DEVELOPMENT OF FISH CONTAMINANT GOALS AND ADVISORY TISSUE LEVELS FOR COMMON CONTAMINANTS IN CALIFORNIA SPORT FISH:

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

June 2008

Arnold Schwarzenegger
Governor
State of California

Linda Adams
Agency Secretary
California Environmental Protection Agency

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

DEVELOPMENT OF FISH CONTAMINANT GOALS AND ADVISORY TISSUE LEVELS FOR COMMON CONTAMINANTS IN CALIFORNIA SPORT FISH: CHLORDANE, DDTs, DIELDRIN, METHYLMERCURY, PCBs, SELENIUM, AND TOXAPHENE

June 2008

Susan Klasing, Ph.D.
Robert Brodberg, Ph.D.

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

LIST OF CONTRIBUTORS

Reviewers
Margy Gassel, Ph.D.
James Sanborn, Ph.D.
Martha Sandy, Ph.D.
Jim Donald, Ph.D.
Hristo Hristov, M.D., Ph.D.
Robert Blaisdell, Ph.D.
Jim Carlisle, D.V.M.
John Budroe, Ph.D.
David Chan, Ph.D.
Andy Salmon, Ph.D.
David Morry, Ph.D.
Robert Howd, Ph.D.
Jay Schreider, Ph.D.
David McBride, M.S.

Final Reviewers
Anna Fan, Ph.D.
George Alexeeff, Ph.D.

Acknowledgement
The authors would like to specifically thank Margy Gassel for many discussions that were helpful in the completion of this document.

FOREWORD

This report describes the process of developing Fish Contaminant Goals and Advisory Tissue Levels for evaluating methylmercury, chlordane, DDTs, dieldrin, PCBs, selenium, and toxaphene, common contaminants in California sport fish. Fish provide unique nutritional benefits while also serving as a significant exposure pathway for several chemicals of concern. Fish Contaminant Goals (FCGs) are estimates of contaminant levels in fish that pose no significant health risk to individuals consuming sport fish at a standard consumption rate of eight ounces per week (32 g/day), prior to cooking, over a lifetime and can provide a starting point for OEHHA to assist other agencies that wish to develop fish tissue-based criteria with a goal toward pollution mitigation or elimination. FCGs prevent consumers from being exposed to more than the daily RfD for non-carcinogens or to a risk level greater than $1x10^{-6}$ for carcinogens (not more than one additional cancer case in a population of 1,000,000 people consuming fish at the given consumption rate over a lifetime). FCGs are based solely on public health considerations without regard to economic considerations, technical feasibility, or the counterbalancing benefits of fish consumption.

Advisory Tissue Levels (ATLs), while still conferring no significant health risk to individuals consuming sport fish in the quantities shown over a lifetime, were developed with the recognition that there are unique health benefits associated with fish consumption and that the advisory process should be expanded beyond a simple risk paradigm in order to best promote the overall health of the fish consumer. ATLs provide a number of recommended fish servings that correspond to the range of contaminant concentrations found in fish and are used to provide 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 (not more than one additional cancer case in a population of 10,000 people consuming fish at the given consumption rate over a lifetime). ATLs are designed to encourage consumption of fish that can be eaten in quantities likely to provide significant health benefits, while discouraging consumption of fish that, because of contaminant concentrations, should not be eaten or cannot be eaten in amounts recommended for improving overall health (eight ounces total, prior to cooking, per week). ATLs are one of the criteria that will be used by OEHHA for issuing fish consumption guidelines.

For further information, contact:
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1515 Clay Street, 16th Floor
Oakland, California 94612
Telephone: (510) 622-3170

OR:

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1001 I Street, P.O. Box 4010
Sacramento, CA 95812-4010
Telephone: (916) 327-7319

TABLE OF CONTENTS

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 basis for these advisories, polychlorinated biphenyls (PCBs) and chlorinated pesticides such as chlordane and dichlorodiphenyltrichloroethane (DDT) are also often implicated. In California, the Office of Environmental Health Hazard Assessment (OEHHA) is the agency solely responsible for evaluating the potential public health risks of chemical contaminants in sport fish and issuing state advisories, when appropriate. OEHHA is also consulted by other agencies interested in assessing the health risks of fish consumption during the process of developing water quality or clean-up "criteria." There are key differences between fish consumption advisories and other environmental risk criteria; advisories consider the significant benefits of fish consumption, while criteria may be strictly risk-based and may not take into account other factors.

In order to develop water quality criteria or fish consumption advisories, appropriate toxicity values for a chemical must be established. In this document, cancer and non-cancer health effects were evaluated for seven common contaminants found in California sport fish: chlordane, DDT and its metabolites (DDTs), dieldrin, mercury (as methylmercury), PCBs, selenium, and toxaphene. For each chemical, the toxicological literature was reviewed to establish an acceptable non-cancer reference dose (RfD; 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).

Fish Contaminant Goals (FCGs) were then developed for these seven contaminants. FCGs are estimates of contaminant levels in fish that pose no significant health risk to individuals consuming sport fish at a standard consumption rate of eight ounces per week (32 g/day), prior to cooking, over a lifetime and can provide a starting point for OEHHA to assist other agencies that wish to develop fish tissue-based criteria with a goal toward pollution mitigation or elimination. FCGs prevent consumers from being exposed to more than the daily RfD for non-carcinogens or to a risk level greater than $1x10^{-6}$ for carcinogens (not more than one additional cancer case in a population of 1,000,000 people consuming fish at the given consumption rate over a lifetime). FCGs are based solely on public health considerations relating to exposure to each individual contaminant, without regard to economic considerations, technical feasibility, or the counterbalancing benefits of fish consumption. FCGs were developed using an 8-ounce (227 g) serving size (prior to cooking; approximately six ounces after cooking) for adults who weigh 70 kg.

As a prelude to developing tissue-based values to be used for advisories, OEHHA reviewed the scientific literature on the benefits of fish and fish oil consumption. Although decreased incidence of coronary heart disease is perhaps the most recognized benefit of fish consumption, there is considerable evidence that other, particularly

inflammatory, disorders may also be mitigated or prevented by inclusion of fish in the diet. Additionally, maternal fish consumption is likely to provide cognitive benefits to the fetus. Following this review, OEHHA determined that there is a compelling body of evidence and general scientific consensus that eating fish at dietary levels that are easily achievable, but well above national average consumption rates, appears to promote significant health benefits, including decreased mortality. With the recognition that there are unique health benefits associated with fish consumption, it was concluded that the advisory process should be expanded beyond a simple risk paradigm, as is used in criteria development, in order to best promote the overall health of the fish consumer.

The first step in the advisory process, then, was to develop Advisory Tissue Levels (ATLs). ATLs were calculated using the same general formulas as those used to calculate FCGs, with some adjustments in order to incorporate the benefits of fish consumption. ATLs provide a number of recommended fish servings that correspond to the range of contaminant concentrations found in fish and are designed 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 (not more than one additional cancer case in a population of 10,000 people consuming fish at the given consumption rate over a lifetime). The use of ATLs still confers no significant health risk to individuals consuming sport fish in the quantities shown over a lifetime, while encouraging consumption of fish that can be eaten in quantities likely to provide significant health benefits and discouraging consumption of fish that, because of contaminant concentrations, should not be eaten or cannot be recommended in amounts suggested for improving overall health (i.e., eight ounces total, prior to cooking, per week).

ATLs are used as part of the process to develop traditional health advisories (which focus on fish whose consumption should be avoided) as well as the newer "safe eating guidelines," which inform consumers of fish with low contaminant levels considered safe to eat frequently. ATLs should not be misinterpreted as static "bright lines" that others can use to duplicate state fish consumption advisories. ATLs are but one component of a complex process of data evaluation and interpretation used by OEHHA in the assessment and communication of fish consumption risks. The nature of the contaminant data or omega-3 fatty acid concentrations in a given species in a water body, as well as risk communication needs, may alter strict application of ATLs when developing site-specific advisories. OEHHA will use the guidelines set forth in this report as a framework, along with best professional judgment, to provide fish consumption guidance on an *ad hoc* basis that best combines the need for health protection and ease of communication for each site.

This document represents current knowledge of the toxicity of seven common fish contaminants and the overall benefits of fish consumption; FCGs and ATLs for individual chemicals may be revised, if necessary, as information becomes available. FCGs and ATLs may also be developed in the future for additional contaminants, as appropriate, using the same methodology.

INTRODUCTION

Fish consumption advisories have been issued in most states and cover approximately 35 percent and 24 percent of the country's total lake acreage and river miles, respectively (U.S. EPA, 2004a). 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, 2004a). Polychlorinated biphenyls (PCBs) and chlorinated pesticides such as chlordane and dichlorodiphenyltrichloroethane (DDT) are also a frequent basis for fish consumption advisories throughout the United States (U.S. EPA, 2004a). 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 state 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. OEHHA is also consulted by other agencies interested in assessing the health risks of fish consumption during the process of developing water quality or clean-up "criteria." There are key differences between fish consumption advisories and other environmental risk criteria; advisories consider the significant benefits of fish consumption, while criteria may be strictly risk-based and may not take into account other factors.

In order to develop advisories or criteria, appropriate toxicity values for a chemical must be established. In this document, cancer and non-cancer health effects were evaluated for seven common contaminants found in California sport fish: chlordane, DDT and its metabolites (DDTs), dieldrin, mercury (as methylmercury), PCBs, selenium, and toxaphene. For each chemical, the toxicological literature was reviewed to establish an acceptable non-cancer reference dose (RfD; 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). Limited background information on the chemistry, environmental fate, metabolism, and typical exposure routes for each chemical is also provided.

Fish Contaminant Goals (FCGs) were then developed for these seven contaminants. FCGs are estimates of contaminant levels in fish that pose no significant health risk to individuals consuming sport fish at a standard consumption rate of eight ounces per week (32 g/day), prior to cooking, over a lifetime and can provide a starting point for OEHHA to assist other agencies that wish to develop fish tissue-based criteria with a goal toward pollution mitigation or elimination. FCGs are based solely on public health considerations relating to exposure to each individual contaminant, without regard to economic considerations, technical feasibility, or the counterbalancing benefits of fish consumption.

FCGs for non-cancer risk for non-nutrients were derived from the following basic equation:

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

FCGs for cancer risk for non-nutrients were derived from the following basic equation:

$$\text{Tissue concentration} = \frac{(\text{Risk level})(\text{Body weight})}{(\text{Cancer slope factor})(\text{Daily consumption rate})}$$

Additional discussion and examples of FCG development can be found in the section "Equations used to calculate Fish Contaminant Goals."

As a prelude to developing tissue-based values to be used for advisories, OEHHA reviewed the scientific literature on the benefits of fish and fish oil consumption to determine to what degree the advisory process should be expanded beyond a simple risk paradigm, as is used in criteria development, in order to best promote the overall health of the fish consumer. Advisory Tissue Levels (ATLs), while still conferring no significant health risk to individuals consuming sport fish in the quantities shown over a lifetime, use the same general equations as those used to develop FCGs, with some adjustments to take into account benefits that are provided by fish consumption. ATLs were designed to encourage consumption of fish that can be eaten in quantities likely to provide significant health benefits, while discouraging consumption of fish that, because of contaminant concentrations, should not be eaten or cannot be recommended in amounts suggested for improving overall health (i.e., eight ounces total, prior to cooking, per week).

This report provides critical toxicity values, FCGs and ATLs for seven common contaminants in California sport fish. 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 document because of historic use in the state and natural occurrence, respectively. At this time, limited available analytical data for dioxins in fish throughout the state do not show widespread or high dioxin contamination. Several former point sources have been eliminated and subsequent concentrations in fish at associated sites were below a level of concern (Fan, 1994). Consequently, OEHHA did not develop an FCG or ATLs for dioxins at this time. However, FCGs and ATLs may be developed in the future for dioxins or other contaminants, as resources permit, using the same methodology. OEHHA staff is available for consultation on any fish contaminant of concern.

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 21to 88 days (Aldrich and Holmes, 1969; ATSDR, 1994; Curley and Garrettson, 1969; Olanoff et al., 1983).

The Agency for Toxic Substances and Disease Registry (ATSDR, 1994), U.S. Environmental Protection Agency (U.S. EPA, 1997), and OEHHA (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). The World Health Organization (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, causing incomplete 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 limitations 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 dose-rates, 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 an RfD is that, unlike most carcinogens, there is a threshold dose below which certain toxic effects will not occur. The RfD 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, an RfD 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).

As required under Health and Safety Code Section 901(g), OEHHA developed a child-specific reference dose (chRD) for chlordane for the purpose of assessing risk at proposed or existing California school sites (OEHHA, 2005). The Cassidy et al. (1994) paper was selected as the most useful study for determination of a chRD, based on endocrine disruption in the developing offspring. Pregnant Sprague-Dawley rats were fed doses of 100, 500, or 5,000 ng/g technical chlordane from day 4 of gestation until day 21 of lactation. Offspring were dosed from postnatal day (PND) 22 to PND 80 and began behavioral testing on PND 76; serum testosterone was measured on PND 85. Body weights were significantly increased in the 500 ng/g dose group compared to controls for females only. Serum testosterone levels were significantly reduced in female offspring dosed with 500 and 5,000 ng/g, although not in a dose-dependent fashion. Male offspring showed only a slight, non-significant, reduction of serum testosterone in the highest (5,000 ng/g) exposure group. Following repeated testing in the Cincinnati water

maze, time to escape was significantly improved in female rat dosed with 100 and 500 ng/g chlordane compared to controls; male rats were not affected by treatment. Intromission latency was significantly reduced in 100 and 500 ng/g treated males; however, the high-dose group was similar to controls. Intromissions prior to ejaculation and total intromissions were significantly increased only in the 500 ng/g dose group. Latency to ejaculation was not different among groups. Open field activity was not affected by treatment in male or female offspring. In tests of reaction to auditory startle, only the maximum response parameter was significantly different from controls and only in the 100 ng/g dose group. OEHHA determined that the LOAEL from this study was 100 ng/g chlordane, based on disruption of sex hormone-mediated behaviors. To the LOAEL, OEHHA applied a 3000-fold uncertainty factor (10 for LOAEL to NOAEL, 10 for interspecies extrapolation, 10 for intraspecies variation, and 3 for inadequate database for hematotoxicity, immunotoxicity, neurotoxicity, and the lack of a valid developmental study), leading to an chRD of $3.3x10^{-5}$ mg/kg-day (OEHHA, 2005).

Although Cassidy et al. (1994) was the best study available to establish a chRD, there are significant limitations with the data as noted by U.S. EPA (1997). Nonetheless, OEHHA concludes that it is appropriate to use the chRD for developing a non-cancer FCG for chlordane. FCGs are, as noted, strictly risk-based and, thus, a study need not be eliminated from consideration solely on the basis of data strength. However, in setting an ATL, it is important to balance the risks and benefits of fish consumption (see the Advisory Tissue Level section, later in this document). For this reason, OEHHA has chosen to use the cancer risk basis for establishing the ATL for chlordane (see below), rather than non-cancer risk based on Cassidy et al. (1994), even though this results in a slightly higher ATL. Chlordane is well-established as a potential human carcinogen; thus, protection against the carcinogenic effects of chlordane is generally accepted by regulatory agencies. Additionally, the 3000-fold uncertainty factor incorporated into the Cassidy et al. study-based chRD should not be used to outweigh the certainty of benefits associated with fish consumption. In using the cancer basis for developing the ATL, OEHHA determines that there is still a large margin of safety (approximately 550- to 1,000-fold, over the range of exposures) for potential endocrine-disrupting health effects of chlordane that is adequate to protect children who would also receive the benefits from consuming fish. OEHHA similarly chose to use the cancer endpoint in developing a Public Health Goal (PHG) for chlordane in drinking water (OEHHA, 1997) although non-cancer health effects, based on the Cassidy study, would have resulted in a lower PHG. Thus, the chRD of $3.3x10^{-5}$ will be used to evaluate non-cancer risk for a chlordane FCG, but only cancer risk will be considered in the development of chlordane ATLs.

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-day)$^{-1}$; a geometric mean of these values was then calculated to derive an oral CSF for chlordane of 0.35 (mg/kg-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-day)$^{-1}$ (IRIS, 1998). These guidelines have since been finalized by U.S. EPA (U.S. EPA, 2005).

In the PHG 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 CSF; the male ICR mice study (Khasawinah and Grutsch,1989b) included in the U.S. EPA assessment (IRIS, 1998) was not used (OEHHA, 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 CSFs 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 (OEHHA, 1997). OEHHA then calculated the geometric mean of the best fitting four data sets to determine a CSF of 1.3 (mg/kg-day)$^{-1}$. This CSF will be used to evaluate chlordane cancer risk for OEHHA fish consumption guidelines.

In summary, the non-cancer value used to evaluate chlordane in fish for the development of FCGs will be **$3.3x10^{-5}$ mg/kd-day**. The cancer value used to evaluate chlordane in fish for the development of FCGs and ATLs will be **1.3 (mg/kg-day)$^{-1}$**.

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 U.S. EPA 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; Eicobichon, 1991). Humans are typically exposed to a mixture of DDT and its principal metabolites, DDD (tetrachlorodiphenylethane) and DDE (dichlorodiphenyl-dichloroethylene) (U.S. EPA, 2000), which are referred to collectively as total DDTs. U.S. EPA recommends that fish consumption limits be based on the sum of DDT, DDD, and DDE (i.e., total DDTs) (U.S. EPA, 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 from the gastrointestinal tract following dietary exposure and are 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; U.S. EPA, 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; U.S. EPA, 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). Occasional and slight, but significant, decrements on the Bayley scales of infant development were seen in offspring at 6, 12 or 24 months of age corresponding to a ten-fold increase in maternal serum levels of *p,p*'-DDT, *o,p*'-DDT, or *p,p*'-DDE (Eskenazi et al., 2006).

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, 1990b, 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 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 lowest 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., 1990a, 1990b, 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). 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 CSF 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 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. 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, which can vary based on differences in pH, redox potential, temperature, alkalinity, buffering capacity, suspended sediment load, and geomorphology of individual water bodies (Andren and Nriagu, 1979; Berlin, 1986; WHO, 1989). Other factors also affect the accumulation of mercury in fish tissue, including fish diet, species and age (as inferred from length) (WHO, 1989; 1990). Fish at the highest trophic levels (i.e., predatory fish) generally have the highest levels of mercury. Additionally, because of the long biological half-life of methylmercury in fish (approximately 2 years), tissue concentrations in fish increase with increased duration of exposure (Krehl, 1972; Stopford and Goldwater, 1975; Tollefson and Cordle, 1986). As a result, tissue methylmercury concentrations are expected to increase with increasing age and length within a given species, particularly in piscivorous fish.

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 were 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).

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 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 in adults at blood and hair concentrations ranging from 200-500 μg/L and 50-125 μg/g, respectively. 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 the U.S. Food and Drug Administration (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 $1x10^{-4}$ 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 (NSA) 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 NAS 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 women aged 18 to 45 years and children aged 1 to17 years.

In an effort to address the risks of methylmercury contamination in different populations, two separate RfDs will be used to assess risk for different population groups. OEHHA has formerly used a separate methylmercury RfD for sensitive populations to formulate advisories for methylmercury contamination of sport fish (Stratton et al., 1987). Additionally, the majority of states issue separate consumption advice for sensitive (e.g., children) and general population groups**.** OEHHA chooses to use both the current and previous U.S. EPA RfDs 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 18 to 45 years and children aged 1 to17 years. The previous RfD of $3x10^{-4}$ mg/kg-day, based on effects in adults, will be used for women over 45 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 aged 18 to 45 years and children aged 1 to 17 years, and **$3x10^{-4}$ mg/kg-day**, for women over 45 years 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; U.S. EPA, 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 (U.S. EPA, 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 potential sources and to the technical Aroclor mixture they most closely resemble (Newman, et al., 1998).

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 (U.S. EPA, 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 (U.S. EPA, 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 establishment 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 toxic equivalents (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 large amounts of Great Lakes fish compared to those who consumed little or no Great Lakes fish. However, the same population showed a decrease in verbal memory in one of two standardized tests of memory and learning compared to controls (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 over their lifetimes 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 $CD3^+HLA\text{-}DR^+$ (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 for 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, 1990b; 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 neurological, 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 fingernails 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). 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 CSF 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 of $2x10^{-5}$ mg/kg-day (IRIS, 1996) is based on a series of studies in adult female Rhesus monkeys (Arnold et al., 1993a, 1993b; Tryphonas et al., 1989, 1991a, 1991b) that were treated for 23 to 55 months. The critical effects noted in treated adults were ocular exudate, inflamed Meibomian (tarsal) glands, distorted fingernail 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[1] 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, 1993b) 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 PHG (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

[1] IRIS did not stipulate what the "partial factor" was; however, by deduction, it must have been three.

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 CSF 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 CSFs based on Aroclors 1016, 1242, 1254, and 1260. These Aroclors 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 $(mg/kg\text{-}day)^{-1}$ 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 CSF of 2.0 $(mg/kg\text{-}day)^{-1}$ 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) or a sum of congeners in fish tissue, as recommended by 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 **$2.0\ (mg/kg\text{-}day)^{-1}$**, 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 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, 2003) and has been found to be 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, 1989b). Excessive selenium intakes (a mean of 4,990 µg/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 birds (Ohlendorf, 1986; 1988), there is no evidence that selenium induces terata in humans or other mammals (ATSDR, 2003). Other developmental effects following *in utero* selenium exposure in mammals have only been conclusively demonstrated at doses that cause frank maternal toxicity (Willhite, 1993; ATSDR, 2003).

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), corresponding to 350 μg/day for a 70-kg adult or approximately six-fold higher than the RDA for the general adult population. 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 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 $C_{10}H_{10}C1_8$ (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 $3.5x10^6$ (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 twenty, 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, muscle, 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). IARC 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 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 RfD 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 CSF 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 CSF for toxaphene in this study to be 1.1 $(mg/kg\text{-}day)^{-1}$ (IRIS, 1991). OEHHA (2003) employed a CSF 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 CSF 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.

FISH CONTAMINANT GOALS FOR CHLORDANE, DDTs, DIELDRIN, METHYLMERCURY, PCBs, SELENIUM, AND TOXAPHENE

As is also the case for air, drinking water, or any other food, the ultimate goal of agencies responsible for the protection of public health is for fish to be devoid of biological or chemical contamination. FCGs can be derived for chemicals found in fish, comparable to PHGs for drinking water (Health and Safety Code, Section 116365). FCGs are estimates of contaminant levels in fish that pose no significant health risk to individuals consuming sport fish at a standard consumption rate of eight ounces per week (32 g/day), prior to cooking, over a lifetime and can provide a starting point for OEHHA to assist other agencies that wish to develop fish tissue-based criteria with a goal toward pollution mitigation or elimination. FCGs were developed for chlordane, DDTs, dieldrin, methylmercury, PCBs, selenium, and toxaphene. FCGs are based solely on public health considerations relating to exposure to each individual contaminant, without regard to economic considerations, feasibility, the counterbalancing benefits of fish consumption, or alternative risks of other protein sources that may be consumed in place of fish.

FCGs can be found in Table 1. OEHHA used the following assumptions in the development of FCGs for fish contaminants. Agencies developing fish tissue-based criteria may choose to alter one or more of these assumptions in order to meet their own specific goals or requirements:

Body Weight:

The default value for adult body weight for these calculations was assumed to be 70 kg, which is recommended in most risk assessment guidelines. While, at one time, 70 kg was the approximate combined average weight for adult males and females in the United States, it is now significantly less than the average weight for both adult females and males in this country (about 75 and 87 kg, respectively) (Ogden et al., 2004). The use of a lower default body weight for risk assessment calculations results in lower allowable contaminant concentrations in fish.

Serving Size and Consumption Rate:

Serving size assumptions vary considerably. The American Heart Association (AHA) recommends eating fish at least two times a week (AHA, 2006), and considers a single serving size to be four ounces (113.5 g) of fish prior to cooking (corresponding to three ounces [85 g] of cooked fish). The Institute of Medicine (IOM) also considers serving size to be three ounces of cooked fish, based on the National Health and Nutrition Examination Survey (NHANES) 1999-2002 data showing three ounces to be the average daily consumption rate for people who eat fish (IOM, 2007). In their 2006 food pyramid, the U.S. Department of Agriculture recommends five to six ounces, *total*, of meat, poultry, fish, dried beans or peas, eggs, nuts, and seeds *per day* for adult women and men,

suggesting that the typical serving size of a single animal protein source in a given day is three to four ounces (USDA, 2006). In contrast, U.S. EPA assumed a serving size of eight ounces of fish, prior to cooking, in their fish advisory guidance document (U.S. EPA, 2000b), as did both U.S. EPA and FDA in their joint national advisory for mercury in fish (U.S. EPA, 2004c). While OEHHA contemplated reducing serving sizes to four ounces, prior to cooking, to align with federal nutrition, IOM and AHA guidelines, focus groups interviewed by the California Department of Public Health indicated that sport fishers typically consume significantly larger portion sizes. Thus, an 8-ounce serving size was retained for use in fish advisories. OEHHA considers it to be a reasonable goal to provide recreational fish that, at a minimum, are safe to eat at the AHA recommended consumption rate for adults of at least eight ounces of fish per week, prior to cooking (an average of 32 g/day) and that this is an appropriate consumption rate for development of an FCG. Because of their smaller body weights, children will be advised to eat approximately one-half as much fish (in either quantity or frequency) as are women aged 18 to 45 years.

Hazard Quotient:

Standard risk assessment guidelines generally recommend limiting non-cancer exposures to no more than the RfD, which results in a hazard quotient (HQ; the ratio of exposure to the RfD) that does not exceed 1. FCGs were set using a maximum HQ of 1 at the consumption rate of 32 g/day.

Risk Level:

FCGs were developed using a maximum cancer risk level (RL) of $1x10^{-6}$, estimating that, at a given consumption rate, not more than one additional cancer case would be expected in a population of one million people consuming fish over a lifetime. This risk level is at the lower end of 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 is provided as an example of an acceptable risk level in U.S. EPA's Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories (U.S. EPA, 2000a,b). FCGs were set using a maximum RL of $1x10^{-6}$ at the consumption rate of 32 g/day.

Exposure Duration and Averaging Time:

For carcinogenic chemicals, the exposure duration and averaging time was assumed to be 30 years over a 70 year lifespan, based on the 95th percentile of U.S. residence time (U.S. EPA, 1997). This may be modified in cases where a carcinogenic contaminant is widespread throughout state water bodies and the source is relatively ubiquitous.

Cooking Reduction Factor:

OEHHA strongly recommends to all consumers that they skin and thoroughly cook their fish prior to eating. Skinning and cooking remove or reduce a variety of chemical and

biological hazards. FCGs take into account organochlorine 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 was included in the FCG 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 using 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). Mercury and selenium concentrations in fish are not reduced by cooking or cleaning techniques and, thus, no reduction factor has been applied for these chemicals.

Nutrients:

Unlike the case for other fish contaminants listed above, selenium is a required nutrient and fish are a major dietary source of selenium. Thus, it should be ensured that the FCGs 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 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 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. Thus, the mean selenium intake from diet alone (114 µg/day; IOM, 2000) will be used as the background dietary selenium consumption rate for developing FCGs for selenium. As in all cases of supplement intake, consumers who take selenium supplements should take them with caution and under the advisement of their physician.

Use/Application of FCGs:

OEHHA has developed FCGs, using standard exposure factors and a consumption rate of eight ounces prior to cooking (six ounces after cooking), to provide a starting point to assist other agencies that wish to develop fish tissue-based criteria with a goal toward pollution mitigation or elimination. Any agency using FCGs provided in this report to establish fish tissue-based criteria for their own purposes must accept the assumptions described herein.

Table 1. Fish Contaminant Goals (FCGs) for Selected Fish Contaminants Based on Cancer and Non-Cancer Risk* Using an 8-Ounce/Week (prior to cooking) Consumption Rate (32 g/day)**	
	FCGs (ppb, wet weight)
Contaminant Cancer Slope Factor $(mg/kg/day)^{-1}$	
Chlordane (1.3)	**5.6**
DDTs (0.34)	**21**
Dieldrin (16)	**0.46**
PCBs (2)	**3.6**
Toxaphene (1.2)	**6.1**
Contaminant Reference Dose (mg/kg-day)	
Chlordane ($3.3x10^{-5}$)	100
DDTs ($5x10^{-4}$)	1600
Dieldrin ($5x10^{-5}$)	160
Methylmercury ($1x10^{-4}$)^{S}	**220**
PCBs ($2x10^{-5}$)	63
Selenium ($5x10^{-3}$)	**7400**
Toxaphene ($3.5x10^{-4}$)	1100

*The most health protective Fish Contaminant Goal for each chemical (cancer slope factor- versus reference dose-derived) for each meal category is bolded.
**g/day represents the average amount of fish consumed daily, distributed over a 7-day period, using an 8-ounce serving size, prior to cooking.
^{S}Fish Contaminant Goal for sensitive populations (i.e., women aged 18 to 45 years and children aged 1 to 17 years.)

Tabled values are rounded based on laboratory reporting of three significant digits in results, where the third reported digit is uncertain (estimated). Tabled values are rounded to the second digit, which is certain. When data are compared to this table they should also first be rounded to the second significant digit as in this table.

EQUATIONS USED TO CALCULATE FISH CONTAMINANT GOALS

The following general equations were used to calculate Fish Contaminant Goals for chemicals at the consumption rates listed in Table 1, using an 8-ounce (prior to cooking) serving size. 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 Contaminant Goals (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 any consumption level:

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

As an example, for dieldrin, the Fish Contaminant Goal using a risk level of $1x10^{-6}$ and a consumption rate of one, 8-ounce serving per week (32.0 g/day) would be calculated as follows:

$$\frac{(1x10^{-6})(70\text{ kg})(1000\text{ µg/mg})}{[16\text{ (mg/kg/day)}^{-1}](0.032\text{ kg/day})(30/70)(0.7)} = 0.46\text{ ppb}$$

The following general equation can be used to calculate Fish Contaminant Goals (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:

$$\text{Tissue concentration (ppb)} = \frac{\text{(RfD mg/kg-day)(kg BW)(1000 µg/mg)}}{\text{(CR kg/day)(CRF)}}$$

As an example, for mercury, the Fish Contaminant Goal using a consumption rate of one, 8-ounce serving per week (32.0 g/day) for women aged 18 to 45 years and children aged 1 to 17 years would be calculated as follows:

$$\frac{(1x10^{-4}\text{ mg/kg-day})(70\text{ kg BW})(1000\text{ µg/mg})}{(0.032\text{ kg/day})(1)} = 219\text{ ppb}$$

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

Tissue Concentration (ppb) =

$$\frac{\text{[(RfD mg/kg-day)(kg BW) – mg/day Background Dietary Level](1000 µg/mg)}}{\text{(CR kg/day)}}$$

As an example, for selenium, the Fish Contaminant Goal using a consumption rate of one, 8-ounce serving per week (32.0 g/day) would be calculated as follows:

$$\frac{[(5\text{x}10^{-3}\ \text{mg/kg-day})(70\ \text{kg}) - 0.114\ \text{mg/day}](1000\ \mu\text{g/mg})}{0.032\ \text{kg/day}} = 7{,}375\ \text{ppb}$$

Where,
Risk Level = $1\text{x}10^{-6}$
BW = Body weight of consumer (70 kg default)
CSF = Cancer Slope Factor
CR = Consumption Rate as the daily amount of fish consumed
CRF = Cooking Reduction Factor (0.7 for organic contaminants in skin-off fillet)
ED/AT = Exposure Duration/Averaging Time (30 yr exposure/70 yr lifetime)
RfD = Chemical specific reference dose or other reference level

POTENTIAL BENEFITS OF FISH CONSUMPTION

Fish consumption advice is generally provided to the public from disparate arms of the biomedical community: physicians and nutritionists, who focus on the health benefits of eating fish, and toxicologists, who concentrate on the risks from exposure to contaminants that may be found in fish. The conflicting messages that often result likely confuse the consumer, who may then ignore recommendations to limit consumption of contaminated fish or, alternatively, avoid eating fish altogether (see, e.g., Oken et al., 2003). Only recently has there been a more focused attempt to craft unified guidance that addresses benefits and risks of fish consumption, although beneficial aspects are generally only discussed qualitatively.

With the discovery in the 1970s that, despite their high fat diet, Greenlandic Eskimos were virtually devoid of ischemic heart disease and diabetes mellitus, came the earliest recognition that fatty acids found in fish and marine mammals may have particular benefits to human health (Bang and Dyerberg, 1972; Dyerberg et al., 1975; Bang et al., 1976; Dyerberg et al., 1978; Dyerberg and Bang, 1979; Bang et al., 1980). The diet and blood lipid profile of the Eskimos were found to be very high in omega-3 fatty acids and very low in omega-6 fatty acids, in direct contrast to a typical "Western" diet in which the reverse is true (Dyerberg et al., 1975; Bang et al., 1980).

Omega-3 fatty acids, such as α-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are long-chain polyunsaturated fatty acids (PUFAs) with the first double bond inserted at the *third* carbon atom from the methyl end, while omega-6 fatty acids, such as linoleic acid, γ-linolenic acid and arachidonic acid, have the first double bond inserted at the *sixth* carbon atom from the methyl end (IOM, 2005). Fatty acids are designated by their number of carbon atoms, followed by the number of double bonds and the placement of the first double bond. For example, linoleic acid is denoted as 18:2n-6 because it has 18 carbons and two double bonds, with the first double bond located six carbons from the methyl end (the "n" or "omega" position). α-Linolenic (18:3n-3) and linoleic acids cannot be synthesized by humans and are thus required in the diet (IOM, 2005). α-Linolenic acid's only known function is as the precursor to the very long chain PUFAs EPA (20:5n-3) and DHA (22:6n-3), omega-3 fatty acids that are also consumed directly from fish (IOM, 2005). Because the conversion of α-linolenic acid to EPA and DHA is so inefficient (estimated at less than 5 percent) (Wang et al., 2006), and DHA and EPA levels are so low in other foods, fish or fish oil consumption is by far the most important dietary source of these fatty acids (Marszalek and Lodish, 2005). DHA serves as an important structural lipid in nervous tissue, spermatozoa, and the retina, and may be retroconverted to EPA; linoleic acid (18:2n-6), the most common dietary PUFA, is the precursor to arachidonic acid (20:4n-6) (IOM, 2005; Kris-Etherton et al., 2000). Arachidonic acid is also consumed directly from dietary sources such as meat, egg yolk and dairy (Calder, 2006; Richardson, 2006).

Once dietary omega-3 and omega-6 fatty acid precursors are converted *in vivo* to EPA or arachidonic acid, respectively, they can then be metabolized to produce different

eicosanoids, including various prostaglandins, thromboxanes, and leukotrienes, which, in turn, have contravening physiological actions (Robinson and Stone, 2006; Calder, 2006). The omega-3 derived eicosanoids, such as thromboxane A_3 and B_3, prostaglandins PGI_3 and PGE_3, and leukotriene B_5, induce vasodilation, inhibit arrhythmia, decrease platelet aggregation, and are anti-inflammatory. In contrast, eicosanoids derived from omega-6 fatty acids, such as thromboxane A_2 and B_2, prostaglandins PGI_2 and PGE_2, and leukotriene B_4, cause vasoconstriction, are pro-arrhythmic, and increase platelet aggregation and inflammation (Robinson and Stone, 2006; Simopoulos, 1999; DeFilippis and Sperling, 2006). A proper ratio of dietary omega-6 to omega-3 fatty acids is thus imperative to protect health (Simopoulos, 1999; 2002), particularly since high dietary omega-6 levels inhibit the *in vivo* conversion of α-linolenic acid to DHA and EPA (Kris-Etherton et al., 2000). Similarly, high dietary omega-3 fatty acid levels reduce the formation of 2-series eicosanoids from arachidonic acid (IOM, 2005). It has been speculated that conflicting results in clinical trials on the benefits of dietary omega-3 fatty acids may have resulted from failure to take into account background dietary omega-6 fatty acid consumption, high levels of which may inhibit the production of anti-aggregatory eicosanoids and thus undermine the effectiveness of omega-3 fatty acids in disease prevention (Hibbeln et al., 2006).

Humans evolved consuming a diet that was largely equivalent in omega-6 and omega-3 fatty acids. In the 1960s, however, a dramatic shift in the level and composition of dietary fat occurred following the recommendation that saturated fats in the diet be replaced with vegetable oils, such as corn oil and safflower oil, which contain omega-6 to omega-3 ratios greater than 60:1 (Simopoulos, 2001). At the same time, the proportion of farm-raised to wild fish consumption increased (DeFilippis and Sperling, 2006). Farm-raised fish, like farm-raised cows, pigs, and chickens, are often fed diets rich in omega-6 fatty acids and many have tissue omega-6 to omega-3 ratios considerably higher than wild fish of the same species (Hamilton et al., 2005; DeFilippis and Sperling, 2006; Kris-Etherton et al., 2002; Foran et al., 2005; Marszalek and Lodish, 2005). The typical "Western" diet has been estimated to have an omega-6 to omega-3 ratio of 10:1 to 20:1 (Simopoulos, 2003), with a total omega-3 fatty acid consumption of approximately 1.6 g/day (Johnson and Schaefer, 2006). Of that, mean consumption of EPA + DHA is about 0.1 g/day (IOM, 2007). In NHANES 1999-2002, all age/sex population groups were reported to consume an average of less than 0.2 g/day EPA + DHA (IOM, 2007).

Since the Greenlandic Eskimo studies in the 1970s, an explosion of research has examined potential health benefits of fish consumption, with a particular emphasis on omega-3 fatty acids. In 1996, the AHA published their first statement on fish consumption, fish oils, lipids, and coronary heart disease (Stone, 1996). While considering it "premature" at that time to recommend the use of fish oil supplements for the prevention of cardiovascular disease by the general public, the AHA did nonetheless recognize that consumption of marine sources of omega-3 fatty acids seemed "reasonable" because of the low content of saturated fat in fish compared to other meat products and the potential for cardiovascular benefits that might be borne out by future research (Stone, 1996). Subsequently, the most recent AHA statement on the subject

(Kris-Etherton et al., 2002) was strengthened significantly from its original version, as additional research since 1996 has provided even more compelling evidence of the benefits of fish and fish oil consumption.

Currently, the AHA recommends that *individuals without documented coronary heart disease* "eat a variety of (preferably fatty) fish at least twice a week," *individuals with documented coronary heart disease* "consume about 1 g of EPA + DHA per day, preferably from fatty fish (EPA + DHA from capsule form could be considered in consultation with the physician)," and *individuals who need to reduce triglycerides* should consume "two to four grams of EPA + DHA per day provided as capsules under a physician's care" (AHA, 2006). The AHA considers a serving size to be four ounces of fish prior to cooking, or three ounces after cooking, one-half of the serving size typically assumed in fish consumption advisories. The WHO also recommends consumption of 1-2 servings of fish per week (to provide 200-500 mg of EPA + DHA per serving) to protect against coronary heart disease and ischemic stroke (WHO, 2003), while the 2005 Dietary Guidelines Advisory Committee (DGAC) Report concludes that "consumption of two servings (approximately eight ounces) per week of fish high in EPA and DHA is associated with reduced risk of both sudden death and CHD (coronary heart disease) death in adults." The Committee further states that "to benefit from the potential cardioprotective effects of EPA and DHA, the weekly consumption of two serving of fish, particularly fish rich in EPA and DHA, is suggested" (DGAC, 2005). In their report assessing the risks and benefits of fish consumption, the Scientific Advisory Committee on Nutrition (SACN) of the Food Standards Agency and Department of Health in the United Kingdom recommends that all individuals, including pregnant women, "eat at least two portions of fish per week, of which one should be oily," providing approximately 450 mg/day long chain omega-3 fatty acids (SACN, 2004; see also IOM, 2007, for additional discussion).

Presented below is a brief summary of many of the potential benefits of fish or fish oil consumption, given the current state of scientific knowledge. This review is not intended as an exhaustive evaluation of the merits and weaknesses of the vast number of articles on this subject, but merely to be illustrative of significant, and generally recent, research or review articles in the field. Many studies are observational, as is also commonly the case with human toxicity studies on fish contaminants, and cannot prove cause and effect relationships with certainty. Even randomized controlled trials (RCTs), the gold standard of human medical experimentation, may suffer in the case of fish or fish oil studies from the inability to blind the subject to the treatment. Although current scientific consensus recommends fish consumption as a likely way to prevent specific chronic disease conditions, it is unclear to what extent potential benefits from fish or fish oil consumption listed below may be realized through the following mechanisms: increased consumption of omega-3 fatty acids, decreased dietary omega-6 to omega-3 fatty acid ratio (as generally occurs to a lesser extent with fish oil supplementation and to a greater extent with fish consumption), simple replacement of other high fat dietary protein sources with fish, or other nutritive or non-nutritive factors that may covary with fish consumption

(e.g., an overall healthy lifestyle). Many of these issues are discussed in the recent IOM report on balancing the risks and benefits of seafood consumption (IOM, 2007).

Cardiovascular Disease and Total Mortality:

The most thoroughly evaluated potential beneficial effect of fish or fish oil consumption has been on the prevention and treatment of cardiovascular disease. In a recent meta-analysis, Hooper et al. (2006) concluded that evidence to date does not support the position that short or long chain omega-3 fatty acids have a clear effect on this condition. Numerous researchers criticized this review, however, particularly with respect to inappropriate pooling of study participants, outcomes, and marine- and plant-based omega-3 fatty acids, as well as the inclusion of a "methodologically poor" study, which, in and of itself, "changed the conclusion of the meta-analysis from clear benefit to no benefit" (Deckelbaum and Akabas, 2006; Geleijnse et al., 2006; He and Song, 2006; Twisselmann, 2006; von Schacky et al., 2006). A subsequent systematic review of the literature addressed some of these shortcomings (Deckelbaum and Akabas, 2006). After evaluating 46 studies meeting strict selection criteria, Wang et al. (2006) found that omega-3 fatty acids from fish or fish oil supplements, but not α-linolenic acid, appeared to reduce the risk of all-cause mortality, cardiac and sudden death, and stroke. Because RCTs on the effects of omega-3 fatty acids in individuals already suffering from cardiovascular disease (secondary prevention) have been conducted, the strength of the evidence for that outcome is greater than that for prevention of cardiovascular disease in healthy individuals (primary prevention), for which only cohort studies are available (Wang et al., 2006). Mozaffarian and Rimm (2006) also reported that evidence generated from pooling published prospective or randomized primary and secondary prevention trials indicated that consumption of 250 to 500 mg/d of EPA + DHA reduced the relative risk of coronary heart disease death by 36 percent compared to little or no EPA + DHA intake. Additional intake did not appear to confer additional benefits; risk reduction was most closely linked to consumption of fatty fish, not lean fish. Other recent meta-analyses or systematic literature reviews have supported the conclusion that omega-3 fatty acid consumption has a significant beneficial effect on cardiovascular disease (He et al., 2004a; Bucher et al., 2002; Jacobson, 2006; Whelton et al., 2004; Konig et al., 2005; Harper et al., 2005).

Several studies have suggested that mercury may attenuate cardioprotective effects of omega-3 fatty acids in fish (e.g., Salonen et al., 1995; Rissanen et al., 2000; Guallar et al., 2002; Virtanen et al., 2005), particularly in Finnish men, although at least one study did not find such an association (Yoshizawa et al., 2002). Current evidence suggests that fish or fish oils provide more health benefits to those individuals who also have low methylmercury body burdens (IOM, 2007).

Stroke:

Early research on the potentially protective effects of omega-3 fatty acid and/or fish consumption and stroke showed conflicting results (see, for example, Gillum et al., 1996;

Keli et al., 1994; Orencia et al., 1996). This may have occurred, in part, because of a failure to differentiate ischemic and hemorrhagic strokes in study populations (He et al., 2004b), which are caused by opposing mechanisms. A recent meta-analysis of nine cohorts suggested that fish consumption and ischemic stroke were inversely related, with the possibility that as few as one to three fish meals a month might significantly reduce the incidence of this disorder (He et al., 2004b). In a study of 79,839 women, Iso et al. (2001) found that risk of thrombotic infarction was decreased 48 percent for women who ate fish two to four times per week compared to those who ate fish less than once per month. In another analysis of published studies, Bouzan et al. (2005) found that any fish consumption provided significant reduction in stroke risk compared to no fish consumption. The authors noted that an incremental increase in fish consumption may reduce stroke risk even further. In a review of the literature, Wang et al. (2006) found that studies on the effect of marine-based omega-3 fatty acids on stroke were not consistent, but suggested a possible role of fish or fish oils in the prevention of stroke.

Cognitive Function:

Brain tissue is highly enriched in DHA, which is considered essential for the functional development of neural tissues. Much of DHA and other long chain PUFA content of fetal brain is obtained from the maternal blood supply, as *in vivo* synthesis from shorter chain PUFAs is minimal during this period (Cheruku et al., 2002; Marszalek and Lodish, 2005; Uauy and Dangour, 2006). Studies have suggested that fish consumption by the mother during pregnancy or by the young child may improve several neurological outcomes during early development (Mozaffarian and Rim, 2006). Language and social skills, for example, were higher in 6- and 12-month-old infants who ate fish once or more per week compared to those who rarely or never ate fish (Daniels et al., 2004). Maternal fish intake was also positively associated with infant cognitive scores in this study. Sleep-state patterns indicative of greater cognitive maturity were seen in infants whose mothers had higher plasma phospholipid DHA levels compared to those whose mothers had lower plasma phospholipid DHA levels (Cheruku et al., 2002). Oken et al. (2005) showed that infant cognitive scores were positively correlated with fish consumption, but inversely related to maternal hair mercury concentrations. Scores were highest among infants whose mothers had hair mercury concentrations of 1.2 ppm or less and consumed two or more fish meals per week. Conversely, scores were lowest among infants whose mothers had hair mercury concentrations greater than 1.2 ppm and ate two or fewer fish meals per week. Hibbeln et al. (2007) found that, after adjusting for 28 potentially confounding variables, the risk of suboptimal scores for verbal intelligence, prosocial behavior, fine motor, communication, and social development in children six months to eight years old was greater when maternal fish consumption was less than 340 g per week compared to when maternal fish consumption was greater than 340 g per week.

Several studies have shown that DHA levels are reduced in brain and plasma of patients with Alzheimer disease (AD) or other forms of dementia (Johnson and Schaefer, 2006). Potential mechanisms by which these fatty acids may modify the risk for dementia include the prevention or reduction of atherosclerosis, thrombosis, and inflammation

(Barberger-Gateau et al., 2002). In one of the first studies to investigate the potential relationship between fish consumption and dementia, Kalmijn et al. (1997) found that the incident risk of developing all forms of dementia was reduced 60 percent in people 55 years or older who consumed 18.5 or more g/day of fish compared to those consuming 3.0 or fewer g/day fish. The risk for developing AD without cerebrovascular disease in these respective populations was reduced 70 percent. Similarly, Morris et al. (2003) found that people who ate fish at least once per week reduced their risk of incident AD by 60 percent compared to those who rarely or never ate fish. In a subsequent study using the same population group, fish consumption was also found to be significantly inversely related to expected cognitive decline in individuals 65 years and older over a six year period (Morris et al., 2005). Fatty fish consumption and EPA + DHA consumption were also inversely related to mild cognitive decline in a cross-sectional study of middle-aged males and females (Kalmijn et al., 2004). Huang et al. (2005) specifically showed that fatty fish consumption, but not consumption of lean or fried fish, decreased the risk of dementia in a dose-dependent fashion in individuals who did not carry the *APOE* ε4 allele (a risk factor for AD). Fatty fish consumption more than twice per week decreased the risk of incident dementia and AD by 28 and 41 percent, respectively, compared to those eating fish less than once per month. Using a more accurate estimate of omega-3 fatty acid exposure, Heude et al. (2003) found that omega-3 fatty acid concentration and omega-3 to omega-6 ratio of erythrocyte membranes was inversely related to cognitive decline in 63-74 year-old men and women over a four year period.

Although omega-3 fatty acids are often considered the physiologically active agents responsible for positive health effects of fish, some research indicates that other components may have benefits as well. For example, fish, but not omega-3 fatty acid, consumption was inversely associated with a reduced rate of cognitive deterioration over a six-year period in a study of 6,158 males and females, aged 65 or older (Morris et al., 2005). Consumers who ate fish once a week or more maintained the mental status of a person three to four years younger compared to those who ate fish less than once a week.

Preliminary studies have found that omega-3 fatty acids mitigate symptoms in some children with attention-deficit/hyperactivity disorder; however, other studies have not supported these results (Richardson, 2006; Young and Conquer, 2005). Additionally, several epidemiological studies and intervention trials have shown that fish or omega-3 fatty acid consumption may be useful for the prevention or treatment of depression or other mood disorders, which may reflect the well-recognized link between depression and cardiovascular disease (see Parker et al., 2006; Nemets et al., 2006). Numerous authors have reported decreased blood omega-3 fatty acid levels in patients with psychiatric disorders (Tiemeier et al., 2003; Peet and Stokes, 2005; Sublette et al., 2006; Young and Conquer, 2005; Richardson, 2006). Additional research is needed to elucidate the potential role of fish or fish oils in the treatment of neuropsychiatric disorders (Parker et al., 2006; Richardson, 2006; Young and Conquer, 2005).

Visual Function:

DHA is found in very high concentrations in the retina and has a functional role in visual development (Connor et al., 1992; Neuringer, 2000; Cho et al., 2001; Uauy and Dangour, 2006; Johnson and Schaefer, 2006). As noted above, fetal DHA is largely obtained through the maternal blood supply and, postnatally, through breast milk (Marszalek and Lodish, 2005). The degree to which DHA supplementation of infant formulas is necessary or beneficial is not known (Mozaffarian and Rimm, 2006), although the evidence supporting its benefit for preterm infants is more persuasive than it is for term infants (Heird and Lapillonne, 2005; Cheatham et al., 2006). A recent meta-analysis of 14 controlled trials of DHA supplementation of infant formulas showed a strong positive relationship between DHA dose and visual acuity measurements in four-month-old infants (Uauy et al., 2003). Some studies show that the relationship between low dietary omega-3 fatty acids and slowed development of visual acuity may be transitory; however, long-term sequelae of early visual impairments that may occur with low-DHA diets have not been studied and could be significant (Neuringer, 2000).

Numerous studies have also shown that fish and/or omega-3 fatty acid consumption provides benefits to the aging eye and may protect against retinal pathologies associated with ischemia, light, oxygen, inflammation, and age (SanGiovanni and Chew, 2005). Age-related macular degeneration (AMD) is the primary cause of visual disability and blindness in older Americans (Chua et al. 2006; Seddon et al., 2006). In a cross-sectional population-based study, Smith et al. (2000) reported that individuals consuming fish more than once per week were at significantly lower risk of developing late AMD than individuals consuming fish less than once per month. Similarly, in two large prospective cohort studies, fish consumption was inversely related to AMD development; consumption of four or more servings per week reduced the risk of AMD 35 percent compared to eating fish three or fewer times per week. DHA consumption had a smaller, but still significant, inverse relation with AMD development, indicating that substances in fish other than fatty acids may also decrease AMD risk (Cho et al., 2001). In prospective cohort and case control studies, Seddon et al. (2001; 2003; 2006) showed that the risk for development and progression of AMD was significantly reduced or slowed, respectively, with increasing fish or omega-3 fatty acid consumption. In two of the three studies, however, this relationship existed only if consumption of linoleic acid was also low, indicating that the omega-6 to omega-3 ratio may be an important component to the protective effect of omega-3 fatty acids in the development and progression of this disease (Seddon et al., 2006). Chua et al. (2006) found that weekly fish consumption reduced the 5-year incidence of early AMD about 40 percent, while eating fish three times per week or more reduced the 5-year incidence of late AMD about 75 percent. In a review of published studies, Hodge et al. (2006) found that, while there is evidence to suggest that omega-3 fatty acids may play a role in prevention of AMD, variability among studies and the lack of a RCT prevent clinical conclusions from being drawn.

Inflammatory Diseases:

The effect of omega-3 fatty acids on inflammation and inflammatory diseases has been recently reviewed (Ariza-Ariza et al., 1998; Calder, 2006; Cleland et al., 2005; Simopoulos, 2002). Omega-3 fatty acids have been theorized to be useful as anti-inflammatory agents because they generate anti-inflammatory mediators, decrease production of arachidonic acid-derived pro-inflammatory eicosanoids, and modify the expression of inflammatory genes (Calder, 2006). Research has strongly supported the role of long-chain omega-3 fatty acids in the treatment of rheumatoid arthritis (Calder, 2006), including the reduced need for traditional non-steroidal anti-inflammatory drugs (NSAIDS) in patients taking sufficient doses of fish oils (Ariza-Ariza et al., 1998; Cleland, 2005; 2006). However, the data are less robust for the use of long chain omega-3 fatty acids in the treatment of other inflammatory diseases, such as inflammatory bowel disease or asthma, and additional clinical trials are recommended to further define their potential role in the treatment of these conditions (Calder, 2006). Currently, the effective dose for anti-inflammatory effect in rheumatoid arthritis is estimated to be 2.7 g/day EPA + DHA (Cleland, 2005), a dose not easily obtainable through fish consumption alone. It is recommended that this dose not be achieved through the use of cod liver oil supplementation because of the high vitamin A concentration of this product (Cleland, 2005). The shorter chain α-linolenic acid has not been shown to possess anti-inflammatory properties at practical intakes (Calder, 2006).

CONSIDERATION OF THE RISKS AND BENEFITS OF FISH CONSUMPTION

Since the recognition in the 1960s and 1970s that dietary fish might play a significant role in both health and disease, a vast number of studies have been conducted on the benefits and risks of fish consumption. As noted above, though, these areas of research are typically evaluated independently. Risk assessments on contaminants found in fish are occasionally published in the peer-reviewed literature (e.g., Hites et al., 2004; Mahaffey et al., 2004; Knobeloch et al., 2006); a recent risk assessment of organic contaminants in wild and farmed salmon (Hites et al., 2004) sparked intense controversy over whether the known benefits of fish consumption had been adequately considered in comparison to the relatively small lifetime cancer risks associated with organochlorine compounds (Stokstad, 2004; Rembold, 2004; Tuomisto et al., 2004; Lund et al., 2004; Foran et al., 2006; Willett, 2005; 2006). Recently, a few authors have published risk-benefit analyses for fish consumption that considered one or more contaminants and incorporated a quantitative estimate of benefit (Anderson and Wiener, 1995; Foran et al. 2005; Cohen et al., 2005; Gochfeld and Burger, 2005; Ponce et al., 2000; Sidhu, 2003). Using one method of calculating the combined risks and benefits of fish consumption, for example, Foran et al. (2005) found that consumption of farmed salmon was estimated to prevent nearly 300 times more cardiac-related deaths than it potentially caused from PCB-associated cancer. In most assessments, the comparative risks of alternate foods are not taken into account. Other sources of animal protein that may be consumed in place of fish, such as beef, pork, or chicken, also contain undesirable components (e.g., PCBs, dioxins, saturated fat, and hormone or antibiotic residues) whose risk has not been characterized or estimated in a fashion similar to that of fish.

As early as 1986, OEHHA held a workshop on balancing the risks and benefits of fish consumption (CDHS, 1988). In more recent years, OEHHA, and similar agencies from other states, have incorporated benefit statements into their fish consumption advisories that assure the public that fish should be part of a healthy diet. In a technical memorandum describing the derivation of a noncommercial fish consumption recommendation for women who may become pregnant, pregnant women, nursing mothers, and young children, U.S. EPA and FDA noted that their advice "balances the risk from mercury with the benefits of fish" (U.S. EPA, 2004).

Conclusions:

OEHHA determines that there is a significant body of evidence and general scientific consensus that eating fish at dietary levels that are easily achievable, but well above national average consumption rates, appears to promote significant health benefits, including decreased mortality**.** As is the case with all foods, fish contain constituents that may be harmful when consumed in unrestricted quantities. However, because of the unique health benefits associated with fish consumption, the advisory process should be

expanded beyond a simple risk paradigm in order to best promote the overall health of the fish consumer.

ADVISORY TISSUE LEVELS FOR CHLORDANE, DDTs, DIELDRIN, METHYLMERCURY, PCBs, SELENIUM, AND TOXAPHENE

To include the benefits of fish consumption in the advisory process, ATLs were calculated for each of the contaminants for which FCGs were derived. In comparison to FCGs, which were based on a single meal frequency, ATLs were calculated for several meal frequency categories that are used to provide advice to the consumer that balances the benefits and risks of fish consumption. This yields a range of corresponding contaminant concentrations in fish within categories as shown in Table 2. ATLs were calculated using the same general formulas as those used to calculate FCGs, with some adjustments in order to incorporate the benefits of fish consumption. Because benefits are integrated differently into ATL equations for cancer and non-cancer risk, these methods are discussed separately. All factors and assumptions not specifically addressed are the same as those used to develop FCGs.

Cancer Risk:

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

Risk Level:

For FCGs, the maximum risk level was set at $1x10^{-6}$, estimating that, at the given consumption rate, not more than one additional cancer case would be expected in a population of one million people consuming fish over a lifetime. OEHHA acknowledges that, while it should be a goal to maintain a risk level of $1x10^{-6}$ for fish and other foods, the counterbalancing nutritional benefits of foods, particularly the unique benefits of fish, must be considered. Setting the risk level at $1x10^{-5}$ or $1x10^{-6}$ would restrict fish consumption to the extent that it could largely deny fishers the numerous health benefits that can be accrued through fish consumption.

Thus, OEHHA concludes that, for the purposes of developing fish consumption advisories, ATLs should be calculated using a maximum risk level of $1x10^{-4}$, estimating that, at the given consumption rate, not more than one additional cancer case would be expected in a population of 10,000 people consuming fish over a lifetime. 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 is provided as an example of a maximum acceptable risk level in U.S. EPA's Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories (U.S. EPA, 2000a). OEHHA considers that a maximum risk level of $1x10^{-4}$ appropriately balances the cancer risk associated with fish consumption with the numerous known health benefits that can be accrued from eating fish. Because each meal frequency category encompasses a range of fish

contaminant levels (see consumption rate discussion and ATL table below), fishers, over time, will be exposed to a range of risk levels as they catch and eat different fish. Thus, when the *maximum* risk level is set at $1x10^{-4}$ for each meal frequency category, the actual *average* cancer risk for fish consumers over their lifetime is less than $1x10^{-4}$ (ranging from approximately $5x10^{-5}$ to $1x10^{-4}$), when consumption advisories are based on carcinogens detected in fish.

Consumption Rate (CR):

FCGs were calculated using a single consumption rate (32 g/day, or a single serving of eight ounces of fish, prior to cooking, per week) aligning with the AHA's minimum recommended fish consumption rate for adults and exceeding the typical consumption rate for the vast majority of sport fishers (see, for example, SFEI, 2000). This consumption rate is also used to begin issuing fish consumption advisories that are based on cancer risk using the ATLs and other considerations. Because OEHHA also considers it important to offer advice for the small segment of fishers who choose to consume fish more frequently than one 8-ounce serving per week, ATLs for two and three 8-ounce servings per week, prior to cooking (64 and 96 g/day, respectively), were also calculated based on cancer risk.

Example Calculation:

Using a risk level of $1x10^{-4}$, the slope factor for each chemical, and consumption rates of 32, 64, and 96 g of fish/day in the above equation will yield three numbers that are the cutoff values for one, two, and three servings per week, respectively, for cancer risk.

As an example, for dieldrin, the ATL using a risk level of $1x10^{-4}$ and a consumption rate of one, 8-ounce serving per week (32.0 g/day) would be calculated as follows:

$$\frac{(1x10^{-4})(70\text{ kg})(1000\ \mu g/mg)}{[16\ (mg/kg/day)^{-1}](0.032\text{ kg/day})(30/70)(0.7)} = 46\text{ ppb}$$

Thus, fish containing 46 ppb dieldrin, or less, can be consumed in the amount of at least one, 8-ounce serving per week.

Non-Cancer Risk:

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

Hazard Quotient and Consumption Rate:

For FCGs, the maximum HQ was set at 1, indicating that the *maximum* exposure (based on CR in the equation) is equivalent to the RfD. In order to balance the risks and benefits

of fish consumption when considering non-cancer risk, however, OEHHA determined that the *average* exposure should be equivalent to the RfD. With the ATLs, each meal frequency category (one, two and three servings per week) encompasses a range of fish contaminant levels, as noted above. Thus, fishers over time will be exposed to a range of HQs as they catch and eat different fish. When the *maximum* HQ for each meal consumption frequency is set at 1, using the maximum consumption rate in the equation (32, 64, and 96 g/day for one, two, and three servings per week, respectively) to set the cutoff for each meal frequency leads to an actual *average* HQ for fish consumers, over a multiple week basis, of less than 1. This is because the majority of fish caught in each meal frequency category will have a lower contaminant level than the maximum contaminant level used to set the cutoff. However, if the cutoffs are adjusted slightly so that the *average* rather than the maximum HQ is 1, over a multiple week basis, and an acceptable maximum HQ is still maintained, fishers who follow the advice will be able to consume a greater amount of fish and consequently enjoy a higher level of health benefits without incurring significant non-cancer risks from contaminants in fish.

U.S. EPA adjusted a meal frequency cutoff to establish its national advisory for mercury of one serving per week of sport fish from untested water bodies. They combined several meal categories (two, three and four servings per month), as do many states, in order to balance the risks and benefits of fish consumption and simplify communication (U.S. EPA, 2004). U.S. EPA used the contaminant concentration that would otherwise be associated with a recommendation of two servings per month as the cutoff for the one serving per week advice. Although this results in an HQ higher than 1 for some fish that fall into the 1 serving per week category, this advice is still health protective because, on average, fishers will be consuming fish with lower mercury levels than those used to establish the one serving per week cutoff.

OEHHA incorporated an "average HQ" concept into the ATLs by modifying the fish consumption rate used in the ATL equation. As explained above, one, 8-ounce serving of fish per week is equivalent to a consumption rate of 32 g/day. Consumption of two servings of fish per month would be equivalent to 0.5 servings per week, or 16 g/day. Following the example of U.S. EPA in their national advisory (see above), OEHHA also used a 16 g/d consumption rate to calculate the cutoff for the one serving per week category when considering non-cancer risk for the ATLs. As can be seen in the sample calculation below, this allows for greater consumption of fish (and a better balancing of risks and benefits) than if a consumption rate of 32 g/day were used. In a similar fashion, OEHHA used a consumption rate of 48 g/day (approximately 1.5 servings per week) to compute the ATLs for the two servings per week category for non-cancer risk. A consumption rate of 96 g/day was used, as it was for cancer risk, to determine the ATLs for three servings per week. As a consequence of making these adjustments, the *average* HQ, over the entire range of potential exposures, is approximately 1. OEHHA considers this average HQ appropriate to balance the risk and benefits of fish consumption when considering non-cancer risk.

Example Calculation:

Using the RfD for each chemical, and consumption rates of 16, 48, and 96 g/day, in the above equation will yield three numbers that are the cutoff values for one, two, and three servings per week, respectively, for non-cancer risk.

As an example, for mercury, the ATL for one, 8-ounce serving per week for women aged 18-45 years would be calculated as follows:

$$\frac{(1\times10^{-4}\ \text{mg/kg-day})(70\ \text{kg BW})(1000\ \mu\text{g/mg})}{(0.016\ \text{kg/day})(1)} = 440\ \text{ppb}$$

Thus, fish containing 440 ppb mercury, or less, can be consumed in the amount of at least one, 8-ounce serving per week.

Final ATL Calculations:

For each chemical, ATLs were calculated separately for cancer and non-cancer risk, if appropriate, for consumption frequency categories of one, two, and three 8-ounce servings per week. Values for cancer and non-cancer risk were then compared to determine whether the cancer or non-cancer value was the most health-protective. For all chemicals except DDTs, either cancer or non-cancer risk determined the ATL for each consumption frequency category. For DDTs, consumption advice for one serving per week was based on cancer risk, while consumption advice for two and three servings per week was based on non-cancer risk.

OTHER CONSIDERATIONS USED IN THE DEVELOPMENT OF FISH CONSUMPTION ADVISORIES AND SAFE EATING GUIDELINES

ATLs are used as part of the process to develop traditional health advisories (which focus on fish whose consumption should be restricted or avoided altogether) as well as the newer "safe eating guidelines," which inform consumers of fish with low contaminant levels considered safe to eat frequently. Other factors, including the following, will also be used by OEHHA to develop advisories and safe eating guidelines, as appropriate.

Omega-3 Fatty Acid Levels:

The fatty acid content of fish is highly variable within and among species; fish diet, sex, age, and reproductive status, as well as location and season all affect the total concentration and composition of tissue fat (Nettleton, 1995). At the present time, omega-3 fatty acids levels are not available specifically for California sport fish, although applicable national averages have been published for some species. If acceptable surrogate or actual omega-3 fatty acid data exist for California sport fish, this information may be used to alter fish consumption advice. For example, OEHHA may recommend higher consumption of fish with high omega-3 levels than fish with identical levels of contaminants but lower omega-3 levels.

Contaminant Data:

Once the consumption frequency categories and ATLs are established, the data must then be carefully examined to determine what contaminant values will be compared to the ATLs. Fish contaminant data collected from a water body are often highly variable, reflecting environmental factors such as seasonal effects and localized sources or sediment methylation processes. Evaluating these data prior to developing site-specific (water body) or regional consumption advice is a complex process that may involve one or more approaches. The most common and simplest method of interpreting fish contaminant data collected from a site is to calculate a value of central tendency such as the geometric mean, arithmetic mean, median or mode. OEHHA often uses the arithmetic mean for developing safe eating guidelines; however, each of these measurements is helpful in interpreting the distribution of the data. Another method of interpreting a 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, provided adequate creel data are available to make this determination. This method is most useful for contaminants, such as mercury, where the concentration is largely dependent on fish size in specific fish species.

After careful selection of an appropriate contaminant concentration for each species at a site (e.g., an arithmetic mean, mode or a regression analysis), that value or values can then be compared to the range of concentrations presented in the ATL table (Table 2).

Risk Communication:

After thorough evaluation of fish contaminant data for a site and comparison of appropriate contaminant values to the ATLs, OEHHA may determine that strict adherence to established consumption frequency categories results in consumption advice that is too complex for the fisher to follow, particular for large water bodies. In these cases, OEHHA may make minor adjustments to recommended consumption limits for a species in order to best facilitate communication. For example, if contaminant levels in a species vary along a discreet coastal region, OEHHA may choose the most restrictive or most common advice for that species for the entire region, depending on circumstances and communication considerations. Additionally, in safe eating guidelines, fishers who do not skin or cook their fish may be advised to consume less fish than guidelines recommend for their population group, if organochlorine contaminants are present in quantities that affect consumption guidelines. Skinning and cooking do not reduce methylmercury concentrations in fish tissue. Serving sizes are based on fish consumption by an average 160 pound person. Individuals weighing less than 160 pounds will be encouraged to eat proportionately smaller amounts. As noted previously, because of their smaller body weights, children will be advised to eat approximately one-half as much fish (in either quantity or frequency) as are women of childbearing age.

Conclusions:

The ATLs described in this report should not be misinterpreted as static "bright lines" that others can use to duplicate state fish consumption advisories. As noted, ATLs are but one component of a complex process of data evaluation and interpretation used by OEHHA in the assessment and communication of fish consumption risks. The nature of the contaminant data or omega-3 fatty acid concentrations in a given species in a water body, as well as risk communication needs, may alter strict application of ATLs when developing site-specific advisories. For example, OEHHA may recommend that consumers eat fish containing low levels of omega-3 fatty acids less often than the ATL table would suggest based solely on contaminant concentrations. OEHHA will use the guidelines set forth in this report as a framework, along with best professional judgment, to provide fish consumption guidance on an *ad hoc* basis that best combines the needs for health protection and ease of communication for each site.

Table 2. Advisory Tissue Levels (ATLs) for Selected Fish Contaminants Based on Cancer or Non-Cancer Risk Using an 8-Ounce Serving Size (Prior to Cooking) (ppb, wet weight)				
Contaminant	**Three 8-ounce Servings* a Week**	**Two 8-ounce Servings* a Week**	**One 8-ounce Servings* a Week**	**No Consumption**
Chlordane[c]	≤190	>190-280	>280-560	>560
DDTs[nc**]	≤520	>520-1,000	>1,000-2,100	>2,100
Dieldrin[c]	≤15	>15-23	>23-46	>46
Methylmercury (Women aged 18-45 years and children aged 1-17 years)[nc]	≤70	>70-150	>150-440	>440
Methylmercury (Women over 45 years and men)[nc]	≤220	>220-440	>440-1,310	>1,310
PCBs[nc]	≤21	>21-42	>42-120	>120
Selenium[nc]	≤2500	>2500-4,900	>4,900-15,000	>15,000
Toxaphene[c]	≤200	>200-300	>300-610	>610

[c]ATLs are based on cancer risk

[nc]ATLs are based on non-cancer risk

*Serving sizes are based on an average 160 pound person. Individuals weighing less than 160 pounds should eat proportionately smaller amounts (for example, individuals weighing 80 pounds should eat one 4-ounce serving a week when the table recommends eating one 8-ounce serving a week).

**ATLS for DDTs are based on non-cancer risk for two and three servings per week and cancer risk for one serving per week.

Tabled values are rounded based on laboratory reporting of three significant digits in results, where the third reported digit is uncertain (estimated). Tabled values are rounded to the second digit, which is certain. When data are compared to this table they should also first be rounded to the second significant digit as in this table.

GENERAL REFERENCES

Anderson, H.A.; Amrhein, J.F.; Shubat, P.; Hesse, J. 1993. Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory. Great Lakes Fish Advisory Task Force Protocol Drafting Committee.

Fan, A.M. 1994. Justification for removal of pulp mill-related fish consumption advisories at Samoa Peninsula and on Sacramento River. Memorandum to Charles M. Shulock. Office of Environmental Health Hazard Asessment. Oakland, California. November 18, 1994.

Federal Register. 1998. Draft Water Quality Criteria Methodology Revisions: Human Health; Notice. Vol. 63 (157):43755-43828.

Hites, R.A.; Foran, J.A.; Carpenter, D.O.; Hamilton, M.C.; Knuth, B.A.; Schwager, S.J. 2004. Global assessment of organic contaminants in farmed salmon. Science 303:226-229.

Knobeloch, L.; Gliori, G.; Anderson, H. 2006. Assessment of methylmercury exposure in Wisconsin. Environ. Res. Doi:1016/j.envres.2006.05.012.

Mahaffey, K.R.; Clickner, R.P.; Bodurow, C.C. 2004. Blood organic mercury and dietary mercury intake: National Health and Nutrition Examination Survey, 1999 and 2000. Environ. Health Perspect. 112:562-570.

Ogden, C.L.; Fryar, C.D.; Carroll, M.D.; Flegal, K.M. 2004. Mean body weight, height, and body mass index, United States 1960-2002. Advance Data from Vital and Health Statistics. Number 347. October 27, 2004. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. Online at: http://www.cdc.gov/nchs/data/ad/ad347.pdf

Santerre, C.R.. 2000. Chlordane and toxaphene residues following cooking of treated channel catfish fillets. J. Food Prot. 63:763-767.

SFEI. 2000. San Francisco Bay Seafood Consumption Study. Richmond, CA:San Francisco Estuary Institute. Available: http://www.sfei.org/rmp/reports/Seafood_consumption/SCstudy_final.pdf

Sherer, R.A.; Price, P.S. 1993. The effect of cooking processes on PCB levels in edible fish tissue. Qual. Assur. 2:396-407.

U.S. EPA. 1997. Exposure Factors Handbook. Vol. III. Activity Factors. EPA/600/P-95-002Fa.

U.S. EPA. 2000a. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories. Volume 2. Risk Assessment and Fish Consumption Limits. 3rd Ed. EPA 823-B-00-007.

U.S. EPA. 2000b. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories. Volume 1. Fish Sampling and Analysis. 3rd Ed. EPA 823-B-00-008.
U.S. EPA. 2004a. Fact Sheet. National Listing of Fish and Wildlife Advisories. Online at: http://www.epa.gov/waterscience/fish/advisories/factsheet.pdf.

U.S. EPA. 2004b. Technical Memorandum. Origin of 1 meal/week noncommercial fish consumption rate in National Advisory for Mercury. Online at: http://www.epa.gov/ost/fishadvice/1-meal-per-week.pdf.

U.S. EPA. 2004c. Joint Federal Advisory for Mercury in Fish. What You Need to Know about Mercury in Fish and Shellfish. Online at: http://www.epa.gov/waterscience/fishadvice/advice.html

U.S. EPA. 2005. Basic Information. Fish Advisories. Online at: http://epa.gov/waterscience/fish/basic.htm

Wilson, N.D.; Shear, N.M.; Paustenbach, D.J.; Price, P.S. 1998. The effect of cooking practices on the concentration of DDT and compounds in the edible tissue of fish. J. Expo. Anal. Environ. Epidemiol. 8:423-440.

Zabik, M.E.; Booren, A.; Zabik, M.J.; Welch, R.; Humphrey, H. 1996. Pesticide residues, PCBs, and PAHs in baked, charbroiled, salt boiled and smoked Great Lakes lake trout. Food Chemistry 55:231-239.

CHLORDANE REFERENCES

ATSDR. 1994. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Chlordane (Update). Prepared by Syracuse Research Corporation under contract number 205-88-0608 for U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Aldrich, F.D.; Holmes, J.H. 1969. Acute chlordane intoxication in a child: Case report with toxicological data. Arch. Environ. Health 19:129-132.

Al-Hachim, G.M.; Al-Baker, A. 1973. Effects of chlordane on conditioned avoidance response, brain seizure threshold and open-field performance of prenatally-treated mice. Br. J. Pharmacol. 49:311-315.

Al-Omar, M.A.; Abbas, A.K.; Al-Obaidy, S.A. 2000. Combined effect of exposure to lead and chlordane on the testicular tissues of Swiss mice. Toxicol. Lett. 115:1-8.

Balash, K.J.; Al-Omar, M.A.; Abdul-Latif, B. 1987. Effect of chlordane on testicular tissues of Swiss mice. Bull. Environ. Contam. Toxicol. 39:434-442.

Barnett, J.B.; Holcomb, D.; Menna, J.H.; Soderberg, L.S. 1985a. The effect of prenatal chlordane exposure on specific anti-influenza cell-mediated immunity. Toxicol. Lett. 25(3):229-238.

Barnett, J.B.; Soderberg, L.S.; Menna, J.H. 1985b. The effect of prenatal chlordane exposure on the delayed hypersensitivity response of BABL/c mice. Toxicol. Lett. 25(2):173-183.

Barnett, J.B.; Blaylock, B.L.; Gandy, J.; Menna, J.H.; Denton, R.; Soderberg, L.S. 1990a. Alteration of fetal liver colony formation by prenatal chlordane exposure. Fundam. Appl. Toxicol. 15(4):820-822.

Barnett, J.B.; Blaylock, B.L.; Gandy, J.; Menna, J.H.; Denton, R.; Soderberg, L.S. 1990b. Long-term alteration of adult bone marrow colony formation by prenatal chlordane exposure. Fundam. Appl. Toxicol. 14(4):688-695.

Blaylock, B.L.; Soderberg, L.S.; Gandy, J.; Menna, J.H.; Denton, R.; Barnett, J.B. 1990. Cytotoxic T-lymphocyte and NK responses in mice treated prenatally with chlordane. Toxicol. Lett. 51(1):41-49.

Bondy, G.; Armstrong, C.; Coady, L.; Doucet, J.; Robertson, P.; Feeley, M.; Barker, M. 2003. Toxicity of the chlordane metabolite oxychlordane in female rats: Clinical and histopathological changes. Food Chem. Toxicol. 41:291-301.

Brown, D.P. 1992. Mortality of workers employed at organochlorines pesticide manufacturing plants – an update. Scand. J. Work Environ. Health 18:155-161.

Brown, L.M.; Blair, A.; Gibson, R.; Everett, G.D.; Cantor, K.P.; Schuman, M.; Burmeister, L.F.; Van Lier, S.F.; Dick, F. 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res. 50:6585-6591.

Brown, L.M.; Burmeister, L.F.; Everett, F.D.; Blair, A. 1993. Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes Control 4:153-156.

Cantor, K.P.; Blair, A.; Everett, G.; Gibson, R.; Burmeister, L.F.; Brown, L.M.; Schuman, L.; Dick, F.R. 1992. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res. 52:2447-2455.

Cassidy, R.A.; Vorhees, C.V.; Minnema, D.J.; Hastings, L. 1994. The Effects of Chlordane Exposure during Pre- and Postnatal Periods at Environmentally Relevant

Levels on Sex Steroid-Mediated Behaviors and Functions in the Rat. Toxicol. Appl. Pharmacol. 126:326-337.

Curley, A.; Garrettson, L.K. 1969. Acute chlordane poisoning. Arch. Environ. Health 18:211-215.

Dougherty, C.P.; Holtz, S.H.; Reinert, J.C.; Panyacosit, L.; Axelrad, D.A.; Woodruff, T.J. 2000. Dietary exposures to food contaminants across the United States. Environ. Res. Section A 84:170-85.

Ecobichon, D.J. 1991. Toxic effects of pesticides. In: Casarett and Doull's Toxicology. The Basic Science of Poisons. 4th Ed. Amdur, M.O.; Doull, J.; Klaassen, C.D., eds. New York: Pergamon Press. pp. 565-622.

Ecobichon, D.J. 2003. Toxic Effects of Pesticides. In: Casarett & Doull's Essentials of Toxicology. Klaassen, C.D.; Watkins, J.B. III, eds. New York: McGraw-Hill. pp. 333-347.

Fisher, B.E. 1999. Most unwanted. Environ. Health Perspect. 107:A18-23.

Grutsch, J.F.; Khasawinah, A. 1991. Signs and mechanisms of chlordane intoxication. Biomed. Environ. Sci. 4:317-326.

IARC. 2001. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans: Some thyrotropic agents. Chlordane and Heptachlor. Volume 79.

IRDC. 1973. International Research and Development Corporation. Eighteen-month oral carcinogenic study of chlordane in mice. Unpublished report to Velsicol Chemical Corporation. MRID No. 00067568. Available from U.S. EPA.

IRIS. 1993. Integrated Risk Information System. Online at: http://www.epa.gov/iris/rfd.htm. Background Document 1A. Database maintained by the Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

IRIS. 1995. Integrated Risk Information System. Online at: http://www.epa.gov/iris/subst/0073.htm. Methylmercury (MeHg) (CASRN 22967-92-6). Database maintained by the Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

IRIS. 1998. Integrated Risk Information System. Online at: http://www.epa.gov/iris/subst/0142.htm. Chlordane (Technical) (CASRN 12789-03-6). Database maintained by the Office of Health and Environmental Assessment. U.S.

Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio.

Khasawinah, A.M.; Grutsch, J.F. 1989a. Chlordane: Thirty-month tumorigenicity and chronic toxicity test in rats. Regul. Toxicol. Pharmacol. 10:95-109.

Khasawinah, A.M.; Grutsch, J.F. 1989b. Chordane: 24-Month tumorigenicity and chronic toxicity test in mice. Regul. Toxicol. Pharmacol. 10:244-254.

Kilburn, K.H. 1997. Chlordane as a neurotoxin in humans. Southern Med. J. 90:299-304.

Kilburn, K.H.; Thornton, J.C. 1995. Protracted neurotoxicity from chlordane sprayed to kill termites. Environ. Health Perspect. 103:690-4.

Klaassen, C.D.; Watkins, J.B. 1999. Casarett and Doull's Toxicology. The Basic Science of Poisons. 5th Ed. Companion Handbook. The toxic effects of pesticides. New York: McGraw-Hill.539-577.

Matsumura, F. 1985. Toxicology of Insecticides. 2nd Ed. New York: Plenum Press.

Menna, J.H.; Barnett, J.B.; Soderberg, L.S. 1985. Influenza type A virus infection of mice exposed in utero to chlordane; survival and antibody studies. Toxicol. Lett. 24(1):45-52.

NCI. 1977. National Cancer Institute. Bioassay of chlordane for possible carcinogenicity. Technical Report Series No. 8. U.S. Dept. Health, Education, and Welfare; National Institutes of Health. PB 271 977.

NIOSH. 1981. National Institute of Occupational Safety and Health. Occupational Guidelines for Chemical Hazards. Occupational Health Guideline for Chlordane. NIOSH Publication No. 81-123.

NIOSH. 2003. National Institute of Occupational Safety and Health. NIOSH Pocket Guide to Chemical Hazards. Chlordane. Online at: http://www.cdc.gov/niosh/npg/npgd0112.html

OEHHA. 1997. Public Health Goal for Chlordane in Drinking Water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. December 1997.

OEHHA. 2005. Child-Specific Reference Doses (chRDs) for School Site Risk Assessment – Cadmium, Chlordane, Heptachlor, Heptachlor Epoxide, Methoxychlor, and Nickel. Final Report. Office of Environmental Health Hazard Assessment, California

Environmental Protection Agency. December, 2005. Online at: http://www.oehha.ca.gov/public_info/public/kids/schools1205.html

Olanoff, L.S.; Bristow, W.J.; Colcolough, J. Jr.; Reigart, J.R. 1983. Acute chlordane intoxication. J. Toxiocol. Clin. Toxicol. 20(4):291-306.

Tryphonas, H.; Bondy, G.; Hodgen, M.; Coady, L.; Parenteau, M.; Armstrong, C.; Hayward, S.; Liston, V. 2003. Effects of *cis*-nonachlor, *trans*nonaclor and chlordane on the immune system of Sprague-Dawley rats following a 28-day oral (gavage) treatment. Food Chem. Toxicol. 41:107-118.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund. Vol. 1. Human Health Evaluation Manual. Part A. EPA/540/1-89-002. U.S. Environmental Protection Agency. Office of Emergency and Remedial Response. Washington, DC.

U.S. EPA. 1996. Proposed Guidelines for Carcinogen Risk Assessment. Online at: http://www.epa.gov/ordntrnt/ORD/WebPubs/carcinogen/.

U.S. EPA. 1997. Toxicological Review of Chlordane (Technical). In Support of Summary Information on the Integrated Risk Information System (IRIS). Online at: http://www.epa.gov/iris/toxreviews/0142-tr.pdf.

U.S. EPA. 2000. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories. Volume 2. Risk Assessment and Fish Consumption Limits. 3rd Ed. EPA 823-B-00-008.

U.S. EPA. 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Online at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283.

Woods, J.S.; Polissar, L. 1989. Non-Hodgkin's lymphoma among phenoyx herbicide-exposed farm workers in western Washington State. Chemosphere 18:401-406.

WHO. 1984. World Health Organization. Environmental Health Criteria 34. Chlordane. Geneva: World Health Organization.

DDT REFERENCES

ATSDR. 1994. Agency for Toxic Substances and Disease Registry. Toxicological Profile for 4,4'-DDT, 4,4'-DDE, 4,4'-DDD (Update). Prepared by Clement International Corporation under contract number 205-88-0608 for U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

ATSDR. 2002. Agency for Toxic Substances and Disease Registry. Toxicological Profile for DDT, DDE, and DDD. Prepared by Syracuse Research Corporation under

contract number 205-1999-00024 for U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Cabral, J.R.P.; Hall, R.K.; Rossi, L.; Bronczyk, S.A.; Shubik, P. 1982. Effects of long-term intake of DDT on rats. Tumorigenesis. 68:11-17.

Clement, J.G.; Okey, A.B. 1972. Estrogenic and anti-estrogenic effects of DDT administered in the diet to immature female rats. Can. J. Physiol. Pharmacol. 50(10):971-5.

Cooper, G.S.; Martin, S.A.; Longnecker, M.P.; Sandler, D.P.; Germolec, D.R. 2004. Associations between plasma DDE levels and immunologic measures in African-American farmers in north Carolina. Environ. Health Perspect. 112:1080-1084.

Crosby, D.G. 1998. Chapter 14. Refractory pollutants. In: Environmental Toxicology and Chemistry. Oxford University Press: New York. pp. 261-280.

Diel, P.; Schulz, T.; Smolnikar, K.; Strunck, E.; Vollmer, G.; Michna, H. 2000. Ability of xeno- and phytoestrogens to modulate expression of estrogen-sensitive genes in rat uterus: Estrogenicity profiles and uterotropic activity. J. Steroid Biochem. Mol. Biol. 73:1-10.

Dougherty, C.P.; Holtz, S.H.; Reinert, J.C.; Panyacosit, L.; Axelrad, D.A.; Woodruff, T.J. 2000. Dietary exposures to food contaminants across the United States. Environ. Res. Section A 84:170-185.

Ecobichon, D.J. 1991. Toxic effects of pesticides. In: Casarett and Doull's Toxicology. The Basic Science of Poisons. 4th Ed. Amdur, M.O.; Doull, J.; Klaassen, C.D., eds. New York: Pergamon Press. pp. 565-622.

Ecobichon, D.J. 2003. Toxic Effects of Pesticides. In: Casarett & Doull's Essentials of Toxicology. Klaassen, C.D.; Watkins, J.B. III, eds. New York: McGraw-Hill. pp. 333-347.

Eriksson. P.; Nordberg, A. 1986. The effects of DDT, DDOH-palmitic acid, and chlorinated paraffin on muscarinic receptors and the sodium-dependent chlorine uptake in the central nervous system of immature mice. Toxicol. Appl. Pharmacol. 85:121-127.

Eriksson, P; Ahlbom, J.; Fredriksson, A. 1992. Exposure to DDT during a defined period in neonatal life induces permanent changes in brain muscarinic receptors and behaviour in adult mice. Brain Res. 582:277-281.

Eriksson, P.; Archer, T.; Fredriksson, A. 1990a. Altered behaviour in adult mice exposed to a sinle low dose of DDT and its fatty acid conjugate as neonates. Brain Res. 514:141-142.

Eriksson, P.; Johansson, U.; Ahlbom, J. et al., 1993. Neonatal exposure to DDT induces increased susceptibility to pyrethroid (bioallethrin) exposure at adult age – changes in cholinergic muscarinic receptor and behavioural variables. Toxicology 77:21-30.

Eriksson, P.; Nilsson; Hakansson, L.; Nordberg, A., et al. 1990b. Neonatal exposure to DDT and its fatty acid conjugate: Effects on cholinergic and behavioural variables in the adult mouse. Neurotoxicology 11:345-354.

Eskenazi, B.; Marks, A.R.; Bradman, A.; Fenster, L.; Johnson, C.; Barr, D.B.; Jewell, N.P. 2006. In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American Children. Pediatrics 118:233-241.

Gladen, B.C.; Rogan, W.J. 1995. DDE and shortened duration of lactation in a northern Mexican town. Am. J. Public Health 85:504-508.

Hodgson, E.; Mailman, R.B.; Chambers, J., eds. 1998. Dictionary of toxicology. MacMillan Reference LTD: London. pp.141-142.

IARC. 1991. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans: Occupational Exposures in Insecticide Application and Some Pesticides. DDT and associated compounds. Vol. 53. World Health Organization.

IRIS. 1996. Integrated Risk Information System. p,p'-Dichlorodiphenyltrichloroethane (DDT). (CASRN 50-29-3). Database maintained by the Office of Research and Development, National Center for Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0147.htm.

Johansson, U.; Fredriksson, A.; Eriksson, P. 1995. Bioallethrin causes permanent changes in behavioral and muscarinic acetylcholine receptor variables in adult mice exposed neonatally to DDT. Eur. J. Pharmacol. 293:159-166.

Johansson, U.; Fredriksson, A.; Eriksson, P. 1996. Low-dose effects of paraoxon in adult mice exposed neonatally to DDT: Changes in behavioural and cholinergic receptor variables. Environ. Toxiocol. Pharmacol. 2:307-314.

Klaassen, C.D. 2001. Nonmetallic Environmental Toxicants. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics. 10th Ed. Goodman, L.S.; Limbird, L.E.; Hardman, J.G.; Gilman, A.G., eds. New York: McGraw-Hill. pp. 1889-1890.

Laug, E.P.; Nelson, A.A.; Fitzhugh, O.G.; Kunze, F.M. 1950. Liver cell alteration and DDT storage in the fat of the rat induced by dietary levels of 1 to 50 ppm DDT. J. Pharmacol. Exp. Therap. 98:268-273.

Longnecker, M.P.; Klebanoff, M.A.; Zhou, H.; Brock, J.W. 2001. Association between maternal serum concentration of the DDT metabolite and preterm and small-for-gestational-age babies at birth. Lancet 358:110-114.

Menzer, R.E. 1991. Water and soil pollutants. In: Casarett and Doull's Toxicology. The Basic Science of Poisons. 4th Ed. Amdur, M.O.; Doull, J.; Klaassen, C.D., eds. New York: Pergamon Press. pp. 872-902.

Rossi, L.; Ravera, M.; Repetti, G.; Santi, L. 1977. Long-term administration of DDT or phenobarbital-Na in Wistar rats. Int. J. Cancer 19:179-185.

Safe, S.H. 1995. Environmental and dietary estrogens and human health: Is there a problem? Environ. Health Persp. 103:346-351.
Saxena, M.C.; Siddiqui, M.K.; Bhargava, A.K.; Murti, C.R.; Kutty, D. 1981. Placental transfer of pesticides in humans. Arch. Toxicol. 48:127-34.

Takayama, S.; Sieber, S.M.; Dalgard, D.W.; Thorgeirsson, U.P.; Adamson, R.H. 1999. Effects of long-term oral administration of DDT on nonhuman primates. J. Cancer Res. Clin. Oncol. 135:219-225.

Talts, U.; Talts, J.F.; Eriksson, P. 1998. Differential expression of muscarinic subtype mRNAs after exposure to neurotoxic pesticides. Neurobiol. Aging 19(6):553-9.

Terracini, B.; Testa, M.C.; Cabral, J.R.; Day, N. 1973. The effects of long-term feeding of DDT to BABL/c mice. Int. J. Cancer 11:747-764.

Thorpe, E.; Walker, A.I.T. 1973. The toxicology of dieldrin (HEOD*). II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, β-BHC and γ-BHC. Fd. Cosmet. Toxicol. 11:433-442.

Tomatis, L.; Turusov, V. 1975. Studies on the carcinogenicity of DDT. GANN Monograph on Cancer Research 17:219-241.

Turusov, V.S.; Day, N.E.; Tomatis, L.; Gati, E.; Charles, R.T. 1973. Tumors in CF-1 mice exposed for six consecutive generations to DDT. J. Natl. Cancer Inst. 51:983-997.

U.S. EPA. 2000. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories. Vol. 2. Risk assessment and fish consumption limits. 3rd Ed. EPA 823-B-00-008.

van Wendel de Joode, B.; Wesseling, C.; Kromhout, H.; Monge, P.; Garcia, M.; Mergler, D. 2001. Chronic nervous-system effects of long-term occupational exposure to DDT. Lancet 357:1014-6.

Vine, M.F.; Stein, L.; Weigle, K.; Schroeder, J.; Degnan, D.; Tse, C-K.J.; Hanchette, C.; Backer, L. 2000. Effects on the immune system associated with living near a pesticide dumpsite. Environ. Health Perspect. 108:1113-1124.

Vine, M.F.; Stein, L.; Weigle, K.; Schroeder, J.; Degnan, D.; Tse, C-K.J.; Hanchette, C.; Backer, L. 2001. Plasma 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) levels and immune response. Am. J. Epidemiol. 153:53-63.

Waliszewski, S.M.; Aguirre, A.A.; Infanzon, R.M.; Siliceo, J. 2000. Partitioning coefficients of organochlorine pesticides between mother blood serum and umbilical blood serum. Bull. Environ. Contam. Toxicol. 65:292-299.

Waliszewski, S.M.; Aguirre, A.A.; Infanzon, R.M.; Silva, C.S.; Siliceo, J. 2001. Organochlorine pesticide levels in maternal adipose tissue, maternal blood serum, umbilical blood serum, and milk from inhabitants of Veracruz, Mexico. Arch. Environ. Contamin. Toxicol. 40: 432-438.

WHO. 1989. World Health Organization. DDT and its derivatives – environmental aspects. Environmental Health Criteria 83. Geneva: World Health Organization.

DIELDRIN REFERENCES

Amoateng-Adjepong, Y.; Sathiakumar, N.; Delzell, E.; Cole, P. 1995. Mortality among workers at a pesticide manufacturing plant. J. Occup. Environ. Med. 37:471-478.

ATSDR. 2002. Agency for Toxic Substances and Disease Registry. Toxicological profile for aldrin/dieldrin. Public Health Service, U.S. Department of Health and Human Services.

Cantor, K.P.; Strickland, P.T.; Brock, J.W.; Bush, D.; Helzlsouer, K.; Needham, L.L.; Zahm, S.H.; Comstock, G.W.; Rothman, N. 2003. Risk of non-Hodgkin's lymphoma and prediagnostic serum organochlorines: β-Hexachlorocyclohexane, chlordane/heptachlor-related compounds, dieldrin, and hexachlorobenzene. Environ. Health Perspect. 111:179-183.

Carlson, J.N.; Rosellini, R.A. 1987. Exposure to low doses of the environmental chemical dieldrin causes behavioral deficits in animals prevented from coping with stress. Psychopharmacology 91:122-126.

Chernoff, N.; Kavlock, R.J.; Kathrein, J.R.; Dunn, J.M.; Haseman, J.K. 1975. Prenatal effects of dieldrin and photodieldrin in mice and rats. Toxicol. Appl. Pharamcol. 31:302-308.

Curley, A.; Copeland, M.F.; Kimbrough, R.D. 1969. Chlorinated hydrocarbon insecticides in organs of stillborn and blood of newborn babies. Arch. Environ. Health 19:628-632.

Deichmann W.B.; MacDonald, W.E.; Beasley, A.G.; et al. 1971. Subnormal reproduction in beagle dogs induced by DDT and aldrin. Ind. Med. Surg. 40:10-20.
de Vlieger, M.; Robinson, J.; Baldwin, M.K.; Crabtree, A.N.; van Dijk, M.C. 1968. The organochlorine insecticide content of human tissues. Arch. Environ. Health 17:759-767.
.
Dougherty, C.P.; Holtz, S.H.; Reinert, J.C.; Panyacosit, L.; Axelrad, D.A.; Woodruff, T.J. 2000. Dietary exposures to food contaminants across the United States. Environ. Res. Section A 84:170-85.

Ecobichon, D.J. 1991. Toxic effects of pesticides. In: Casarett and Doull's Toxicology. The Basic Science of Poisons. 4th Ed. Amdur, M.O.; Doull, J.; Klaassen, C.D., eds. New York: Pergamon Press. pp. 565-622.

Ecobichon, D.J. 2003. Toxic effects of pesticides. In: Casarett and Doull's Essentials of Toxicology. Klaassen, C.D.; Watkins, J.B., eds. New York: McGraw-Hill. pp. 333-347.

Fisher, B.E. 1999. Most unwanted. Environ. Health Perspect. 107:A18-23.

Geyer, H.J.; Scheunert, I.; Rapp, K.; Geberfugi, I.; Steinberg, C.; Kettrup, A. 1993. The relevance of fat content in toxicity of lipophilic chemicals to terrestrial animals with special reference to dieldrin and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Ecotoxicol. Environ. Safety 26:45-60.

Good, E.E.; Ware, G.W. 1969. Effects of insecticides on reproduction in the laboratory mouse. IV. Endrin and Dieldrin. Toxicol. Appl. Pharmacol. 14:201-203.

Harr, J.R.; Claeys, R.R.; Bone, J.F.; McCorcle, T.W. 1970. Dieldrin toxicosis: Rat reproduction. Am. J. Vet. Res. 31:181-189.

Hergenrather, J.; Hlady, G.; Wallace, B.; Savage, E. 1981. Pollutants in breast milk of vegetarians. N. Engl. J. Med. 304:792.

Hoogendam, I.; Versteeg, J.P.J.; de Vlieger, M. 1962. Electroencephalograms in insecticide toxicity. Arch. Environ. Health 4:86-94.

Hoogendam, I.; Versteeg, J.P.J.; de Vlieger, M. 1965. Nine years' toxicity control in insecticide plants. Arch. Environ. Health 10:441-448.

Hunter, C.G.; Robinson, J. 1967. Pharmacodynamics of dieldrin (HEOD). Arch. Environ. Health 15:614-626.

Hunter, C.G.; Robinson, J. 1968. Aldrin, dieldrin and man. Food Cosmet. Toxicol. 6:253-260.

IARC. 1987. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans. Supplement 7. Overall evaluation of carcinogenicity: An updating of IARC Monographs volumes 1 to 42. Online at: http://www-cie.iarc.fr/htdocs/monographs/suppl7/dieldrin.html.

IRIS. 1990. Integrated Risk Information System. Dieldrin. (CASRN 60-57-1). Database maintained by the Office of Research and Development, National Center for Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0225.htm.

IRIS. 1993. Integrated Risk Information System. Dieldrin. (CASRN 60-57-1). Database maintained by the Office of Research and Development, National Center for Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0225.htm.

Kitselman, C.H. 1953. Long term studies on dogs fed aldrin and dieldrin in sublethal dosages, with reference to the histopathological findings and reproduction. J. Am. Vet. Med. Assoc. 123:28-30.

Klaassen, C.D.; Watkins, J.B. 1999. Casarett and Doull's Toxicology. The Basic Science of Poisons. 5th Ed. Companion Handbook. The toxic effects of pesticides. New York: McGraw-Hill. pp. 539-577.

Krzystyniak, K.; Hugo, P.; Flipo, D.; Fournier, M. 1985. Increased susceptibility to mouse hepatitis virus 3 of peritoneal macrophages exposed to dieldrin. Toxicol. Appl. Pharmacol. 80:397-408.

Loose, L.D. 1982. Macrophage induction of T-suppressor cells in pesticide-exposed and protozoan-infected mice. Environ. Health Perspect. 43:89-97.

Matsumura, F. 1985. Toxicology of Insecticides. 2nd Ed. New York: Plenum Press.

Morgan, D.P.; Roan, C.C. 1970. Chlorinated hydrocarbon pesticide residue in human tissues. Arch. Environ. Health 20:452-457.

Polishuk, Z.W.; Wassermann, D.; Wassermann, M.; Cucos, S.; Ron, M. 1977. Organochlorine compounds in mother and fetus during labor. Environ. Res. 13:278-284.

Quintana, P.J.; Delfino, R.J.; Korrick, S.; Ziogas, A.; Kutz, F.W.; Jones, E.L.; Laden, F.; Garshick, E. 2004. Adipose tissue levels of organochlorine pesticides and

polychlorinated biphenyls and risk of non-Hodgkin's lymphoma. Environ. Health Perspect. 112:854-861.

Rathore, M.; Bhatnagar, P.; Mathur, D.; Saxena, G.N. 2002. Burden of organochlorine pesticides in blood and its effect on thyroid hormones in women. Sci. Total Environ. 295:207-15.

Ribbens, P.H. 1985. Mortality study of industrial workers exposed to aldrin, dieldrin and endrin. Int. Arch. Occup. Environ. Health 56:75-79.

Richardson, A.; Robinson, J. 1971. The identification of a major metabolite of HEOD (dieldrin) in human faeces. Xenobiotica 1:213-9.

Schecter, A.; Furst, P.; Kruger, C.; et al. 1989. Levels of polychlorinated dibenzofurans, dibenzodioxins, PCBs, DDT and DDE, hexachlorobenzene, dieldrin, hexachlorocyclohexanes and oxychlordane in human breast milk from the United States, Thailand, Vietnam, and Germany. Chemosphere 18:445-454.

Scheele, J.S. 1998. A comparison of the concentrations of certain pesticides and polychlorinated hydrocarbons in bone marrow and fat tissue. J. Environ. Pathol. Toxicol. Oncol. 17:65-68.

Smith, R.M.; Cunningham, W.L.; Van Gelder, G.A. 1976. Dieldrin toxicity and successive discrimination reversal in squirrel monkeys (*Saimiri sciureus*). J. Toxicol. Environ. Health 1:737-747.

Stevenson, D.E.; Walborg, E.F., Jr.; North, D.W.; Sielken, R.L.; Ross, C.E.; Wright, A.S.; Xu, Y.; Kamendulis, L.M.; Klaunig, J.E. 1999. Monograph: Reassessment of human cancer risk of aldrin/dieldrin. Toxicol. Lett. 109:123-186.

Stevens, M.F.; Ebell, G.F.; Psaila-Savona, P. 1993. Organochlorine pesticides in western Australian nursing mothers. Med. J. Aust. 158:238-241.

Swaen, G.; de Jong, G.; Slangen, J.; van Amelsvoort, L. 2002. Cancer mortality in workers exposed to dieldrin and aldrin: an update. Toxicol. Ind. Health 18:63-70.

Thorpe, E.; Walker, A.I.T. 1973. The toxicology of dieldrin (HEOD*). II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, β-BHC, and γ-BHC. Fd. Cosmet. Toxicol. 11:433-442.

Treon, J.F.; Cleveland, F.P. 1955. Toxicity of certain chlorinated hydrocarbon insecticides for laboratory animals, with special reference to aldrin and dieldrin. J. Agric. Food Chem. 3:402-408.

Virgo, B.B.; Bellward, G.D. 1975. Effects of dietary dieldrin on reproduction in the Swiss-Vancouver (SWV) mouse. Environ. Physiol. Biochem. 5:440-450.

Walker, A.I.T.; Stevenson, D.E.; Robinson, J.; Thorpe, E.; Roberts, M. 1969. The toxicology and pharmacodynamics of dieldrin (HEOD): Two-year oral exposures of rats and dogs. Toxicol. Appl. Pharmacol. 15: 345-373.

WHO. World Health Organization. 1989. Environmental Health Criteria 19. Aldrin and Dieldrin. Geneva: World Health Organization.

Wright, A.S.; Donninger, C.; Greenland, R.D.; Stemmer, K.L.; Zavon, M.R. 1978. The effects of prolonged ingestion of dieldrin on the livers of male rhesus monkeys. Ecotox. Environ. Safety 1:477-502.

METHYLMERCURY REFERENCES

Aberg, B.; Ekman, L.; Falk, R.; Greitz, U.; Persson, G.; Snihs, J-O. 1969. Metabolism of methyl mercury (^{203}Hg) compounds in man. Arch. Environ. Health. 19:478-485.

Adams, J.; Barone, S., Jr.; LaMantia, A.; Philen, R.; Rice, D.C.; Spear, L.; Susser, E. 2000. Workshop to identify critical windows of exposure for children's health: Neurobehavioral Work Group summary. Environ. Health Perspect. 108 (suppl. 3):535-544.

Andren, A.W.; Nriagu, J.O. 1979. The global cycle of mercury. In: Nriagu, J.O., ed. The biogeochemistry of mercury in the environment. Topics in environmental health, Vol. 3. Amsterdam: Elsevier/North-Holland Biomedical Press. pp. 1-21.

ATSDR. 1999. Agency for Toxic Substances and Disease Registry. Toxicological profile for mercury (update). Prepared by Research Triangle Institute under contract no. 205-93-0606. Public Health Service, U.S. Department of Health and Human Services.

Bakir, F.; Damluji, S.F.; Amin-Zaki, L.; Murtadha, M.; Khalidi, A.; Al-Rawi, N.Y.; Tikriti, S.; Dhahir, H.I.; Clarkson, T.W.; Smith, J.C.; Doherty, R.A. 1973. Methylmercury poisoning in Iraq. Science 181:230-241.

Berlin, M. 1986. Mercury. In: Friberg, L.; Nordberg, G.F.; Vouk, V.B., eds. Handbook on the toxicology of metals. 2nd Ed. Vol. II. Specific metals. New York, Elsevier pp. 387-445.

Bloom, N.S. 1992. On the chemical form of mercury in edible fish and marine invertebrate tissue. Can. J. Fish. Aquat. Sci. 49(5):1010-1017.

Clarkson, T.W.; Amin-Zaki, L.; Al-Tikriti. 1976. An outbreak of methyl mercury poisoning due to consumption of contaminated grain. Fed. Proc. 35:2395-2399.

Davidson, P.W.; Myers, G.J.; Cox, C.; Axtell, C.; Shamlaye, C.; Sloane-Reeves, J.; Cernichiari, E.; Needham, L.; Choi, A.; Wang, Y.; Berlin, M.; Clarkson, T.W. 1998. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment. JAMA 280:701-707.

Davidson, P.W.; Myers, G.J.; Cox, C.; Shamlaye, C.F.; Marsh, D.O.; Tanner, M.A.; Berlin, M.; Sloane-Reeves, J.; Cernichiari, E.; Choisy, O.; Choi, A.; Clarkson, T.W. 1995. Longitudinal neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from maternal fish ingestion: outcomes at 19 and 29 months. Neurotoxicology 16(4):677-688.

Elhassani, S.B. 1982-83. The many faces of methylmercury poisoning. J. Toxicol. Clin. Toxicol. 19(8):875-906.

Giedd, J.N.; Blumenthal, J.; Jeffries, N.O.; Castellanos, F.X.; Liu, H.; Zijdenbos, A.; Paus, T.; Evans, A.C.; Rapoport, J.L. 1999. Brain development during childhood and adolescence: A longitudinal MRI study. Nature Neuroscience 2(10):861-863.

Grandjean, P.; Budtz-Jorgensen, E.; White, R.F.; Weihe, P.; Debes, F.; Keiding, N. 1999. Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years. Am. J. Epidemiol. 150(3):310-305.

Grandjean, P.; Weihe, P.; White, R.; Debes, F.; Arai, S.; Yokoyama, K.; Murata, N.; Sorensen, N.; Dahl, R.; Jorgensen, P. 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol. Teratol. 19:417-428.

Grandjean, P.; Weihe, P.; White, R.F.; Keiding, N.; Budtz-Jorgensen, K.; Murato, K.; Needham, L. 1998. Prenatal exposure to methylmercury in the Faroe Islands and neurobehavioral performance at age seven years. Response to workgroup questions for presentation on 18-20 Nov. 1998. In Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury. Appendix II-B. Faroe Islands Studies. National Institute for Environmental Health Sciences. Online at: http://ntp-server.niehs.nih.gov/Main_Pages/PUBS/MethMercWkshpRpt.html.

Harada, M. 1978. Congenital Minamata Disease: Intrauterine methylmercury poisoning. Teratology. 18:285-288.

IARC. 1993. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans: Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. Vol. 58. World Health Organization.

IRIS. 1995. Integrated Risk Information System. Methylmercury (MeHg) (CASRN 22967-92-6). Database maintained by the Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0073.htm.

IRIS. 2001. Integrated Risk Information System. Methylmercury (MeHg) (CASRN 22967-92-6). Database maintained by the Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0073.htm.

Kjellstrom, T.; Kennedy, P.; Wallis, S.; Mantell, C. 1986. Physical and mental development of children with prenatal exposure to mercury from fish. Stage I: Preliminary tests at age 4. National Swedish Environmental Protection Board Report 3080. Solna, Sweden.

Kjellstrom, T.; Kennedy, P.; Wallis, S.; Stewart, A.; Friberg, L.; Lind, B.; Wutherspoon, T.; Mantell, C. 1989. Physical and mental development of children with prenatal exposure to mercury from fish. Stage II: Interviews and psychological tests at age 6. National Swedish Environmental Protection Board Report 3642. Solna, Sweden.

Krehl, W.A. 1972. Mercury, the slippery metal. Nutr. Today November/December 90-102.

Marsh, D.O. 1987. Dose-response relationships in humans: Methyl mercury epidemics in Japan and Iraq. In: The Toxicity of Methyl Mercury. Eccles, C.U.; Annau, Z., eds. Baltimore, MD: John Hopkins University Press. pp. 45-53.

Marsh, D.O.; Clarkson, T.W.; Cox, C.; Myers, G.J.; Amin-Zaki, L.; Al-Tikriti, S. 1987. Fetal methylmercury poisoning: Relationship between concentration in single strands of maternal hair and child effects. Arch. Neurol. 44:1017-1022.

Marsh, D.O.; Myers, G.J.; Clarkson, T.W.; Amin-Zaki, L.; Tikriti, S.; Majeed, M.A. 1980. Fetal methylmercury poisoning: Clinical and toxicological data on 29 cases. Ann. Neurol. 7:348-353.

Matsumoto, H.; Koya, G.; Takeuchi, T. 1964. Fetal Minamata Disease: A neuropathological study of two cases of intrauterine intoxication by a methyl mercury compound. J. Neuropathol. Exp. Neurol. 24:563-574.

Mishima, A. 1992. Bitter Sea: The Human Cost of Minamata Disease. Tokyo: Kosei Publishing Co. 231 p.

Myers, G.J.; Davidson, P.W.; Palumbo, D.; Shamlaye, C.; Cox, C.; Cernichiari, E.; Clarkson, T.W. 2000. Secondary analysis from the Seychelles Child Development Study: The child behavior checklist. Environ. Research. Section A 84:12-19.

NAS/NRC. 2000. Toxicological effects of methylmercury. Report of the National Research Council, Committee on the toxicological effects of methylmercury. Washington DC: National Academy Press.

Paus, T.; Zijdenbos, A.; Worsley, K.; Collins, D.L.; Blumenthal, J.; Giedd, J.N.; Rapoport, J.L.; Evans, A.C. 1999. Structural maturation of neural pathways in children and adolescents: In vivo study. Science 283:1908-1911.

Rice, D.; Barone, S., Jr. 2000. Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. Environ. Health Perspect. 108 (suppl. 3):511-33.

Seafood Safety. 1991. Committee on Evaluation of the Safety of Fishery Products, Chapter on Methylmercury: FDA Risk Assessment and Current Regulations, National Academy Press, Washington, DC. p.196-221.

Smith, J.C.; Allen, P.V.; Turner, M.D.; Most, B.; Fisher, H.L.; Hall, L.L. 1994. The kinetics of intravenously administered methyl mercury in man. Toxicol. Appl. Pharmacol. 128(2):251-256.

Snyder, R.D. 1971. Congenital mercury poisoning. New Engl. J. Med. 218:1014-1016.

Stopford, W.; Goldwater, L.J. 1975. Methylmercury in the environment: A review of current understanding. Environ. Health Perspectives 12:115-118.

Stratton, J.W.; Smith, D.F.; Fan, A.M.; Book, S.A. 1987. Methyl Mercury in Northern Coastal Mountain Lakes: Guidelines for Sport Fish Consumption for Clear Lake (Lake County), Lake Berryessa (Napa County), and Lake Herman (Solano County). Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.

Tollefson, L.; Cordle, F. 1986. Methyl mercury in fish: A review of residue levels, fish consumption and regulatory action in the United States. Environ. Health Perspectives 68:203-208.

U.S. EPA. 1997. Mercury Study Report to Congress. Volume VII: Characterization of Human Health and Wildlife Risks from Mercury Exposure in the United States. EPA-452/R-97-009. U.S. Environmental Protection Agency, Office of Air Quality Planning & Standards and Office of Research and Development, Washington, DC.

U.S. EPA. 2004. Joint Federal Advisory for Mercury in Fish. What You Need to Know about Mercury in Fish and Shellfish. Online at:
http://www.epa.gov/waterscience/fishadvice/advice.html

WHO. 1976. World Health Organization. Environmental Health Criteria. Mercury. Geneva: World Health Organization.

WHO. 1989. World Health Organization. Mercury – Environmental Aspects. Environmental Health Criteria 86. Geneva: World Health Organization.

WHO. 1990. World Health Organization. Methylmercury. Environmental Health Criteria 101. Geneva: World Health Organization.

PCB REFERENCES

ATSDR. 2000. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Polychlorinated Biphenyls (PCBs) (Update). Prepared by Syracuse Research Corporation under contract number 205-1999-00024 for U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Arnold, D.L.; Bryce, F.; Stapley, R.; McGuire, P.F.; Burns, D.; Tanner, J.R.; Karpinski, K. 1993a. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (Macaca mulatta) monkeys, Part 1A: Prebreeding phase – clinical health findings. Food Chem. Toxicol. 31:799-810.

Arnold, D.L.; Bryce, F.; Karpinski, K.; Mes, J.; Fernie, S.; Tryphonas, H.; Truelove, J.; McGuire, P.F.; Burns, D.; Tanner, J.R.; Stapley, R.; Zawidzka, Z.Z.; Basford, D. 1993b. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (Macaca mulatta) monkeys, Part 1B: Prebreeding phase – clinical and analytical laboratory findings. Food Chem. Toxicol. 31:811-824.

Arnold, D.L; Bryce, F.; McGuire, P.F.; Stapley, R.; Tanner, J.R.; Wrenshall, E.; Mes, J.; Fernie, S.; Tryphonas, H.; Hayward, S.; Malcolm, S. 1995. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (*Macaca mulatta*) monkeys. Part 2. Reproduction and infant findings. Food Chem. Toxicol. 33:457-474.

Arnold, D.L.; Nera, E.A.; Stapley, R.; Bryce, F.; Fernie, S.; Tolnai, G.; Miller, D.; Hayward, S.; Campbell, J.S.; Greer, I. 1997. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (*Macaca mulatta*) monkeys and their nursing infants. Part 3: Post-reproduction and pathological findings. Food Chem. Toxicol. 35:1191-1207.

Avalos, J., Brodberg, R. 2004. Draft Public Health Goal for Water Soluble Polychlorinated Biphenyls Expected to be Found in Drinking Water. Office of Environmental Health Hazard Assessment.

Brodberg, R.K.; Pollock, G.A. 1999. Prevalence of selected target chemical contaminants in sport fish from two California Lakes: Public health designed screening study. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency.

Brodberg, R.K.; Pollock, G.A. 1999. Prevalence of selected target chemical contaminants in sport fish from two California lakes: Public health designed screening study. Final project report. EPA Assistance Agreement No. CX 825856-01-0.

California Environmental Protection Agency. Office of Environmental Health Hazard Assessment. Sacramento, California. June, 1999.

Brunner, M.J.; Sullivan, T.M.; Singer, A.W., et al. 1996. An assessment of the chronic toxicity and oncogenicity of Aroclor-1016, Aroclor-1242, Aroclor 1254, and Aroclor-1260 administered in diets to rats. Study No. SC920192. Chronic toxicity and oncogenicity report. Battelle, Columbus, OH.

Buck, G.M.; Sever, L.E.; Mendola, P.; Zielezny, M.; Vena, J.E. 1997. Consumption of contaminated sport fish from Lake Ontario and time-to-pregnancy. New York State Angler Cohort. Am. J. Epidemiol. 146:949-954.

Buck, G.M.; Tee, G.P.; Fitzgerald, E.F.; Vena, J.E.; Weiner, J.M.; Swanson, M.; Msall, M.E. 2003. Maternal fish consumption and infant birth size and gestation: New York State Angler Cohort Study. Environ. Health 2:7-15.

Buck G.M.; Vena, J.E.; Schisterman, E.F.; Dmochowski, J.; Mendola, P.; Sever, L.E.; Fitzgerald, E.; Kostyniak, P.; Greizerstein, H; Olson, J. 2000. Parental consumption of contaminated sport fish from Lake Ontario and predicted fecundability. Epidemiology 11:388-393.

Cogliano, V.J. 2001. Considerations for setting reference values for environmental PCBs. In: PCBs. Recent advances in environmental toxicology and health effects. Robertson, L.W.; Hansen, L.G., eds. University of Kentucky Press: Lexington, KY. pp. 429-435.

Cogliano, V.J. 1998. Assessing the cancer risk from environmental PCBs. Environ. Health Perspect. 106:317-323.

Courval, J.M.; DeHoog, J.V.; Stein, A.D.; Tay, E.M.; He, J.; Humphrey, H.E.B.; Paneth, N. 1999. Sport-caught fish consumption and conception delay in licensed Michigan anglers. Environ. Res. Section A 80:S183-S188.

Dahl, P.; Lindstrom, G.; Wiberg, K.; Rappe, C. 1995. Absorption of polychlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans by breast-fed infants. Chemosphere 30(12):2297-306.

Dar, E.; Kanarek, M.S.; Anderson, H.A. et al., 1992. Fish consumption and reproductive outcomes in Green Bay, Wisconsin. Environ. Res. 59:189-201.

Dekoning, E.P., Karmaus, W. 2000. PCB exposure *in utero* and via breast milk. A review. J. Expo. Anal. Environ. Epidemiol. 10:285-293.

Dougherty, C.P.; Holtz, S.H.; Reinert, J.C.; Panyacosit, L.; Axelrad, D.A.; Woodruff, T.J. 2000. Dietary exposures to food contaminants across the United States. Environ. Res. Section A 84:170-85.

Eisler, R.; Belisle, A.A. 1996. Planar PCB hazards to fish, wildlife, and invertebrates: A synoptic review. Contaminant Hazard Reviews. Biological Report 31. U.S. Department of the Interior. Washington DC.

Erickson, M.D. 2001. Introduction: PCB properties, uses, occurrence, and regulatory history. In: PCBs. Recent advances in environmental toxicology and health effects. Robertson, L.W.; Hansen, L.G., eds. University of Kentucky Press: Lexington, KY. pp. xi-xxx.

Gladen, B.C., Rogan, W.J. 1991. Effects of perinatal polycholorinated biphenyls and dichlorodiphenyl dichloroethene on later development. J. Pediatr 199:58-63.

Gladen, B.C.; Rogan, W.J.; Hardy, P; Thullen, J; Tingelstad, J.; Tully, M. 1988. Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. J. Pediatr 113:991-995.

Hanrahan, L.P.; Falk, C.; Anderson, H.A.; Draheim, L.; Kanarek, M.S.; Olson, J.; Great Lakes Consortium. 1999. Serum PCB and DDE levels of frequent Great Lakes sport fish consumers - a first look. Environ. Res. 80:S26-S37.

IARC. 1987. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans: Supplement 7. World Health Organization.

Ikeda, M. 1996. Comparison of clinical picture between Yusho/Yucheng cases and occupational PCB poisoning cases. Chemosphere 32(3):559-66.

IRIS. 1996. Integrated Risk Information System. Aroclor 1254 (CASRN 11097-69-1). Database maintained by the Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0294.htm.

IRIS. 1997. Integrated Risk Information System. Polychlorinated biphenyls (PCBs) (CASRN 1336-36-3). Database maintained by the Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0294.htm.

Jacobson, J.L.; Jacobson, S.W. 1996. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N. Engl. J. Med. 335(11):783-789.

Jacobson, J.L.; Jacobson, S.W.; Humphrey, H.E.B. 1990a. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J. Pediatr. 116:38-45.

Jacobson, J.L.; Jacobson, S.W.; Humphrey, H.E.B. 1990b. Effects of exposure to PCBs and related compounds on growth and activity in children. Neurotoxicol. Teratol. 12:319-326.

Jacobson, J.L.; Jacobson, S.W.; Padgett, R.J.; Brumitt, G.A.; Billings, R.L. 1992. Effects of prenatal PCB exposure on cognitive processing efficiency and sustained attention. Dev. Psychol. 28:297-306.

Juan, C.-Y.; Thomas, G.O.; Sweetman, A.J.; Jones, K.C. 2002. An input-output balance study for PCBs in humans. Environ. Int. 28:203-214.

Kreiss, K. 1985. Studies on populations exposed to polychlorinated biphenyls. Environ. Health Perspect. 60:193-9.

Kunita, N.; Kashimoto, T.; Miyata, H.; Fukshima, S.; Hori, S.; Obana, H. 1984. Causal Agents of Yusho. Am. J. Indus. Med. 5:45-58.

Kuratsune, M.; Nakamura, Y.; Ikeda, M., Hirohata, T. 1987. Analysis of deaths seen among patients with Yusho – A preliminary report. Chemosphere 16:2085-2088.

LACSD. 2000. Los Angeles County Sanitation District. Palos Verdes Ocean Monitoring, Annual Report.

Lonky, E.; Reihman, J.; Darvill, T., et al. 1996. Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. J. Great Lakes Res. 22:198-212.

McLachlan, M.S. 1993. Digestive tract absorption of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in a nursing infant. Toxicol. Appl. Pharmacol. 123:68-72.

Mendola, P.; Buck, G.M.; Sever, L.E.; Zielezny, M.; Vena, J.E. 1997. Consumption of PCB-contaminated freshwater fish and shortened menstrual cycle length. Am. J. Epidemiol. 146(11):955-960.

Mendola, P.; Buck, G.M.; Vena, J.E.; Zielezny, M.; Sever, L.E. 1995. Consumption of PCB-contaminated sport fish and risk of spontaneous fetal death. Environ. Health Perspect. 103:498-502.

Menzer, R.E. 1991. Water and soil pollutants. In: Casarett and Doull's Toxicology. The Basic Science of Poisons. 4th Ed. Amdur, M.O.; Doull, J.; Klaassen, C.D., eds. New York: Pergamon Press. pp. 872-902.

Moser, G.A.; McLachlan, M.S. 2001. The influence of dietary concentration on the absorption and excretion of persistent lipophilic organic pollutants in the human intestinal tract. Chemosphere. 45(2):201-211.

Newman, J.W., Becker, J.S., Blondina, G., Tjeerdema, R.S. 1998. Quantitation of Aroclors using congener-specific results. Environ. Toxicol. Chem. 17:2159-2167.

Nessel, C.S.; Gallo, M.A. 1992. Dioxins and related compounds. In: Environmental Toxicants: Human exposures and their health effects. Lippman, M., ed. Van Nostrand Reinhold: New York.

Norback, D.H.; Weltman, R.H. 1985. Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. Environ. Health Perspect. 60:97-105.

Persky, V.W. 2001. Health Effects of Occupational Exposure to PCBs. In: PCBs. Recent advances in environmental toxicology and health effects. Robertson, L.W.; Hansen, L.G., eds. University of Kentucky Press: Lexington, KY. pp. 99-102.

Rogan W.J.; Gladen B.C. 1991. PCBs, DDE, and child development at 18 and 24 months. Ann. Epidemiol. 1:407-413.

Rylander, L.; Stromberg, U.; Hagmar, L. 1995. Decreased birthweight among infants born to women with a high dietary intake of fish contaminated with persistent organochlorine compounds. Scand. J. Work Environ. Health 21:368-375.

Schantz, S.L.; Levin E.D.; Bowman R.E.; Heironimus M.P.; Laughlin N.K. 1989. Effects of perinatal PCB exposure discrimination-reversal learning in monkeys. Neurotoxicol. Teratol. 11(3):243-250.

Schantz, S.L. 1996. Developmental neurotoxicity of PCBs in humans: What do we know and where do we go from here? Neurotoxicol. Teratol. 18(3):217-27.

Schantz, S.L.; Gardiner, J.C.; Gasior, D.M.; Sweeney, A.M.; Humphrey, H.E.B.; McCaffrey, R.J. 1999. Motor function in aging Great Lakes fisheaters. Environ. Res. 80:S46-S56.

Schantz, S.L.; Gasior, D.M.; Polverejan, E.; McCaffrey, R.J.; Sweeney, A.M.; Humphrey, H.E.; Gardiner, J.C. 2001. Impairments of memory and learning in older adults exposed to polychlorinated biphenyls via consumption of great lakes fish. Environ. Health Perspect. 109(6):605-11.

Schlummer, M.; Moser, G.A.; McLachlan, M.S. 1998. Digestive tract absorption of PCDD/Fs, PCBs, and HCB in humans: mass balances and mechanistic considerations. Toxicol. Appl. Pharmacol. 152:128-137.

Seegal, R.F. 1996. Can epidemiological studies discern subtle neurological effects due to perinatal exposure to PCBs? Neurotox. Teratol. 18:251-254.

Seegal, R.F. 1999. Are PCBs the major neurotoxicant in Great Lakes salmon? Environ. Res. Section A 80:S38-S45.

Shirai, J.H.; Kissel, J.C. 1996. Uncertainty in estimated half-lives of PCBs in humans: Impact on exposure assessment. Sci. Total Environ. 187:199-210.

Smith, B.J. 1984. PCB levels in human fluids: Sheboygan case study. University of Wisconsin Sea Grant Institute, Madison, WI. Technical report WIS-SG-83-240.

Stewart, P.; Reihman, J.; Lonky, E.; Darvill, T.; Dagano, J. 2000. Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. Neurotox. Teratol. 22:21-29.

Swanson, G.M.; Ratcliffe, H.E.; Fischer, L.J. 1995. Human exposure to polychlorinated biphenyls (PCBs): A critical assessment of the evidence for adverse health effects. Reg. Toxicol. Pharmacol. 21:136-150.

Tryphonas, H.; Hayward, S.; O'Grady, L.; Loo, J.C.K.; Arnold, D.L.; Bryce, F.; Zawidzka, Z.Z. 1989. Immunotoxicity studies of PCB (Aroclor 1254) in the adult rhesus (Macaca mulatta) monkey – preliminary report. Int. J. Immunopharmacol. 11:199-206.

Tryphonas, H.; Luster, M.I.; Schiffman, G.; Dawson, L.-L.; Hodgen, M.; Germolec, D.; Hayward, S.; Bryce, F.; Loo, J.C.K.; Mandy, F.; Arnold, D.L. 1991a. Effect of chronic exposure of PCB (Aroclor 1254) on specific and nonspecific immune parameters in the rhesus (Macaca mulatta) monkey. Fund. Appl. Toxicol. 16(4):773-786.

Tryphonas, H.; Luster, M.I.; White, K.L.; Jr., Naylor, P.H.; Erdos, M.R.; Burleson, G.R.; Germolec, D.; Hodgen, M.; Hayward, S.; Arnold, D.L. 1991b. Effects of PCB (Aroclor 1254) on non-specific immune parameters in Rhesus (Macaca mulatta) monkeys. Int. J. Immunopharmacol. 13:639-648.

U.S. EPA. 1996. PCBs: Cancer dose-response assessment and application to environmental mixtures. EPA/600/P-96/001F.

U.S. EPA. 2000a. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories. Vol. 2. Risk assessment and fish consumption limits. 3rd Ed. EPA 823-B-00-008.

U.S. EPA. 2000b. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories. Vol. 1. Fish sampling and analysis. 3rd Ed. EPA 823-B-00-007.

Weisglas-Kuperus, N.; Patandin, S.; Berbers, G.A.M.; Sas, T.C.J.; Mulder, P.G.H.; Pieter, J.J. 2000. Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. Environ. Health Perspect. 108:1203-1207.

WHO. 1993. World Health Organization. Polychlorinated biphenyls and terphenyls. Environmental Health Criteria 140. 2nd Ed. Geneva: World Health Organization.

Wilson, J.D. 1987. A Dose-response curve for Yusho Syndrome. Regul. Toxicol. Pharmacol. 7:364-369.

Winneke, G.; Bucholski, A.; Heinzow, B.; Kramer, U.; Schmidt, E.; Walkowiak, J.; Wiener, J.-A.; Steingruber, H.-J. 1998. Developmental neurotoxicity of polychlorinated biphenyls (PCBs): cognitive and psychomotor functions in 7-month old children. Toxicol. Lett. 102-103:423-428.

Winneke, G.; Walkowiak, J.; Lilienthal, H. 2002. PCB-induced neurodevelopmental toxicity in human infants and its potential mediation by endocrine dysfunction. Toxicology 181-182:161-165.

Wolff, M.S.; Thornton, J.; Fischbein, A.; Lilis, R.; Selikoff, I.J. 1982. Disposition of polychlorinated biphenyl congeners in occupationally exposed persons. Toxicol. Appl. Pharmacol. 62:294-306.

Yao, Y.; Takasuga, T.; Masunaga, S.; Nakanishi, J. 2002. Detailed study on the levels of polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans and polychlorinated biphenyls in Yusho rice oil. Chemosphere 46:1461-1469.

SELENIUM REFERENCES

Aronow, L.; Kerdel-Vegas, F. 1965. Seleno-cystathionine, a pharmacologically active factor in the seeds of *Lecythis ollaria*. Nature 205:1185-1186.

ATSDR. 1999. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Selenium (update). Public Health Service, U.S. Department of Health and Human Services.

ATSDR. 2003. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Selenium. Public Health Service, U.S. Department of Health and Human Services.

Barceloux, D.G. 1999. Selenium. Clin. Toxicol. 37:145-172.

Chang, J.C.; Gutenmann, W.H.; Reid, C.M.; Lisk, D.J. 1995. Selenium content of Brazil nuts from two geographic locations in Brazil. Chemosphere 30:801-802.

Civil, I.D.S.; McDonald, M.J.A. 1978. Acute selenium poisoning: Case report. New Zealand Med. J. 87:354-356.

Combs, G.F., Jr.; Combs, S.B. 1986. The role of selenium in nutrition. Academic Press: New York.

Fan, A.M.; Book, S.A.; Neutra, R.R.; Epstein, D.M. 1988. Selenium and human health implications in California's San Joaquin Valley. J. Toxicol. Environ. Health 23:539-559.

FDA Drug Bulletin. 1984. Toxicity with superpotent selenium. FDA Drug Bulletin 14:19

Franke, K.W.; Potter, W.R. 1935. A new toxicant occurring naturally in certain samples of plant foodstuffs. IX. Toxic effects of orally ingested selenium. J. Nutr. 10:213-231.

Gasmi, A.; Garnier, R.; Galliot-Guilley, M.; Gaudillat, C.; Quartenoud, B.; Buisine, A.; Djebbar, D. 1997. Acute selenium poisoning. Vet. Human Toxicol. 39:304-308.

Haygarth, P.M. 1994. Global importance and global cycling of selenium. In: Frankenberger, W.T., Jr. and Benson, S., eds. Selenium in the Environment. New York: Marcel Dekker, Inc. pp.1-27.

Helzlsouer, K.; Jacobs, R.; Morris, S. 1984. Acute selenium intoxication in the United States. Fed. Proc. Fed. Am. Soc. Exp. Biol. 44:1670.

IARC. 1975. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans: Selenium and selenium compounds. Vol. 9. World Health Organization.

IOM. 2000. Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academy Press: Washington, D.C.

IRIS. 1991. Integrated Risk Information System. Selenium and Compounds (CASRN 7782-49-2). Database maintained by the Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0472.htm.

IRIS. 1993. Integrated Risk Information System. Selenium and Compounds (CASRN 7782-49-2). Carcinogenicity Assessment. Database maintained by the Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0472.htm.

Jensen, R.; Closson, W.; Rothenberg, R. 1984. Selenium intoxication – New York. Morbidity Mortality Weekly Report 33:1938.

Kerdel-Vegas, F. 1964. Generalized hair loss due to the ingestion of "Coco de Mono" (*Lecythis ollaria*). J. Invest. Derm. 42:91-94.

Kerdel-Vegas, F.; Wagner, F.; Russell, P.B.; Grant, N.H.; Alburn, H.E.; Clark, D.E.; Miller, J.A. 1965. Structure of the pharmacologically active factor in the seeds of *Lecythis ollaria*. Nature 205:1186-1187.

Klaassen, C.D.; Watkins, J.B. 1999. Casaret & Doull's Toxicology. The Basic Science of Poisons. 5th ed. Companion Handbook. Chapter 23. Toxic effects of metals. pp. 578-633.

Lemly, A.D. 1997. Environmental implications of excessive selenium: A review. Biomed. Environ. Sci. 10:415-435.

Levander, O.A. 1987. A global view of human selenium nutrition. Ann. Rev. Nutr. 7:227-50.

Longnecker, M.P.; Taylor, P.R.; Levander, O.A., et al. 1991. Selenium in diet, blood, and toenails in relation to human health in a seleniferous area. Am. J. Clin. Nutr. 53:1288-1294.

May, T.W.; McKinney, G.L. 1981. Cadmium, lead, mercury, arsenic, and selenium concentrations in freshwater fish, 1976-77—National Pesticide Monitoring Program. Pestic. Monit. J. 15:14-38.

Ohlendorf, H.M.; Hoffman, D.J.; Saiki, M.K.; Aldrich, T.W. 1986. Embryonic mortality and abnormalities of aquatic birds: Apparent impacts of selenium from irrigation drainwater. Sci. Total Environ. 52:49-63.

Ohlendorf, H.M.; Kilness, A.W.; Simmons, J.L.; Stroud, R.K.; Hoffman, D.J.; Moore, J.F. 1988. Selenium toxicosis in wild aquatic birds. J. Toxicol. Environ. Health 24:67-92.

Reilly, C. 1996. Selenium in Food and Health. New York: Blackie Academic & Professional.

Schellmann, B.; Raithel, H.J.; Schaller, K.H. 1986. Acute fatal selenium poisoning. Toxicological and occupational medical aspects. Arch. Toxicol. 59:61-3.

Schrauzer, G.N. 2000. Selenomethionine: A review of its nutritional significance, metabolism and toxicity. J. Nutr. 130:1653-6.

Schrauzer, G.N. 2003. The nutritional significance, metabolism and toxicology of selenomethionine. Adv. Food Nutr. Res. 47:72-112.

Schwarz, K.; Foltz, C.M. 1957. Selenium as an integral part of Factor 3 against dietary necrotic liver degeneration. J. Am. Chem. Soc. 79:3292-3293.

Sioris, L.J. 1980. Acute selenium poisoning. Vet. Human Toxicol. 22:364.

Thomson, C.D. 1998. Selenium speciation in human body fluids. Analyst 123:827-831.

USDA. 2004. United States Department of Agriculture. USDA National Nutrient Database for Standard Reference. Release 17. Selenium. Online at: http://www.nal.usda.gov/fnic/foodcomp/Data/SR17/wtrank/sr17w317.pdf

Willite, C.C. 1993. Selenium teratogenesis. Species-dependent response and influence on reproduction. Ann. NY Acad. Sci. 678:169-177.

Yang, G.; Wang, S.; Zhou, R.; Sun, S. 1983. Endemic selenium intoxication of humans in China. Am. J. Clin. Nutr. 37:872-881.

Yang, G.; Zhou, R. 1994. Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. J. Trace. Elem. Electrolytes Health Dis. 8:159-165.

Yang, G; Zhou, R.; Yin, S.; Gu, L.; Yan, B.; Liu, Y.; Liu, Y.; Li, X. 1989a. Studies of safe maximal daily dietary selenium intake in a seleniferous area in China. J. Trace Elem. Electrolytes Health Dis. 3:77-87.

Yang, G.; Yin, S.; Zhou, R.; Gu, L.; Yan, B.; Liu, Y.; Liu, Y. 1989b. Studies of safe maximal daily dietary Se-intake in a seleniferous area in China. II. Relation between Se-intake and the manifestation of clinical signs and certain biochemical alterations in blood and urine. J. Trace Elem. Electrolytes Health Dis. 3:123-130.

TOXAPHENE REFERENCES

Alder, L.; Beck, H.; Khandker, S.; Karl, H.; Lehmann, I. 1997. Levels of toxaphene indicator compounds in fish. Chemosphere 34:1389-1400.

Allen, A.L.; Koller, L.D.; Pollock, G.A. 1983. Effect of toxaphene exposure on immune responses in mice. J. Toxicol. Environ. Health 11:61-69.

ATSDR. 1996. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Toxaphene (PCBs) (Update). Prepared by Research Triangle Institute under contract number 205-93-0606 for U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Boyd, E.M.; Taylor, F.I. 1971. Toxaphene toxicity in protein-deficient rats. Toxicol. Appl. Pharmacol. 18:158-167.

Calciu, C.; Chan, H.M.; Kubow, S. 1997. Toxaphene congeners differ from toxaphene mixtures in their dysmorphogenic effects on cultured rat embryos. Toxicology 124:153-162.

Chan, H.M.; Yeboah, F. 2000. Total toxaphene and specific congeners in fish from the Yukon, Canada. Chemosphere 41:507-515.

Chernoff, N.; Carver, B.D. 1976. Fetal toxicity of toxaphene in rats and mice. Bull. Environ. Contam. Toxicol. 15:660-664.

Chu, I.; Secours, V.; Villeneuve, D.C.; Valli, V.E.; Nakamura, A.; Colin, D.; Clegg, D.J.; Arnold, E.P. 1988. Reproduction study of toxaphene in the rat. J. Environ. Sci. Health B23:101-126.

Chu, I.; Villeneuve, D.C.; Sun, C-W.; Secours, V.; Procter, B.; Arnold, E.; Clegg, D.; Reynolds, L.; Valli, V.E. 1986. Toxicity of toxaphene in the rat and beagle dog. Fund. Appl. Toxicol. 7:406-418.

Crowder, L.A.; Lanzaro, G.C.; Whitson, R.S. 1980. Behavioral effects of methyl parathion and toxaphene exposure in rats. J. Environ. Sci. Health B15:365-378.

de Geus, H.-J.; Besselink, H.; Brouwer, A.; Klungsoyr, J.; McHugh, B.; Nixon, E.; Rimkus, G.G.; Wester, P.G.; de Boer, J. 1999. Environmental occurrence, analysis, and toxicology of toxaphene compounds. Environ. Health Perspect. 107(Supp. l):115-144.

Dewailly, E.; Ayotte, P.; Bruneau, S.; Laliberte, C.; Muir, D.C.G.; Norstrom, R.J. 1993. Inuit exposure to organochlorines through the aquatic food chain in Arctic Quebec. Environ. Health Perspect. 101:618-620.

DHHS. 2002. Department of Health and Human Services. Toxaphene. CAS No. 8001-35-2. Report on Carcinogens. 10th Ed. Public Health Service, National Toxicology Program.

Ecobichon, D.J. 2003. Toxic Effects of Pesticides. In: Casarett & Doull's Essentials of Toxicology. Klaassen, C.D.; Watkins, J.B. III, eds. New York: McGraw-Hill. pp. 333-347.

Gauthier, M.; Roberge, C.J.; Pelletier, M.; Tessier, P.A.; Girard, D. 2001. Activation of human neutrophils by technical toxaphene. Clin. Immunol. 98:46-53.

Geyer, H.J.; Kaune, A.; Schramm, K.-W.; Rimkus, G.; Scheunert, I.; Bruggemann, R.; Altschuh, J.; Steinberg, C.E.; Vetter, W.; Kettrup, A.; Muir, D.C.G. 1999. Predicting

bioconcentration factors (BCFs) of polychlorinated bornane (Toxaphene) congeners in fish and comparison with bioaccumulation factors (BAFs) in biota from the aquatic environment. Chemosphere 39:655-663.

IARC. 2001. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risks to humans: Some thyrotropic agents. Toxaphene. Volume 79.

IRIS. 1991. Integrated Risk Information System. Toxaphene (CASRN 8001-35-2). Database maintained by the Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office, Cincinnati, Ohio. Online at: http://www.epa.gov/iris/subst/0346.htm.

Kennedy, G.L.; Frawley, J.P.; Calandra, J.C. 1973. Multigeneration reproductive effects of three pesticides in rats. Toxicol. Appl. Pharmacol. 25:589-596.

Klaassen, C.D.; Watkins, J.B. 1999. Casarett and Doull's Toxicology. The Basic Science of Poisons. 5th ed. Companion Handbook. The toxic effects of pesticides. New York: McGraw-Hill. pp. 539-577.

Litton Bionetics, Inc. 1978. Carcinogenic evaluation in mice Toxaphene. Final report. LBI Project No. 20602, Kensington, MD. Submitted to Hercules, Inc., Wilmington, Delaware.

McGee, L.C.; Reed, H.L.; Fleming, J.P. 1952. Accidental poisoning by toxaphene. Review of toxicology and case reports. J. Am. Med. Assn. 149:1124-1126.

NCI. 1979. National Cancer Institute. Bioassay of toxaphene for possible carcinogenicity. Natl. Cancer Inst. Carcinog. Tech. Rep. Ser. 37:1-104.

Newsome, W.H.; Ryan, J.J. 1999. Toxaphene and other chlorinated compounds in human milk from northern and southern Canada: A comparison. Chemosphere 39:519-526.

OEHHA. 2003. Office of Environmental Health Hazard Assessment. Public Health Goal for Toxaphene. California Environmental Protection Agency. Online at: http://www.oehha.ca.gov/water/phg/pdf/Ph4Toxap92603.pdf.

Olson, K.L.; Matsumura, F.; Boush, G.M. 1980. Behavioral effects on juvenile rats from perinatal exposure to low levels of toxaphene, and its toxic components, Toxicant A, and Toxicant B. Arch. Environ. Contam. Toxicol. 9:247-257.

Pollock, G.A.; Hillstrand, R. 1982. The elimination, distribution, and metabolism of ^{14}C-toxaphene in the pregnant rat. J. Environ. Sci. Health. B17:635-648.

Pollock, G.A.; Kilgore, W.W. 1978. Toxaphene. Residue Rev. 69:87-140.

Reuber, M.D. 1979. Carcinogenicity of toxaphene: A review. J. Toxicol. Environ. Health 5:729-748.

Ribick, M.A.; Dubay, G.R.; Petty, J.D.; Stalling, D.L.; Schmitt, C.J. 1982. Toxaphene residues in fish: Identification, quantification, and confirmation at part per billion levels. Environ. Sci. Tech. 16:310-318.

Saleh, M.A. 1991. Toxaphene: Chemistry, biochemistry, toxicity and environmental fate. Rev. Environ. Contam. Toxicol. 118:1-85.

Stern, G.A.; Muir, D.C.G.; Ford, C.A.; Grift, N.P.; Dewailly, E.; Bidleman, T.F.; Walla, M.D. 1992. Isolation and identification of two major recalcitrant toxaphene congeners in aquatic biota. Environ. Sci. Tech. 26:1838-1840.

Tryphonas, H.; Arnold, D.L.; Bryce, F.; Huang, J.; Hodgen, M.; Ladouceur, D.T.; Fernie, S.; Lepage-Parenteau, M.; Hayward, S. 2001. Effects of toxaphene on the immune system of cynomolgus (*Macaca fascicularis*) monkeys. Food Chem. Toxicol. 39:947-958.

U.S. EPA. 1987. Drinking Water Criteria Document for Toxaphene. PB91-143404.

U.S. EPA. 2000. Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories. Vol. 2. Risk assessment and fish consumption limits. 3rd Edition. EPA 823-B-00-008.

Vaz, R.; Blomkvist, G. 1985. Traces of toxaphene components in Swedish breast milk analysed by capillary GC using ECD, electron impact and negative ion chemical ionization MS. Chemosphere 14:223-231.

Walker, J.B.; Seddon, L.; McMllen, E.; Houseman, J.; Tofflemire, K.; Corriveau, A.; Weber, J.-P.; Mills, C.; Smith, S.; Van Oostdam, J. 2003. Organochlorine levels in maternal and umbilical cord blood plasma in Arctic Canada. Sci. Total Environ. 302:27-52.

Wells, W.L.; Millhorn, H.T. 1983. Suicide attempt by toxaphene ingestion: A case report. J. Miss. State Med. Assoc. 24:329-330.

WHO. 1984. World Health Organization. Camphechlor. Environmental Health Criteria, 45. Geneva: World Health Organization.

Witt, K.; Niessen, K.H. 2000. Toxaphenes and chlorinated naphthalenes in adipose tissue of children. J. Pediatr. Gastroenterol. Nutr. 30:164-169.

FISH BENEFIT REFERENCES

AHA. 2006. American Heart Association. Fish and omega-3 fatty acids. AHA recommendation. Online at: http://www.americanheart.org/presenter.jhtml?identifier=4632.

Anderson, P.D.; Wiener, J.B. 1995. Eating fish. In: Risk vs. risk: Tradeoffs in protecting health and the environment. Graham, J.D.; Wiener, J.B., eds. Cambridge, MA: Harvard University Press. pp. 104-123.

Ariza-Ariza, R.; Mestanza-Peralta, M.; Cardiel, M.H. 1998. Omega-3 fatty acids in rheumatoid arthritis: An overview. Semin. Arthritis Rheum. 27:366-370.

Bang, H.O.; Dyerberg, J. 1972. Plasma lipids and lipoproteins in Greenlandic west coast Eskimos. Acta Med. Scand. 192:85-94.

Bang, H.O.; Dyerberg, J.; Hjorne, N. 1976. The composition of food consumed by Greenlandic Eskimos. Acta Med. Scand. 200:69-73.

Bang, H.O.; Dyerberg, J.; Sinclair, H.M. 1980. The composition of the Eskimo food in north western Greenland. Am. J. Clin. Nutr. 33:2657-2661.

Barberger-Gateau, P.; Letenneur, L.; Deschamps, V.; Peres, K.; Dartigues, J.-F.; Renaud, S. 2002. Fish, meat and risk of dementia: Cohort study. Br. Med. J. 325:932-933.

Bouzan, C.; Cohen, J.T.; Connor, W.E.; Kris-Etherton, P.M.; Gray, G.M.; Konig, A.; Lawrence, R.S.; Savitz, D.A.; Teutsch, S.M. 2005. A quantitative analysis of fish consumption and stroke risk. Am. J. Prev. Med. 29:347-352.

Bucher, H.C.; Hengstler, P.; Schindler, C.; Meier, G. 2002. N-3 polyunsaturated fatty acids in coronary heart disease: A meta-analysis of randomized controlled trials. Am. J. Med. 112(4):298-304.

Calder, P.C. 2006. n-3 Polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am. J. Clin. Nutr. 83(Suppl):1505S-1519S.

CDHS. 1988. California Department of Health Services. Balancing the scales: Weighing the benefits and risks of fish consumption. Proceedings of a workshop held in Concord, California, October 20, 1988.

Cheatham, C.L.; Colombo, J.; Carlson, S.E. 2006. n-3 Fatty acids and cognitive and visual acuity development: Methodologic and conceptual considerations. Am. J. Clin. Nutr. 83(suppl):1458S-1466S.

Cheruka, S.R.; Montgomery-Downs, H.E.; Farkas, S.L.; Thoman, E.B.; Lammi-Keefe, C.J. 2002. Higher maternal plasma docosahexaenoic acid during pregnancy is associated with more mature neonatal sleep-state patterning. American Journal of Clinical Nutrition 76:608-613.

Cho, E.; Hung, S.; Willett, W.C.; Spiegelman, D.; Rimm, E.B.; Seddon, J.M.; Colditz, G.A.; Hankinson, S.E. 2001. Prospective study of dietary fat and the risk of age-related macular degeneration. Am. J. Clin Nutr. 72:209-218.

Cleland , L.G.; Caughey, G.E.; James, M.J.; Proudman, S.M. 2006. Reduction of cardiovascular risk factors with longterm fish oil treatment in early rheumatoid arthritis. J. Rheumatol. 33:1973-9.

Cleland, L.G.; James, M.J.; Proudman, S.M. 2005. Fish oil: what the prescriber needs to know. Arth. Res. & Therapy 8:202 (doi:10.1186/ar1876).

Connor, W.E.; Neuringer, M.; Reisbick, S. 1992. Essential fatty acids: The importance of n-3 fatty acids in the retina and brain. Nutr. Rev. 50:21-29.

Chua, B.; Flood, V.; Rochtchina, E.; Wang, J.J.; Smith, W.; Mitchell, P. 2006. Dietary fatty acids and the 5-year incidence of age-related maculopathy. Arch. Ophthalmol. 124:981-986.

Cohen, J.T.; Bellinger, D.C.; Connor, W.E.; Kris-Etherton, P.M.; Lawrence, R.S.; Savitz, D.A.; Shaywitz, B.A.; Teutsch, S.M.; Gray, G.M. 2005. A quantitative risk-benefit analysis of changes in population fish consumption. Am. J. Prev. Med. 29(4):325-334.

Daniels, J.L.; Longnecker, M.P.; Rowland, A.S.; Golding, J. 2004. Fish intake during pregnancy and early cognitive development of offspring. Epidemiol. 15:394-402.

DCAG. 2005. Dietary Guidelines Advisory Committee Report. Nutrition and your Health: Dietary guidelines for Americans. Fats. Online at: http://www.health.gov/dietaryguidelines/dga2005/report/PDF/D4_Fats.pdf

Deckelbaum, R.J.; Akabas, S.R. 2006. n-3 Fatty acids and cardiovascular disease: Navigating toward recommendations. Am. J. Clin. Nutr. 84:1-2.

DeFilippis, A.P.; Sperling, L.S. 2006. Understanding omega-3's. Am. Heart J. 151:564-70.

Dyerberg, J.; Bang, H.O. 1979. Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. Lancet 2:433-435.

Dyerberg, J.; Bang, H.O.; Hjorne, N. 1975. Fatty acid composition of the plasma lipids in Greenland Eskimos. 1975. Am. J. Clin. Nutr. 28:958-966.

Dyerberg, J.; Bang, H.O.; Stoffersen, E. 1978. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet 2:117-119.

Foran, J.A.; Carpenter, D.O.; Good, D.H.; Hamilton, M.C.; Hites, R.A.; Knuth, B.A.; Schwager, S.J. 2006. Risks and benefits of seafood consumption. Letter to the Editor. Am. J. Prev. Med. 30:438-439.

Foran, J.A.; Good, D.H.; Carpenter, D.O.; Hamilton, M.C.; Knuth, B.A.; Schwager, S.J. 2005. Quantitative analysis of the benefits and risks of consuming farmed and wild salmon. J. Nutr. 135:2639-2643.

Geleijnse, J.M.; Brouwer, I.A.; Feskens, E.J.M. 2006. Health benefits of omega-3 fats are in doubt. Letter to the editor. Br. Med. J. 332:915.

Gillum, R.F.; Mussolino, M.E.; Madans, J.H. 1996. The relationship between fish consumption and stroke incidence. The NHANES I Epidemiologic Follow-up Study. Arch. Intern. Med. 156:537-542.

Gochfeld, M.; Burger, J. 2005. Good fish/bad fish: A composite benefit-risk by dose curve. Neurotoxicology 26:511-520.

Guallar, E.; Sanz-Gallardo, I.; van't Veer, P.; Bode, P.; Aro, A.; Gomez-Aracena, J.; Kark, J.D.; Riemersma, R.A.; Martin-Morena, J.M.; Kok, F.J. 2002. Mercury, fish oils, and the risk of myocardial infarction. N. Engl. J. Med. 347:1747-1754.

Hamilton, M.C.; Hites, R.A.; Schwager, S.J.; Foran, J.A.; Knuth, B.A.; Carpenter, D.O. 2005. Lipid composition and contaminants in farmed and wild salmon. Environ. Sci. Technol. 39:8622-8629.

Harper, C.R.; Jacobson, T.A. 2005. Usefulness of omega-3 fatty acids and the prevention of coronary heart disease. Am. J. Cardiol. 96:1521-1529.

He, K.; Song, Y. 2006. A few thoughts on systematic reviews. Letter to the editor. Br. Med. J. 332:915.

He, K.; Song, Y.; Daviglus, M.L.; Liu, K.; Van Horn, L.; Dyer, A.R.; Greenland, P. 2004a. Accumulated evidence on fish consumption and coronary heart disease mortality. A meta-analysis of cohort studies. Circulation 109:2705-2711.

He, K.; Song, Y.; Daviglus, M.L.; Liu, K.; Van Horn, L.; Dyer, A.R.; Goldbourt, U.; Greenland, P. 2004b. Fish consumption and incidence of stroke. A meta-analysis of cohort studies. Stroke 35:1538-1542.

Heird, W.C.; Lapillonne, A. 2005. The role of essential fatty acids in development. Annu. Rev. Nutr. 25:549-571.

Heude, B.; Ducimetiere, P.; Berr, C. 2003. Cognitive decline and fatty acid composition of erythrocyte membranes – the EVA Study. Am. J. Clin. Nutr. 77:803-808.

Hibbeln, J.R.; Nieminen, L.R.G.; Blasbalg, T.L.; Riggs, J.A.; Lands, W.E.M. 2006. Healthy intakes of n-3 and n-6 fatty acids: Estimations considering worldwide diversity. Am. J. Clin. Nutr. 83 (suppl):1483S-1493S.

Hibbeln, J.R.; Davis, J.M.; Steer, C.; Emmett, P.; Rogers, I.; Williams, C.; Golding, J. 2007. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): An observational cohort. The Lancet 369:578-585.

Hodge, W.G.; Schachter, H.M.; Barnes, D.; Pan, Y.; Lowcock, E.C.; Zhang, L.; Sampson, M.; Morrison, A.; Tran, K.; Miguelez, M.; Lewin, G. 2006. Efficacy of ω-3 fatty acids in preventing age-related macular degeneration. A systematic review. Ophthalmology 113:1165-1173.

Hooper, L.; Thompson, R.L.; Harrison, R.A.; Summerbell, C.D.; Ness, A.R.; Moore, H.J.; Worthington, H.V.; Durrington, P.N.; Higgins, J.P.T.; Capps, N.E.; Riemersma, R.A.; Ebrahim, S.B.J.; Smith, G.D. 2006. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: Systematic review. Br. Med. J. 332:752-760.

Huang, T.L.; Zandi, P.P.; Tucker, K.L.; Fitzpatrick, A.L.; Kuller, L.H.; Fried, L.P.; Burke, G.L.; Carlson, M.C. 2005. Benefits of fatty fish on dementia risk are stronger for those without APOE ε4. Neurol. 65:1409-1414.

IOM. 2005. Institute of Medicine. Food and Nutrition Board. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington DC: National Academy Press.

IOM. 2007. Institute of Medicine. Food and Nutrition Board. Seafood choices: Balancing benefits and risks. Nesheim, M.C.; Yaktine, A.L., eds. Pre-publication copy available October 17, 2006. Washington DC: National Academy Press.

Iso, H.; Rexrode, K.M.; Stampfer, M.J.; Manson, J.E.; Colditz, G.A.; Speizer, F.E.; Hennekens, C.H.; Willett, W.C. 2001. Intake of fish and omega-3 fatty acids and risk of stroke in women. J. Am. Med. Assoc. 285:304-312.

Jacobson, T.A. 2006. Secondary prevention of coronary artery disease with omega-3 fatty acids. Am. J. Cardiol. 98 (suppl.):61i-70i.

Johnson, E.J.; Schaefer, E.J. 2006. Potential role of dietary n-3 fatty acids in the prevention of dementia and macular degeneration. Am. J. Clin. Nutr. 83(Suppl):1494S-1498S.

Kalmijn, S.; Launer, L.J.; Ott, A.; Witteman, J.C.M.; Hofman, A.; Breteler, M.M.B. 1997. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann. Neurol. 42:776-782.

Kalmijn, S.; van Boxtel, M.P.J.; Ocke, M.; Verschuren, W.M.M.; Kromhout, D.; Launer, L.J. 2004. Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. Neurol. 62:275-280.

Keli, S.O.; Feskens, E.J.M.; Kromhout, D. 1994. Fish consumption and risk of stroke. The Zutphen Study. Stroke 25:328-332.

Konig, A.; Bouzan, C.; Cohen, J.T.; Connor, W.E.; Kris-Etherton, P.; Gray, G.M.; Lawrence, R.S.; Savitz, D.A.; Teutsch, S.M. 2005. A quantitative analysis of fish consumption and coronary heart disease. Am. J. Prev. Med. 29:335-346.

Kris-Etherton, P.M.; Harris, W.S.; Appel, L.J. 2002. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 106:2747-2757.

Kris-Etherton, P.M.; Shaffer Taylor, D.; Yu-Poth, S.; Huth, P.; Moriarty, K.; Fishell, V.; Hargrove, R.L.; Zhao, G.; Etherton, T.D. 2000. Polyunsaturated fatty acids in the food chain in the United States. Am. J. Clin. Nutr. 71(suppl):179S-188S.

Lund, E.; Engeset, D.; Alsaker, E.; Skeie, G.; Hjartaker, A.; Lundebye, A.-K.; Niebor, E. 2004. Cancer risk and salmon intake. Letter to the editor. Science 305:477.

Marszalek, J.R.; Lodish, H.F. 2005. Docosahexaenoic acid, fatty acid-interacting proteins, and neuronal function: Breastmilk and fish are good for you. Annu. Rev. Cell Dev. Biol. 21:633-657.

Morris, M.C.; Evans, D.A.; Bienias, J.L.; Tangney, C.C.; Bennett, D.A.; Wilson, R.S.; Aggarwal, N.; Schneider, J. 2003. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer Disease. Arch. Neurol. 60:940-946.

Morris, M.C.; Evans, D.A.; Tangney, C.C.; Bienias, J.L.; Wilson, R.S. 2005. Fish consumption and cognitive decline with age in a large community study. Arch. Neurol. 62:1849-1853.

Mozaffarian, D.; Rimm, E.B. 2006. Fish intake, contaminants, and human health. Evaluating the risks and the benefits. J. Am. Med. Assoc. 296:1885-1899.

Nemets, H.; Nemets, B.; Apter, A.; Bracha, Z.; Belmaker, R.H. 2006. Omega-3 treatment of childhood depression: A controlled, double-blind pilot study. Am. J. Psychiatry 163:1098-1100.

Nettleton, J.A. 1995. Introduction to Fatty Acids. In: Omega-3 fatty acids and health. New York: Chapman Hall. pp. 1-63.

Neuringer, M. 2000. Infant vision and retinal function in studies of dietary long-chain polyunsaturated fatty acids: Methods, results, and implications. Am. J. Clin. Nutr. 71(suppl):256S-267S.

Oken, E.; Kleinman, K.P.; Berland, W.E.; Simon, S.R.; Rich-Edwards, J.W.; Gillman, M.W. 2003. Decline in fish consumption among pregnant women after a national mercury advisory. Am. Coll. Obst. Gyn. 102:346-351.

Oken, E.; Wright, R.O.; Kleinman, K.P.; Bellinger, D.; Amarasiriwardena, C.J.; Hu, H.; Rich-Edwards, J.W.; Gillman, M.W. 2005. Maternal fish consumption, hair mercury, and infant cognition in a U.S. cohort. Environ. Health Perspect. 113:1376-1380.

Orencia, A.J.; Daviglus, M.L.; Dyer, A.R.; Shekelle, R.B.; Stamler, J. 1996. Fish consumption and stroke in men: 30-Year findings of the Chicago Western Electric Study. Stroke 27:204-209.

Parker, G.; Gibson, N.A.; Brotchie, H.; Heruc, G.; Rees, A.-M.; Hadzi-Pavlovic, D. 2006. Omega-3 fatty acids and mood disorders. Am. J. Psychiatry 163:969-978.

Peet, M.; Stokes, C. 2005. Omega-3 fatty acids in the treatment of psychiatric disorders. Drugs 65:1051-9.

Ponce, R.A.; Bartell, S.M.; Wong, E.Y.; LaFlamme, D.; Carrington, C.; Lee, R.C.; Patrick, D.L.; Faustman, E.M.; Bolger, M. 2000. Use of quality-adjusted life year weights with dose-response models for public health decisions: A case study of the risks and benefits of fish consumption. Risk Anal. 20:529-542.

Rembold, C.M. 2004. The health benefits of eating salmon. Letter to the editor. Science 305:475.

Richardson, A.J. 2006. Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. International Rev. Psychiatry 18:155-172.

Rissanen, T.; Voutilainen, S.; Nyyssonen, K.; Lakka, T.A.; Salonen, J.T. 2000. Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: The Kuopio Ischaemic Heart Disease Risk Factor Study. Circulation 102:2677-2679.

Robinson, J.G.; Stone, N.J. 2006. Antiatherosclerotic and antithrombotic effects of omega-3 fatty acids. Am. J. Cardiol. 98(suppl):38i-49i.

SACN. 2004. Scientific Advisory Committee on Nutrition. Committee on Toxicity. Advice on fish consumption: Benefits and Risks. 222 p. Online at: http://www.sacn.gov.uk/reports/#.

Salonen, J.T.; Seppanen, K.; Nyyssonen, K.; Korpela, H.; Kauhanen, J.; Kantola, M.; Tuomilehto, J.; Esterbauer, H.; Tatzber, F.; Salonen, R. 1995. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in Eastern Finnish men. Circulation 91:645-655.

SanGiovanni, J.P.; Chew, E.Y. 2005. The role of omega-3 long-chain polyunsaturated fatty acids in health and disease of the retina. Prog. Retinal Eye Res. 24:87-138.

Seddon, J.M.; Cote, J.; Rosner, B. 2003. Progression of age-related macular degeneration: Association with dietary fat, transunsaturated fat, nuts, and fish intake. Arch. Ophthalmol. 121:1728-1737.

Seddon, J.M.; George, S.; Rosner, B. 2006. Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration. Arch. Ophthalmol. 124:995-1001.

Seddon, J.M.; Rosner, B.; Sperduto, R.D.; Yannuzzi, L.; Haller, J.A.; Blair, N.P.; Willett, W. 2001. Dietary fat and risk for advanced age-related macular degeneration. Arch. Ophthalmol. 119:1191-1199.

Sidhu, K.S. 2003. Health benefits and potential risks related to consumption of fish or fish oil. Reg. Toxicol. Pharmacol. 38:336-344.

Simopoulos, A.P. 1999. Essential fatty acids in health and chronic disease. Am. J. Clin. Nutr. 70(suppl):560S-569S.

Simopoulos, A.P. 2001. n-3 Fatty acids and human health: Defining strategies for public policy. Lipids 36(suppl):S83-S89.

Simopoulos, A.P. 2002. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomed. Pharmacother. 56:365-379.

Simopoulos, A.P. 2003. Essential fatty acids in health and chronic diseases. Forum Nutr. 56:67-70.

Smith, W.; Mitchell, P.; Leeder, S.R. 2000. Dietary fat and fish intake and age-related maculopathy. Arch. Ophthalmol. 118:401-404.

Stokstad, E. 2004. Salmon survey stokes debate about farmed fish. Science 303:154-155.

Stone, N.J. 1996. Fish consumption, fish oil, lipids, and coronary heart disease. Circulation 94:2337-2340.

Sublette, M.E.; Hibbeln, J.R.; Galfalvy, H.; Oquendo, M.A.; Mann, J.J. 2006. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. Am. J. Psychiatry 163:1100-1102.

Tiemeier, H.; van Tuijl, H.R.; Hofman, A.; Kiliaan, A.J.; Breteler, M.M. 2003. Plasma fatty acid composition and depression are associated in the elderly: The Rotterdam Study. Am. J. Clin. Nutr. 78:40-46.

Tuomisto, J.T.; Tuomisto, J.; Tainio, M.; Niittynen, M.; Verkasalo, P.; Vartiainen, T..; Kiviranta, H.; Pekkanen, J. 2004. Risk-benefit analysis of eating farmed salmon. Letter to the Editor. Science 305:476.

Twisselmann, B. 2006. Summary of responses. Br. Med. J. 332:915-916.

Uauy, R.; Dangour, A.D. 2006. Nutrition in brain development and aging: Role of essential fatty acids. Nutr. Rev. 64:S24-S33.

Uauy, R.; Hoffman, D.R.; Mena, P.; Llanos, A.; Birch, E.E. 2003. Term infant studies of DHA and ARA supplementation on neurodevelopment: Results of randomized controlled trials. J. Pediatr. 143 (4 Suppl):S17-25.

USDA. 2006. United States Department of Agriculture. My pyramid. Online at: http://www.mypyramid.gov/index.html.

U.S. EPA. 2004. Technical Memorandum. Origin of 1 meal/week noncommercial fish consumption rate in National Advisory for Mercury. Dated: March 11, 2004. Online at: http://epa.gov/waterscience/fishadvice/1-meal-per-week.pdf.

Virtanen, J.K.; Voutilainen, S.; Rissanen, T.H.; Mursu, J.; Tuomainen, T.-P.; Korhonen, M.J.; Valkonen, V.-P.; Seppanen, K.; Laukkanen, J.A.; Salonen, J.T. 2005. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in Eastern Finland. Ateriosclerosis. Thromb. Vasc. Biol. 25:228-233.

von Schacky, C.; Harris, W.S.; Mozaffarian, D.; Kris-Etherton, P. 2006. Expert Panel convened by the International Society for the Study of Fatty Acids and Lipids. Online: http://www.issfal.org.uk/HooperRebuttal.asp

Wang, C.; Harris, W.S.; Chung, M.; Lichtenstein, A.H.; Balk, E.M.; Kupelnick, B.; Jordan, H.S.; Lau, J. 2006. n-3 Fatty acids from fish or fish oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: A systematic review. Am. J. Clin. Nutr. 84:5-17.

Whelton, S.P.; He, J.; Whelton, P.K.; Muntner, P. 2004. Meta-analysis of observational studies on fish intake and coronary heart disease. Am. J. Cardiol. 93:1119-1123.

Yoshizawa, K.; Rimm, E.B.; Morris, J.S.; Spate, V.L.; Hsieh, C.-C.; Spiegelman, D.; Stampfer, M.J.; Willett, W.C. 2002. Mercury and the risk of cornary heart disease in men. N. Engl. J. Med. 347:1755-1760.

Young, G.; Conquer, J. 2005. Omega-3 fatty acids and neuropsychiatric disorders. Reprod. Nutr. Dev. 45:1-28.

WHO. 2003. World Health Organization. WHO Technical Report Series 916. Diet, nutrition and the prevention of chronic diseases. Report of a Joint WHO/FAO Expert Consultation. Geneva: WHO.

Willett, W. 2005. Fish: Balancing health risks and benefits. Am. J. Prev. Med. 29:320-321.

Willett, W. 2006. Letter to the editor. Am. J. Prev. Med. 30(5):443-444.

APPENDIX 1: RESPONSE TO COMMENTS

Comments and Responses to the Original Draft Document:
Development of Guidance Tissue Levels and Screening Values for Common Contaminants in California Sport Fish:
Chlordane, DDTs, Dieldrin, Methylmercury, PCBs, Selenium, and Toxaphene.

Commenter 1:
Sheila Hamilton
General Manager
Big Bear Municipal Water District
P.O. Box 2863
Big Bear Lake, CA 92315

Comment 1.1
Because the final guidance tissue levels and screening values will, no doubt, play a significant role in future regulatory decisions throughout the state, we urge OEHHA to be more specific on the proper and improper use of these proposed thresholds. For example, the State Water Resources Control Board recently misinterpreted OEHHA's screening values (SVs) as thresholds defining impaired water quality. The report does not caution against using the screening values as informal Water Quality Objectives or Maximum Contaminant Levels.

Response 1.1
OEHHA has reconsidered the usefulness of establishing SVs as part of our protocol to develop fish consumption recommendations and determined that the SVs should be removed from the final document. We are providing Fish Contaminant Goals that can be used as a starting point for agencies to develop fish tissue-based criteria. Agencies that require screening criteria for mandated activities may still seek OEHHA's advice for their development. Any screening criteria employ numerous assumptions, particularly the consumption rate and risk level, and may be targeted to different population groups. These issues must be considered and agreed upon as relevant to the purpose of the criteria prior to their development and use by any agency.

Comment 1.2
The draft document was developed using a wide variety of assumptions. We recommend that these assumptions be summarized in a single table.

Response 1.2
The assumptions are explained carefully and individually in the text where they are used, which is considered most appropriate.

Comment 1.3
Table 1 shows a range of recommended GTLs that vary in relation to the average amount of fish consumed in a month. The presentation should be expanded to show how changes in other key assumptions will cause the GTL or SV to increase or decrease.

Response 1.3
While Fish Contaminant Goals (FCGs) and GTLs (now the Advisory Tissue Levels, or ATLs) will change if the assumptions change, the assumptions made by OEHHA in development of this document are fairly standard in risk assessment and have been clearly described in the document. As OEHHA is responsible for issuing sport fish consumption guidelines in the state of California, there is no reason to present alternative assumptions that will not be used to issue fish consumption advice.

Comment 1.4:
We recommend that OEHHA develop a simple spreadsheet tool, based on the equations shown on page 39-40 (now page 43-44) of the draft report, that allow end users to modify the underlying assumption and graph the range of recommended values. With minor modifications, that tool could be adapted for general use by other state agencies.

Response 1.4:
As noted previously, it is OEHHA's mandate to issue health advisories for sport fish consumption in the State of California. As such, OEHHA is the only "end user" of the GTLs (now ATLs), although the ATLs may be used by counties to issue interim advice in consultation with OEHHA. The sole purpose of releasing the document was to improve transparency of the fish advisory process, not to provide other agencies with a tool to provide their own fish consumption advice to the public. To prevent such confusion in the future, OEHHA will rename the final document: Development of Fish Contaminant Goals and Advisory Tissue Levels for Common Contaminants in California Sport Fish: Chlordane, DDTs, Dieldrin, Methylmercury, PCBs, selenium, and toxaphene. OEHHA recognizes that use of the word "guidance" in Guidance Tissue Level has led some to think that this is a "guidance document" to be used by other agencies in developing their own advisories. We are making the change to correct this misinterpretation.

Comment 1.5:
The draft document does not describe what constitutes "sufficient fish tissue data" (p. 2) nor does it provide an explanation as to how to perform the highly-specialized risk analyses recommended.

Response 1.5:
The GTL (now ATL) document is not intended as a guidance document to be used by other agencies (see response to comments above) to develop their own advisories. OEHHA performs the risk analyses; recommendations provided to other agencies responsible for data collection and analyses are provided in another document (Gassel and Brodberg, 2006; General Protocol for Sport Fish Sampling and Analysis). Because each water body is unique, agencies should consult OEHHA prior to collecting fish from

California water bodies so that OEHHA can direct sampling and analysis to collect data sufficient to adequately estimate human health risks. The discussion of sampling and analysis has been removed from the document.

Comment 1.6:
We are concerned that OEHHA elected to make very large adjustments to the estimated reference dose to account for various "uncertainty factors." The published GTLs and SVs should be presented with and without such adjustments so that it is clear to other state agencies that a safety factor has already been applied. Otherwise, it is likely that other agencies will incorrectly assume that the GTL or SV represents the No-Observed-Effect-Threshold and seek to add on their own safety factors. It would be useful to explain that the magnitude of adjustment applied was somewhat arbitrary. Higher or lower multipliers may be equally well justified.

Response 1.6:

Uncertainty factors (UFs) are always included in the development of an RfD. After evaluating the original toxicity data, toxicologists apply uncertainty factors to the point of departure value (e.g., the NOAEL or LOAEL), taking into account any deficiencies in the data (such as short-term exposure, the use of an animal model, or lack of a reproductive study) in order to arrive at the RfD. UFs are not arbitrary but are routinely and rather consistently applied using accepted risk assessment principles. With the exception of toxaphene and chlordane, the UFs and RfDs used for each chemical in this document were originally developed by U.S. EPA and are in general use by the risk assessment community. After reviewing the most current literature, OEHHA has chosen to maintain these RfDs. Again, other agencies should not attempt to modify OEHHA advisories by manipulating any of the parameters used by OEHHA in developing the advisories.

Comment 1.7:
It is unclear if OEHHA considered the published recommendation of other federal agencies (e.g., FDA's less restrictive "Action Levels") and, if so, why those recommendations were rejected. Nor is it clear why OEHHA declined to use EPA's more stringent recommendations.

Response 1.7:

OEHHA conducted a thorough evaluation of federal and other state's methods of providing fish consumption recommendations and selected methods that appropriately balanced benefits and risks. FDA action levels are not appropriate for setting sport fish consumption guidelines. In their guidance document, U.S. EPA does not propose a single, specific method of providing fish consumption recommendations but, instead, illustrates one possible scenario using only the RfD and a risk level of 1×10^{-5}. The U.S. EPA acknowledges that states and tribes may modify this method in multiple ways to make it more or less conservative as they see fit. Examples of RLs from 10^{-4} to 10^{-7} are also included in their guidance document. OEHHA uses the most up-to-date data and

methodology and considers sensitive populations. OEHHA's advisories are within the range of guidance provided by U.S. EPA but, in several cases, are more conservative.

Commenter 2:
Alyce Ujihara
Diana Lee
Sharon Lee
Elana Silver
California Department of Health Services
Environmental Health Investigations Branch
850 Marina Bay Parkway
Richmond, CA 94804

Comment 2.1
Clarification of the reduction factor for organic chemicals for skinning of fillets is needed. You have applied a reduction factor to your GTL calculations that assumes people consume fish as skin-off fillets. Since you assume a 30% reduction due to contaminant loss during cooking and you assume a 50% loss due to cooking and skinning combined, skinning alone appears to account for about a 20% reduction in contaminants in your calculations. This reduction factor for skinning should be explicitly stated.

Response 2.1
Data on the contaminant reduction achieved by various trimming and cooking techniques are variable. It is known that removing the skin and associated fat as well as cooking remove a significant amount of organic contaminants. The general cooking reduction factors of 50% and 30% are typical values that have been generated with experiments using either skin-on or skin-off fillets, respectively. Therefore, there is no explicit reduction factor for skinning alone. The 30% and 50% reduction factors are used, for example, by the Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory and by other states in their fish consumption advisories.

Comment 2.2
Incorporating an assumption that people eat skin-off fillets results in GTLs that are not adequately health protective for a significant number of people. In a survey of San Francisco Bay anglers (SFEI 2001), DHS found that significant numbers of anglers report eating the skin of fish. Specifically, we found that 21% of striped bass consumers and 38% of white croaker consumers reported eating the skin more than half of the time. Generally, among anglers who reported eating skin, there were more non-white anglers, particularly African Americans and Asians. Thus, using a skin-off fillet as the default to develop GTLs for organic chemicals will disproportionately affect these groups.

Response 2.2
OEHHA recommends fish preparation methods, such as skinning, that allow anglers to safely eat more fish. In order to protect anglers who choose not to follow these guidelines, however, OEHHA may provide separate advice, as part of risk

communication, to fishers who do not skin or otherwise trim fish or cook it by methods recommended to reduce contaminant levels when guidance is based on chlorinated hydrocarbon contaminants.

Comment 2.3
The draft document states that "if fishers choose not to follow this advice and cook fish as skin-on fillets, they should reduce their consumption by approximately one-fourth…to achieve and equivalent exposure." From a practical perspective, it does not make sense to base the GTLs on a consumption pattern that people "should" follow, rather than what they already do. The GTLs should not assume that a significant proportion of people will take additional measures in order for the advisory to be adequately health protective. Furthermore, advisory messages need to be as simple as possible. Adding another qualifier to the advisory message (e.g., this advice will only be health protective if you remove the skin) complicates the message.

Response 2.3
Based on the study cited, the majority of anglers *do* skin fish, whether doing this of their own accord or following recommendations that OEHHA provides. OEHHA does not issue consumption and cleaning/cooking advice only to protect the most exposed individual but makes recommendations that all fishers can choose to follow – or not – to lower their exposure to contaminants. Fishers who do not follow advice to skin and/or cook their fish also may not follow advice to limit fish consumption. In the case of mercury, separate advice is provided for two populations groups so that less sensitive individuals (women beyond childbearing age and men) do not have their fish consumption unduly restricted by the needs of the other group (women of childbearing age and children). So it should be with cooking and cleaning methods, i.e., the majority of fishers who do consume/prepare fish in the safest manner should be offered advice that allows them to consume the most fish safely while fishers who choose to eat the skin or prepare fish in a way that does not reduce contaminant loads should be offered separate advice tailored to their needs. This is particularly important in the case of subsistence fishers, for example, where unwarranted fish consumption restrictions may impose an economic burden. The draft report recommended that fishers who do not follow advice to skin fish should reduce their consumption by approximately one-fourth. However, newer data indicate that the amount of contaminants found in skin may be more variable (and ultimately higher) that previously thought. In some cases, fish that could be eaten once or twice a week without skin will fall into the "do not consume" category with skin. For additional consideration in the final report and in future advisories for chlorinated hydrocarbons, OEHHA will consider site- or species-specific advice to reduce consumption if fishers do not cook or clean their fish in the safest manner.

Comment 2.4
Additionally, the decision to use skin-off fillets for scaled fish is not consistent with U.S. EPA guidance for fish advisories. U.S. EPA recommends that contaminant concentrations be measured using skin-on fillets for scaled fish species and skinless fillets for scaleless fish species (e.g., catfish).

Response 2.4
Historically, fish monitoring programs in California have analyzed skinless fillets of fish. See response 2.3 for further discussion. Analyzing skin-on fillets actually dilutes the measured mercury concentrations, making the advice less conservative. As mercury is the predominant fish contaminant in California, OEHHA recommends measuring contaminant concentrations in skin-off fillets.

Comment 2.5
On page 39, a correction to the example equation for dieldrin is needed; 1000 μg/kg should be 1000 μg/mg.

Response 2.5
Corrected. The mistake was the result of a typographical error. Calculated values were correct in the original version.

Commenter 3:
Roberta Blank
Chief, Site Cleanup Section 1, Superfund Division
U.S. EPA
Region IX
75 Hawthorne Street
San Francisco, CA 94105

Comment 3.1
A major component of the EPA Institutional Controls Program for the Palos Verdes Shelf site is educating the public on the current state sport fish consumption guidelines. The current state fish advisory for DDTs uses an excess cancer risk of 10^{-5}. The proposed GTLs use a 10^{-4} level. The GTLs guidance cites that other states (e.g., Georgia and West Virginia) use the risk level of 10^{-4} in fish consumption advisories. However, these states have not used a risk level of 10^{-5} before, while California has been using 10^{-5} cancer risk endpoint for at least 15 years. No rationale for this change is provided.

Response 3.1
The rationale for the current protocol was discussed in the draft document. The 10^{-5} risk level was not consistently used for all chemicals in the Southern California sport fish consumption guidelines and has not been the basis for other advisories. Over the last 15 years, a tremendous amount of data has been published on the benefits of fish consumption – information that was not available when the 10^{-5} risk level was initially used. As scientific knowledge and protocols continue to expand or develop, our understanding of the risk and benefits of fish consumption have increased. The revised document has greatly expanded the discussion of the benefits of fish consumption and the reasoning behind the choice of the 10^{-4} risk level. In their fish advisory guidance document, U.S. EPA allows states to choose risk levels ranging from 10^{-4} to 10^{-7}. OEHHA concludes that, while it should be a goal to maintain a risk level of $1x10^{-6}$, when considering the counterbalancing benefits of fish consumption, a risk level of $1x10^{-4}$ is

appropriate. Setting the risk level at $1x10^{-5}$ or $1x10^{-6}$ would restrict fish consumption to the extent that it could largely deny fishers the numerous health benefits that can be accrued by fish consumption.

Comment 3.2
The draft GTLs are consistent with the FDA cancer risk level used for establishing tolerance levels in fish. However, the underlying assumptions used in the FDA methodology were not intended to be protective of recreational, ethnic, and subsistence fishers who typically consume larger quantities of fish than the general population and often harvest the fish and shellfish they consume from the same local water bodies repeatedly over many years, such as in the case for PV Shelf. The EPA national guidance states that "the FDA action levels and tolerances are indicators of chemical residue levels in fish and shellfish typically purchased in supermarkets or fish markets that sell products that are harvested from a wide geographic area, including imported fish and shellfish products."

Response 3.2
The reference to the FDA tolerance level for PCBs has been removed.

Comment 3.3
Using a cooking reduction of 30% in volume of fish consumed would increase the allowable contaminant intake in the screening value. Using this factor is inconsistent with the EPA national guidance for fish advisories. In addition, the assumption of skin-off fillet is not protective of sensitive populations such as ethnic populations who often eat whole fish, and fish stew and/or soup.

Response 3.3
Appendix C in U.S. EPA's Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories, Vol. 2, discusses dose modifications that may be used to adjust for food preparation and cooking. Various surveys in California have shown that the majority of fishers eat skin-off, cooked fish. OEHHA will provide differential advice for those that prepare and cook fish in the safest manner as well as those that do not (see 2.3 above).

Comment 3.4
For chlordane, DDT and PCBs, the noncancer endpoint is not protective of effects for children. The 10^{-5} indirectly provides protection to these sensitive populations as the 10^{-5} value is the more conservative value. However, the use of 10^{-4} risk level does not provide this indirect buffer.

Response 3.4
OEHHA is not aware of any compelling evidence that children have increased susceptibility to DDTs that is not accounted for by the current RfD. OEHHA is currently assessing whether children may have increased susceptibility to PCBs under our SB 25 toxic air contaminants program. RfDs are generated taking into account the most

sensitive population; in particular, the RfD for PCBs is deemed protective of neurodevelopmental effects in fetuses and children as those occurred at a higher dose than the critical effect. The RfDs for DDTs and PCBs have uncertainty factors of 100 and 300, respectively, which should offer ample protection should additional adverse effects of these contaminants be determined later. If new research allows development of a childhood-specific RfD, like that for mercury or chlordane, OEHHA will reevaluate fish consumption guidelines at that time.

Comment 3.5
The draft GTLs guidance states that "Even if fishers fish the same location for 70 years, their exposure to such chemicals will undoubtedly decline significantly over this period" due to decline in levels in the environment. When the duration of exposure increases, even if there is a decline in contaminant levels, it is possible that the increase in the exposure time outweighs the decline in contaminant levels. At this time, we have not fully evaluated the existing and current data to corroborate the assumption that the levels of these contaminants are declining in the environment.

Response 3.5
The assumption of a 30 year exposure from fish consumption for a particular water body is a reasonable high-end health protective assumption for assessing risk from carcinogens, given current knowledge about population mobility from various studies. This assumption may need further consideration for bioaccumulating, carcinogenic contaminants ubiquitously present in water bodies.

Commenter 4
Mark Gold, D. Env.
Director
Kirsten James, MESM
Staff Scientist
Heal the Bay
1444 9th Street
Santa Monica, CA 90401

Comment 4.1
OEHHA should decrease the allowed cancer risk level in calculating GTLs and SVs to maintain the 10^{-5} end point for carcinogens to adequately protect sensitive subpopulations such as ethnic subsistence fishers, pregnant women and children. The lines of reasoning provided by OEHHA for the 10^{-4} risk level are not sufficient to justify the increase in allowed cancer risk. The FDA methodology used to calculate their level of acceptable risk cited in the draft report assumes that the population consumes a smaller number of fish from multiple sources; in this case, the draft report calculations are intended to protect people who consume fish from *local* water bodies. Finally, the draft report implies that consuming a certain amount of fish may be more important than avoiding contaminant exposure. Not only does this conclusion appear to be outside the purview of OEHHA, it is not well justified in the draft report. In sum, there is no appropriate

rationale provided in the Draft Report to justify the change to a less protective endpoint. OEHHA should use an allowed cancer risk level of 10^{-5} in calculating GTLs and SVs to be sufficiently protective of human health particularly under circumstances that occur in California. This lower value would serve as a "buffer" for other non-conservative assumptions relied upon by OEHHA as discussed below.

Reponse 4.1
OEHHA has removed the SVs from the draft report; see additional discussion below. Instead, OEHHA has provided Fish Contaminant Goals (FCGs) that maintain very conservative assumptions and may be used by other agencies as a starting point for developing fish tissue-based criteria.

The reference to the FDA tolerance limit for PCBs has been removed.

OEHHA (formerly of the Department of Health Services) has discussed balancing the risk and benefits of fish consumption since as early as 1986 (California Department of Health Services. Balancing the scales: Weighing the benefits and risks of fish consumption. Proceedings of a workshop held in Concord, California, October 20, 1988.). With the vast amount of data that has become available on the benefits of fish consumption in the last few years, OEHHA determined that this section should be significantly expanded in the final report. OEHHA believes that using a 10^{-4} risk level best balances known health benefits with cancer risks of fish consumption. Setting the risk level at $1x10^{-5}$ or $1x10^{-6}$ would restrict fish consumption to the extent that it could largely deny fishers the numerous health benefits that can be accrued by fish consumption.

Comment 4.2
OEHHA should ensure that GTLs and SVs are protective of the entire population including several sensitive subpopulations. The GTLs and SVs are not protective of certain highly relevant population groups, including children, pregnant women, and ethnic subsistence fishers. For example, the authors make various assumptions about the consumer in developing the GTLs and SVs, such as assuming a body weight of 160 pounds and a normal meal size of 6 ounces after cooking. While these assumptions are accounted for somewhat in the Draft Report by including recommendations to adjust the amount of fish consumed based on the weight of the consumer, OEHHA is also proposing to base the screening values upon the same characteristics of an average adult, thus failing to account for other routinely exposed groups of the population. In addition, under this assumption, OEHHA appears to recommend that children under 40 pounds should not eat any fish at all and kids under 80 pounds should not eat a tuna fish sandwich (based on a 2 oz serving size). This is not realistic. There is ample evidence that children in California consume local fish regularly and often, and thus are exposed to these contaminants. To adequately protect all consumers, OEHHA should use a much more conservative (lower) body weight in calculating the GTLs and SVs.

Response 4.2
The assumption of a 70 kg adult body weight is standard risk assessment protocol and six ounces after cooking is considered a standard fish meal size. Because there is a strong positive correlation between food consumption and body weight, particularly when averaged over a lifetime as the risks and hazards are, most risk assessments simply assume the concomitantly reduced consumption rate for lower body weights rather than stating it explicitly. In the final document, simplified instructions will be added to reduce meal sizes proportionately to body weight. Additionally, 70 kg is currently well below the average adult body weight for males and females, making the use of this default value a conservative assumption.

Comment 4.3
The cooking reduction factor of 30 percent and skin-on reduction factor of 20 percent should be removed from the calculations of GTLs and SVs. The GTL calculations also incorporate a cooking reduction factor of 30 percent and a skin-on reduction factor of 20 percent based on a theory that the process of heating the fish will break down organic contaminants and most consumers do not eat skin-on fish. This may be appropriate under some circumstances, but not in *all* cases. First, the specific method of cooking may determine the extent of breakdown of these organic constituents. For instance, searing the fish or cooking the fish in a stew may lead to a reduction in organic contaminants that is much lower than 30 percent. Second, methylmercury will not likely breakdown during the cooking process. Third, ethnic subsistence fishermen are put at additional risk under this assumption because they often use the whole fish (not a fillet) with skin-on. For instance, a fish consumption study found that of Asian anglers surveyed, 50 percent consume the whole fish. In fact, white croaker, a popular fish in Asian communities, is *rarely* eaten as a fillet. Thus, as just one example, Asian populations are not properly protected using these reduction factor assumptions. And again, while the draft report recommends reducing consumption if skin-on fillets are used, the screening values do not take this variable into account. Plainly, the reduction factors increase the allowable contaminated fish consumption in the screening values and will lead to fewer fish advisories and thus less protection for all groups of consumers. OEHHA should remove the 30 percent cooking reduction factor and 20 percent skin-on reduction factor in calculating the GTLs and SVs.

Response 4.3
See response to comments 2.2, 2.3, and 3.3. As noted in the draft document, the cooking and skinning reduction factors are not applied to mercury data. Mercury analysis of skin-off fillets provides more conservative fish consumption advice than analysis of skin-on fillets would (see response 2.4).

Comment 4.4
OEHHA should consider the policy implications of the draft report. There are additional water quality policy issues tied to the finalization of this draft report. Currently, California's Clean Water Act 303(d) list relies heavily on OEHHA Screening Values to determine fish tissue impairment. In fact, the *Water Quality Control Policy for*

Developing California's Clean Water Act 303(d) List ("Listing Policy") specifies that evaluation guidelines for protection from the consumption of fish and shellfish published by OEHHA can be used in evaluating fish tissue data for 303(d) listing and de-listing purposes. (Listing Policy at 20.) As a result, various listings and delistings in the Draft 2006 303(d) List are based upon the current OEHHA SVs or "benchmarks." In addition, the Listing Policy specifies that a waterbody "…shall be placed on the section 303(d) list if a health advisory against the consumption of edible resident organisms, or a shellfish harvesting ban has been issued by the Office of Environmental Health Hazard Assessment (OEHHA)." (Listing Policy at 5.) Further, numeric targets in certain TMDLs are derived from these screening values.

As discussed above, the Draft Report uses a risk level of 10^{-4}. In contrast, water quality standards, such as CTR standards, were set using the 10^{-6} risk level. Thus, there may be conflict between the protection offered through the Clean Water Act and policy decisions based upon the GTLs and SVs that are calculated using the 10^{-4} risk levels. In addition, the SVs included in the Draft Report are as much as 6 times higher than the 1999 OEHHA SVs. This may result in many inappropriate de-listings from the 303(d) list, resulting, in turn, in a failure to address the underlying problem at the source. Given the seriousness of the risks here, this is entirely inappropriate.

Response 4.4
As noted above, the SVs have been removed from the final document. Fish Contaminant Goals (FCGs), developed in this final report, use a 10^{-6} risk level. Agencies can use these values as a starting point to develop fish tissue-based criteria. GTLs (now ATLs) are not regulatory standards. OEHHA does not determine policies developed by other state programs. However, if other state programs choose to consider or use values that OEHHA has developed for some other purpose, then it is advisable that they consult with OEHHA to avoid any misuse or misinterpretation. (See response 1.1).

Comment 4.5
In general, OEHHA will be taking a step backward in terms of protecting public health if it adopts the non-conservative assumptions proposed in this Draft Report. As discussed above, there are major implications for sensitive subpopulations – particularly children and ethnic Asian subpopulations. An allowable cancer risk level of one in 10,000 is just not acceptable given these variable consumption patterns and practices. Therefore, we *strongly* urge OEHHA to maintain the 10^{-5} endpoint, as well as to use more conservative assumptions in calculating the GTLs and SVs.

Response 4.5
OEHHA has addressed the "non-conservative" assumptions in prior responses to comments. OEHHA has determined that highly conservative assumptions, as used in traditional risk assessment paradigms, are not protective of overall health when considering fish consumption. However, in response to comments regarding the cooking reduction factor, separate advice may be tailored to those who do not cook or clean according to OEHHA recommendations. OEHHA maintains that using a 10^{-4} risk level

best balances the cancer risks and benefits (health and economic) of sport fish consumption as well as the risks of alternate protein sources that might be consumed in place of sport fish. Setting the risk level at $1x10^{-5}$ or $1x10^{-6}$ would restrict fish consumption to the extent that it could largely deny fishers the numerous health benefits that can be accrued by fish consumption. OEHHA does not agree with the premise that "sensitive subpopulations" are not accounted for in the advisory process. All consumers who follow the advice are equally protected based on known sensitivities. When there is compelling evidence that women or children are more susceptible to a contaminant (e.g., mercury), the advisories provide separate advice for their protection.

Commenter 5
Joseph P. Skorupa, Ph.D.
Clean Water Act Biologist
Environmental Contaminants Branch
Division of Environmental Quality
U.S. Fish and Wildlife Service
4401 N. Fairfax Drive, Rm. 322
Arlington, VA 22203

Comment 5.1
This is a wonderfully well done report that should be viewed as "state of the art" in its niche.

Comment 5.2
"Avians" is not an accepted noun.

Response 5.2
Changed "avians" to birds.

Comment 5.3
It would be helpful to provide the reference dose as μg/day, in addition to mg/kg-day, to facilitate comparison to the RDA.

Response 5.3
Additional units included.

Comment 5.4
Is the advice for reducing consumption by approximately one-fourth for skin-on fillets really applicable to selenium?

Response 5.4
Language altered to indicate that, of the chemicals evaluated, reduction of contaminant levels by cooking and skinning is only applicable to chlorinated hydrocarbons, rather than "organics" as stated.

Comment 5.5
The equations presented on page 39 result in calculated outcomes expressed on a ppm (mg/kg) basis, yet the summary table of outcomes, Table 1, presents everything on a ppb basis. It would be an improvement to make the equations and outcomes table internally consistent.

Response 5.5
The equations include mg/kg units because the reference doses and cancer slope factors are presented in those units. Conversion factors were included in the equations to change the outcome units to ppb (μg/kg), to coincide with the most convenient way of expressing fish contaminant levels as presented in Table 1 and Table 2.

Comment 5.6
The selenium screening value is expressed on a wet weight basis. Many historic fish tissue databases are expressed on a dry weight basis without corresponding percent moistures and, thus, there is no way to convert the values to a wet weight basis. EPAs new tissue-based chronic criterion value for selenium will be issued on a dry weight basis. It would be useful to provide a conversion to dry weight basis for a range of fish species.

Response 5.6
Screening values have been eliminated from the document. However, fish collected for human health assessments must be based on wet weight analysis; dry weight data for individual or composite fish samples are not consistently available. OEHHA will leave developing national conversion factors for multiple species to other agencies.

Commenter 6
David McBride
Office of Environmental Health Assessments
Division of Environmental Health
Washington State Department of Health
P.O. Box 47846
Olympia, WA 94504

Comment 6.1
Overall the document read well and its purpose was clearly stated. Calculations of GTLs and screening level values were checked and consistent with our calculations. Appropriate studies are cited to support your selection of toxicity criteria.

Comment 6.2
Within the introduction, it may be useful to give subheadings to the sections dealing with the development of screening level values and for establishing GTLs. A brief description of the equation for deriving GTLs for cancer endpoints similar to the noncancer equation would be useful. The differences in the two equations could be explained, briefly describing the differences in averaging times used in the two calculations.

Response 6.2
An equation for deriving GTLs (now ATLs) for cancer endpoints was included. The SVs are no longer included in the final document.

Comment 6.3
Within the introduction, it would be helpful to list major data sources and give a brief description of the programs that they are collected under. Fish tissue collection and analysis is often conducted for reasons other than to evaluate human health concerns. Therefore, the adequacy of the database should first be determined.

Response 6.3
This information is outside the scope of this document. It is presented in the Health Advisory and Safe Eating Guidelines for each water body. Recommendations for sampling are included in the report "General Protocol for Sport Fish Sampling and Analysis," by Gassel and Brodberg, 2006.

Comment 6.4
A summary table should be included with the contaminants of concern and their corresponding cancer and noncancer values separate from the GTL calculated concentrations.

Response 6.4
Cancer and noncancer values are presented in at least two places in the document, including Table 1. OEHHA feels that including another separate table of these values is not necessary, given that they are clearly presented in the toxicology profiles and in the derivation of the ATLs.

Comment 6.5
A brief discussion on the consumption rate used to establish screening level values. What are they based on and what populations do they protect or not protect?

Response 6.5
The screening values have been removed from the final document.

Comment 6.6
The discussion of the Guidance Tissue Levels for the various contaminants is easy to follow and provides appropriate background on use of various parameters considered.

Comment 6.7
Consider graphing contaminant meal recommendations with contaminant concentrations.

Response 6.7
Graphs were presented by the commenter as another way of looking at GTLs (now ATLs). We didn't find that these added to the clarity or usefulness of the document.

Comment 6.8
We find that people often get hung up on the numbers such as GTLs but are unaware that these values are generally a starting point in determining what the recommended meal limits should be. Left out of the discussion is the risk management and risk communication aspects in evaluating fish.

Response 6.8
OEHHA agrees that the ATLs are just a starting point for developing fish consumption guidelines. We have attempted to strengthen the language in the document to make that point. A brief discussion of risk communication has been added to the document, but risk communication details are developed as part of individual safe eating guidelines for specific water bodies.