approximately 20, eight and two primary congeners have been found in fish, marine mammals, and humans, respectively (Calciu et al., 1997).

Toxaphene is known to be absorbed from all absorption routes, although dermal absorption is comparatively low (ATSDR, 1996; WHO, 1984). Once absorbed, toxaphene is distributed primarily to fat, but also to liver, bone, kidney, brain, heart, muscles, lung, spleen, adrenal gland, and testis (ATSDR, 1996). Rat studies have shown that only a small percent of a maternal toxaphene dose is transferred to the fetus (Pollock and Hillstrand, 1982); however, toxaphene has been found in human breast milk, particularly in women residing in the Arctic region where dietary organochlorine levels can be very high (Dewailly et al., 1993; Chan and Yeboah, 2000; Newsome and Ryan, 1999; Walker et al., 2003; Vaz and Blomkvist, 1985). Breast milk from Inuit women in northern Quebec, for example, has been reported to contain toxaphene concentrations as high as 294 ng/g on a lipid weight basis (Newsome and Ryan, 1999; Stern et al., 1992). Toxaphene is excreted in both urine and feces with the majority of absorbed toxaphene undergoing metabolic transformation (ASTDR, 1996). The excretion half-life of radiolabeled toxaphene has been shown to be approximately nine days in rodents, with about twice as much excreted in feces as in urine over this time period (ATSDR, 1996). Even though the pesticide has been banned for many years, significant toxaphene residues have recently been found in adipose tissue of children in western Europe (Witt and Niessen, 2000).

The toxicity of toxaphene has been well reviewed by several authors (e.g., ASTDR, 1996; Pollock and Kilgore, 1978; WHO, 1984; Saleh, 1991). Like other cyclodiene insecticides, the mechanism of neurotoxic action is believed to be inhibition of chloride transport, resulting in only partial repolarization of neurons and uncontrolled central nervous system stimulation (Ecobichon, 2003; Klassen and Watkins, 1999). Following acute oral toxaphene intoxication in humans, signs and symptoms of central nervous system stimulation are seen such as hypersalivation, restlessness, muscle tremors, and convulsions (U.S. EPA, 1987). Signs often begin within two hours of ingestion; fatal doses generally cause death by respiratory failure within 24 hours (McGee et al., 1952; Wells and Milhorn, 1983). The human acute lethal dose has been estimated to range from 21-100 mg/kg body weight (U.S. EPA, 1987) or about 2 to 7 grams for an adult (WHO, 1984). In addition to nervous system and respiratory effects mentioned above, heart dilation, kidney swelling, and elevated liver enzymes have also been reported in humans following acute toxaphene ingestion (ATSDR, 1996; McGee et al., 1952; Wells and Milhorn, 1983).

In animals, neurological effects similar to those reported in humans have been reported following acute toxaphene toxicity (ATSDR, 1996). Intermediate or chronic toxaphene exposures in various animal species have been shown to cause hepatic and renal effects including increased liver and kidney weights, hepatic enzyme induction, and degenerative histopathological changes in both organs (ATSDR, 1996). Protein deficiency may significantly increase acute toxaphene toxicity (Boyd and Taylor, 1971).

Toxaphene has not been shown to cause reproductive harm in animals at levels that do not also cause parental toxicity. For example, decreased fetal weights, fetal death, or increased incidence of encephaloceles were reported in rats and mice exposed to toxaphene during the period of organogenesis, but only at doses that also caused maternal toxicity and death (Chernoff and Carver, 1976). In a three-generation study, rats fed 0, 25 or 100 ppm toxaphene showed no adverse effects on reproductive outcomes such as litter size, pup survival or weanling body weights; however, liver cytoplasmic vacuolization was seen in the majority of adults at the 100 ppm dose (Kennedy et al., 1973). Similarly, while dietary toxaphene concentrations of 20 ppm and above caused increased liver weights as well as histopathological changes in liver, thyroid and kidney in adults rats during a reproductive study, there were no effects on fertility, litter size, pup weight, or other indices of gestation or survival in rats fed dietary concentrations up to 500 ppm toxaphene (0.38 mg/kg-day) (Chu et al., 1988).

Developmental effects have been reported following toxaphene exposure in rats. Olson et al. (1980) found that juvenile rats exposed to 0.05 mg/kg-day toxaphene in the pre- and postnatal periods had decreased swimming and righting ability compared to controls, although differences in swimming ability between groups had disappeared by postnatal day 16. Time to master righting reflex was also prolonged in offspring of rats exposed to 6 mg/kg-day from gestation day 7 until parturition (Crowder et al., 1980).

A few studies have found immunotoxic effects resulting from toxaphene exposure. Adult mice fed 100 or 200 ppm dietary toxaphene for eight weeks showed a dose-dependent

decrease in antibody response to bovine serum albumin (Allen et al., 1983). Liver-to-body weight ratios were also increased at both dose levels and histopathological changes were noted in livers. Immunological effects were more pronounced in offspring exposed *in utero* or during lactation (Allen et al., 1983). An immunotoxicity study in cynomolgus monkeys is described below (Tryphonas et al., 2001). *In vitro* human studies have confirmed that neutrophils are a significant immunologic target of toxaphene toxicity (Gauthier et al., 2001).

There are no data available to evaluate the carcinogenicity of toxaphene in humans; however, toxaphene has been found to be a liver carcinogen in mice and to cause thyroid cancer in rats (Litton Bionetics, 1978; Reuber, 1979; NCI, 1979). The International Agency for Research on Cancer has listed toxaphene as a possible human carcinogen, based on inadequate data in humans and sufficient evidence in experimental animals (IARC, 2001). U.S. EPA lists toxaphene as a probable human carcinogen, based on no data in humans and sufficient evidence of carcinogenicity in experimental animals (IRIS, 1991). OEHHA has administratively listed toxaphene on the Proposition 65 list of chemicals known to the State of California to cause cancer.

DERIVATION OF A REFERENCE DOSE AND CANCER SLOPE FACTOR FOR TOXAPHENE

U.S. EPA has not developed an RfD for toxaphene. However, in 2003, OEHHA published a Public Health Goal (PHG) for toxaphene in drinking water, selecting a study by Chu et al. (1986) to determine the NOAEL for non-cancer effects (OEHHA, 2003). Rats fed diets containing 20 to 500 ppm toxaphene (corresponding to approximately 0.35 to 63 mg/kg-day) had biologically significant histopathological changes in liver, thyroid, and kidney at doses of approximately 1.8 mg/kg-day and above. Liver-to-body weight ratios and hepatic mixed function oxidase activities were also increased at the highest dose level. The NOAEL and LOAEL values in this study were determined to be 0.35 and 1.8 mg/kg-day, respectively. To the NOAEL, an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for sensitive individuals, and 10 for extrapolation from subchronic to chronic) can be applied to develop a reference dose of 3.5×10^{-4} mg/kg-day.

A more recent study in cynomolgus monkeys by Tryphonas et al. (2001) can also be used to support the reference dose for toxaphene. Monkeys were fed 0, 0.1, 0.4, or 0.8 mg/kg-day toxaphene for 75 weeks. Doses of 0.4 and 0.8 mg/kg-day significantly reduced humoral immunity in female monkeys, as evidenced by decreased primary and secondary immune response to sheep erythrocytes. The NOAEL of 0.1 mg/kg-day in this study was similar to that derived by Chu (Chu et al. (1986). As the Chu et al. study produced the highest NOAEL below the lowest LOAEL, it will be used to set the reference dose to evaluate toxaphene non-cancer risk for fish consumption guidelines.

Human dose-response data for cancer are also inadequate; thus, the toxaphene cancer slope factor has been generated from animal studies. Two long-term rodent carcinogenicity assays have been published for toxaphene (Litton Bionetics, 1978; NCI,

1979). In their 1991 carcinogenicity assessment, U.S. EPA chose the Litton Bionetics study for determination of the toxaphene cancer slope factor. A significantly increased incidence of hepatocellular carcinomas was found in male B6C3F1 mice at a dietary dose of 50 ppm. Using a linearized multistage model, U.S. EPA determined the oral cancer slope factor for toxaphene in this study to be 1.1 $(mg/kg\text{-}day)^{-1}$ (IRIS, 1991). OEHHA (2003) employed a cancer slope factor of 1.2 $(mg/kg\text{-}day)^{-1}$ in their toxaphene PHG, using the same data set as U.S. EPA but making slightly different assumptions regarding the conversion of dietary toxaphene concentrations to mg/kg body weight doses. For the purpose of evaluating cancer risk for fish consumption guidelines, the cancer slope factor of 1.2 $(mg/kg\text{-}day)^{-1}$ will be used.

In summary, the non-cancer and cancer critical values used to evaluate toxaphene in fish for the development of consumption guidelines will be **$3.5x10^{-4}$ mg/kg-day and 1.2 $(mg/kg\text{-}day)^{-1}$**, respectively.

GUIDANCE TISSUE LEVELS FOR CHLORANE, DDTs, DIELDRIN, METHYLMERCURY, PCBs, SELENIUM, AND TOXAPHENE

As noted above, once toxicity values for chemicals have been determined, guidance tissue levels (GTLs) can be developed to provide a number of recommended fish meals that correspond to the range of contaminant concentrations found in fish, similar to risk-based consumption limits recommended by U.S. EPA (U.S. EPA, 2000a). GTLs for chlordane, dieldrin, DDTs, methylmercury, PCBs, selenium, and toxaphene are presented in Table 1. GTLs are used to provide meal consumption advice to prevent consumers from being exposed to more than the average daily reference dose for non-carcinogens or to a risk level greater than $1x10^{-4}$ for carcinogens. This risk level is within the acceptable range of risks ($1x10^{-4}$ to $1x10^{-6}$) used by U.S. EPA in regulatory criteria for drinking water (Fed. Reg., 1998) and for assessing chemical contaminant data in fish (U.S. EPA, 2000a). U.S. FDA used a cancer risk level of approximately $1x10^{-4}$ in their justification for establishing a tolerance level for PCBs in fish (Fed. Reg., 1979), which is not uncommon in the case of inadvertent food contaminants (Rodricks et al., 1987). Other states (e.g., Georgia, West Virginia) also use this risk level in their fish advisory programs (GDNR, 2003; WBPH et al., 2000; U.S. EPA, 1999). Fish consumption advisories are not regulatory in nature, nor are they criteria that prevent pollution; rather, they enable people to modify their exposure to an existing contaminant. Fishing and fish consumption provides recognized social and health benefits (see mercury discussion above); other sources of animal protein that may be consumed in place of fish such as beef, pork, or chicken, may also contain undesirable components (e.g., organic contaminants, saturated fat, and hormone or antibiotic residues). Thus, OEHHA suggests that this risk level is appropriate to balance benefits and risks of fish consumption, in comparison to other animal protein sources, in a context that encourages modified behavior.

GTLs assume that meal size is a standard 8-ounce (227 g) portion of uncooked fish (U. S. EPA, 2000a) (approximately 6 ounces after cooking) for adults who weigh 70 kg (approximately 160 pounds). Consumers are instructed to adjust meal size for higher or lower body weights by adding or subtracting one ounce of fish, respectively, for every twenty-pound difference in body weight. OEHHA's advice allows fishers to consume up to 12 meals per month without exceeding the reference dose or risk level for a specific contaminant. Consumption of twelve meals per month corresponds to an upper bound consumption rate for frequent sport fish consumers in California (Gassel, 2001). OEHHA begins issuing more restrictive consumption advice for specific water bodies if data indicate that consumption of twelve meals per month is potentially hazardous.

GTLs also take into account organic contaminant loss during the cooking process. The concentration of PCBs and other organic contaminants in fish are generally reduced by at least 30 percent, depending on cooking method (Anderson et al., 1993; Sherer and Price, 1993; Santerre, 2000; Wilson et al., 1998; Zabik et al., 1996). As such, a cooking reduction factor of 0.7 is included in the GTL equation for organic compounds (allowing for 70 percent of the contaminant to remain after cooking). Although fish analytical data are generally provided to OEHHA as skin-off fillets, when contaminant levels are

determined on skin-on fillets, a cooking and skinning reduction factor of 0.5 is used to account for organic chemical losses of approximately 50 percent that occur during both processes combined (Anderson et al., 1993). OEHHA recommends that all fish be prepared and consumed as skin-off fillets to reduce contaminant levels to the greatest extent possible. If fishers choose not to follow this advice and cook fish as skin-on fillets, they should reduce their consumption by approximately one-fourth (e.g., if advice allows for consumption of four fish meals per month, consumption should be reduced to three fish meals per month) to achieve an equivalent exposure.

For carcinogenic chemicals, the exposure duration is assumed to be 30 years over a 70 year lifespan ("averaging time"). Thirty years is considered a high-end estimate of residence time for U.S. citizens (U. S. EPA, 1997; OEHHA, 2000). More importantly, levels of legacy sport fish contaminants such as PCBs, DDTs and dieldrin are declining in the environment (see for example, ATSDR, 1996; Bentzen et al., 1999; Huestis et al., 1997; Kannan et al., 1997). The average PCB half-life for Lake Ontario biota is reported to be 12 years (Bentzen et al., 1999). Even if fishers fish the same location for 70 years, their exposure to such chemicals will undoubtedly decline significantly over this period.

Unlike the case for other fish contaminants listed above, selenium is a required nutrient. Thus, it should be ensured that the GTLs for selenium do not unduly limit sport fish as a potential source of selenium and that they also take into account additional dietary exposures to this element. As reported above, the current Recommended Dietary Allowance (RDA) for selenium is 55 µg/day for the general adult population, 60 µg/day for pregnant women, and 70 µg/day during lactation (IOM, 2000). Data from the third National Health and Nutrition Examination Survey (NHANES III) show that the mean selenium intake for all individuals from diet alone is 113.7 µg/day, while the mean intake from diet plus supplements is 116 µg/day (IOM, 2000). This indicates that most individuals in the United States easily meet their nutritional needs for selenium and do not consume selenium supplements. However, because there is some evidence that selenium may have anticancer effects at doses well above those nutritionally required (IOM, 2000), supplements are available in doses of up to 300 µg/day. Consumption of these can substantially increase an individual's selenium exposure. In order to account for this variability of intakes, OEHHA chooses to provide two GTLs for selenium in fish tissue. The first GTL will be recommended for the typical consumer who does not take selenium supplements in excess of the RDA. For these individuals, the mean selenium intake from diet alone (114 µg/day; IOM, 2000) will be used as the background dietary consumption rate. The second GTL will be recommended for consumers who do take selenium supplements in excess of the RDA. For these individuals, the 90th percentile selenium intake for diet plus supplements (175 µg/day; IOM, 2000) will be used as the background dietary selenium consumption rate.

Table 1. Guidance Tissue Levels for Selected Fish Contaminants Based on Cancer and Non-Cancer Risk* (ppb, wet weight)					
	12 Meals/ Month (90.0 g/day)**	8 Meals/ Month (60.0 g/day)**	4 Meals/ Month (30.0 g/day)**	1 Meal/ Month (7.5 g/day)**	No Consumption
Contaminant Cancer Slope Factor (mg/kg/day)$^{-1}$					
Chlordane (1.3)	**≤200**	**>200-300**	**>300-600**	**>600-2,390**	**>2,390**
DDTs (0.34)	≤760	>760-1140	>1140-2,290	>2,290-9150	>9150
Dieldrin (16)	**≤16**	**>16-24**	**>24-49**	**>49-194**	**>194**
PCBs (2)	≤130	>130-190	>190-390	>390-1560	>1560
Toxaphene (1.2)	**≤220**	**>220-320**	**>320-650**	**>650-2,590**	**>2,590**
Contaminant Reference Dose (mg/kg-day)					
Chlordane ($5x10^{-4}$)	≤560	>560-830	>830-1670	>1670-6670	>6670
DDTs ($5x10^{-4}$)	**≤560**	**>560-830**	**>830-1670**	**>1670-6670**	**>6670**
Dieldrin ($5x10^{-5}$)	≤60	>60-80	>80-170	>170-670	>670
Methylmercury ($1x10^{-4}$)^{S}	**≤ 80**	**>80-120**	**>120-230**	**>230-930**	**>930**
Methylmercury ($3x10^{-4}$)^{G}	**≤230**	**>230-350**	**>350-700**	**>700-2,800**	**>2,800**
PCBs ($2x10^{-5}$)	**≤20**	**>20-30**	**>30-70**	**>70-270**	**>270**
Selenium ($5x10^{-3}$)$^{-S}$	**≤2,620**	**>2,620-3,930**	**>3,930-7,870**	**>7,870-31,470**	**>31,470**
Selenium ($5x10^{-3}$)$^{+S}$	**≤1,940**	**>1,940-2,920**	**>2,920-5,830**	**>5,830-23,330**	**>23,330**
Toxaphene ($3.5x10^{-4}$)	≤390	>390-580	>580-1170	>1170-4670	>4670

*The most conservative GTL values for each chemical (cancer slope factor versus reference dose-derived) used for development of fish consumption guidelines are bolded. With the exception of dieldrin, values are rounded to the nearest 10's place.

**g/day represents the average amount of fish consumed daily, distributed over a 30-day period.

^{S}GTL for sensitive populations (i.e., women of childbearing age and children 17 and under.)

^{G}GTL for general populations (i.e., women beyond childbearing age and men.)

$^{-S}$: GTL for consumers who do not take selenium supplements in excess of the RDA;

$^{+S}$: GTL for consumers who take selenium supplements in excess of the RDA

EQUATIONS USED TO CALCULATE GTLs

The following general equations are used to calculate the GTL for a chemical at the consumption rates of twelve, four and one meal per month. No consumption is recommended when tissue concentrations exceed the GTL for one meal per month. Separate equations are used for carcinogenic effects, non-carcinogenic effects, and nutrients with non-carcinogenic effects.

The following general equation can be used to calculate fish tissue concentration (in µg/kg) at which the consumption exposure from a chemical with a ***carcinogenic*** effect is equal to the risk level for that chemical at each consumption level:

$$\text{Tissue concentration} = \frac{(\text{Risk Level})(\text{kg BW})(\text{RSC})(1000\ \mu\text{g/mg})}{[\text{CSF (mg/kg/day)}^{-1}]\ (\text{CR kg/day})(\text{AT})(\text{CRF})}$$

As an example, for dieldrin, the fish tissue level at which consumption would be recommended at no more than four meals per month (30.0 g/day) would be calculated as follows:

$$\frac{(1\times10^{-4})(70\ \text{kg})(1000\ \mu\text{g/kg})}{[16\ (\text{mg/kg/day})^{-1}](0.03\ \text{kg/day})(30/70)(0.7)} = 48.6\ \text{ppb (rounded to 49 ppb)}$$

The following general equation can be used to calculate the fish tissue concentration (in µg/kg) at which the consumption exposure from a chemical with a ***non-carcinogenic effect*** is equal to the reference level for that chemical at any consumption level:

$$\text{Tissue concentration} = \frac{(\text{RfD mg/kg-day})(\text{kg Body Weight})(\text{RSC})(1000\ \mu\text{g/mg})}{(\text{CR kg/day})(\text{CRF})}$$

As an example, for mercury, the fish tissue level at which consumption would be recommended at no more than four meals per month (30.0 g/day) for women of childbearing age and children would be calculated as follows:

$$\frac{(1\times10^{-4}\ \text{mg/kg-day})(70\ \text{kg body weight})(1)\ (1000\ \mu\text{g/mg})}{0.03\ \text{kg/day}} = 233\ \text{ppb}$$

(rounded to 230 ppb)

The following general equation can be used to calculate the fish tissue concentration (in mg/kg) at which consumption exposure from a ***nutrient with a non-carcinogenic effect*** is equal to the reference level for that chemical:

$$\text{Tissue Concentration} = \frac{[(\text{RfD mg/kg-day})(\text{kg Body Weight}) - \text{mg Background Dietary Level}]}{(\text{CR kg/day})}$$

As an example, for selenium, the fish tissue level at which consumption would be recommended at no more than four meals per month (30.0 g/day) would be calculated as follows for individuals who do not take selenium supplements in excess of the RDA:

$$\frac{[(5\times10^{-3}\ \text{mg/kg-day})(70\ \text{kg}) - 0.114\ \text{mg/day}]}{0.03\ \text{kg/day}} = 7.867\ \text{mg/kg or } 7{,}867\ \text{ppb}$$

(rounded to 7870 ppb)

For individuals who do take selenium supplements in excess of the RDA, the following equation would be used to calculate the fish tissue levels at which consumption would be recommended at no more than 4 meals per month (30.0 g/day):

$$\frac{[(5\times10^{-3}\ \text{mg/kg-day})(70\ \text{kg}) - 0.175\ \text{mg/day}]}{0.03\ \text{kg/day}} = 5.833\ \text{mg/kg or } 5{,}833\ \text{ppb}$$

(rounded to 5830 ppb)

Where,
Risk Level = 1×10^{-4}
BW = Body weight of consumer (70 kg default)
RSC = Relative Source Contribution (assumed to be 100 percent)
CSF = Cancer Slope Factor
CR = Consumption rate as the daily amount of fish consumed
CRF = Cooking reduction factor (0.7 for organic contaminants)
AT = Averaging Time (30 yr exposure/70 yr lifetime)
RfD = Chemical specific reference dose or other reference level

APPLICATION OF THE GTL PARADIGM TO FISH CONTAMINANT DATA

Fish contaminant data collected from a site are often highly variable, particularly when collected from large water bodies that may have distinct localized contamination zones. Evaluating these data prior to developing site-specific (water body) or regional consumption advice using the GTL table is a complex process that may involve one or more approaches. The simplest method of assigning consumption advice from the data collected at a site is to calculate an arithmetic mean for each contaminant in each species and compare this value to ranges in the GTL table. When using this technique given the meal consumption categories in Table 1, for example, if the mean mercury concentration in largemouth bass at a site was 0.73 ppm, OEHHA could recommend that all populations restrict their consumption of this species to no more than one meal per month. Another approach is to examine the frequency distribution of the contaminant data with respect to meal categories. Contaminant concentrations for each sample of each species (either an individual fish or a single composite) can be plotted against the frequency of that value. Meal consumption category cutoffs for each contaminant (as shown in the GTL table) can be layered over the resulting histogram and the percent of values falling into each category can be determined. Consumption advice can then be offered that corresponds to the category with the highest number of values or some other distribution characteristic (e.g., a significant proportion of very high values). In this way, the full range of data, including outliers, can be evaluated. A third method of determining consumption advice from an available data set is to examine the regression line between species length and chemical contaminant level. Consumption guidance can then be tailored to different fish size classes or to the predicted contaminant concentration of the most typical length of fish consumed, providing adequate creel data are available to make this determination. This method is most useful for contaminants, such as mercury, in fish species where the concentration is largely dependent on fish size. After careful evaluation of data for a site or region and due consideration of specific public health communication goals for that area, OEHHA may choose to use any one or more of the above or additional methods to issue fish consumption guidelines.

SCREENING VALUES FOR HEALTH ADVISORIES

Screening values (SVs) are defined by U.S. EPA as "concentrations of target analytes in fish or shellfish tissue that are of potential public health concern and that are used as threshold values against which levels of contamination in similar tissue collected from the ambient environment can be compared. Exceedance of these SVs should be taken as an indication that more intensive site-specific monitoring and/or evaluation of human health risk should be conducted" (U.S. EPA, 2000b). OEHHA is establishing SVs to use when developing fish consumption advisories to determine which chemical contaminants are of health concern to the public consuming fish from tested water bodies. In order for SVs to be applied properly, appropriate species must be tested. Screening studies should collect and analyze at least one high trophic level species for methylmercury and other trace metals and a bottom feeding species with high lipid content for pesticides and chlorinated organic chemicals. Ideally, both species should be tested for all common bioaccumulative fish contaminants to identify chemicals of concern. When the measured chemical concentration in any fish sample from a screening study exceeds the SV, that chemical is of potential health concern. Intensive monitoring of a variety of fish species should then be undertaken in this water body to characterize the average concentrations of the chemical(s) of concern in sport fish. Sufficient samples of all sport fish species caught and consumed by anglers from a water body should be collected and analyzed so that fish consumption advisories can be developed. For small- and moderate- sized lakes and reservoirs (approximately 2000 surface acres or less), at least nine legal and/or edible-sized fish per species should be sampled and analyzed as individuals or as three composite samples to support developing advisories. Additional fish should be sampled and analyzed for larger lakes and those with multiple arms. For small- and moderate-sized creeks and river segments (approximately 25 miles in length), at least nine legal and/or edible-sized fish per species should be sampled and analyzed as individuals or as three composites to support developing advisories. Additional fish should be sampled and analyzed from fishing areas spread along larger rivers.

OEHHA is establishing SVs based on the procedures and assumptions used to establish GTLs. At this time, OEHHA will use the lowest GTL value for each chemical at the 12 meals per month consumption rate (the maximum meal consumption level used in advisories) as the SV for that chemical. When fish contaminant concentrations exceed this SV, consumers may exceed the RfD or a cancer risk level of $1x10^{-4}$, levels used to develop consumption advice, depending on their consumption rate. SVs are shown in Table 2. SVs for DDTs, PCBs, methylmercury, and selenium are based on the RfD and associated health effects, while SVs for chlordane, dieldrin, and toxaphene are based on carcinogenic effects.

Because OEHHA is also interested in providing fishers with information on fish with lower levels of contaminants that can be safely consumed more frequently, it is recommended that sufficient sample size ($\geq$ 9 legal/edible-sized fish per species) of multiple sport fish species be collected in a water body even when contaminant levels in screening samples do not exceed the SV.

Table 2. Screening Values[1] for Selected Fish Contaminants (ppb, wet weight)	
Contaminant	**Screening Value**
Chlordane	200
DDTs	560
Dieldrin	16
Methylmercury	80
Selenium	1,940
PCBs	20
Toxaphene	220

[1] Screening values are specific guidance tissue levels used to identify situations where contaminant concentrations in fish are of potential health concern and further action (e.g., additional sampling or developing consumption advice) is recommended.

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