OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

GOOD CATCH CALIFORNIA
*Your Fish Advisor*

# Development of Advisory Tissue Levels for California Sport-harvested Finfish and Shellfish:

# CADMIUM

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# PREFACE

The Office of Environmental Health Hazard Assessment (OEHHA), a department in the California Environmental Protection Agency, is responsible for evaluating potential public health risks from chemical contamination of sport-harvested fish.[1] This includes issuing health advisories for finfish and shellfish consumption, when appropriate, for the State of California. OEHHA's authority to conduct these activities is based on mandates found in the following codes:

- California Health and Safety Code
  - Section 59009, to protect public health
  - Section 59011, to advise local health authorities
- California Water Code
  - Section 13177.5, to issue health advisories.

The health advisories are posted on OEHHA's website and published in the California Department of Fish and Wildlife's inland and ocean sport fishing regulations in the public health advisories section.[2]

Health advisories are based on Advisory Tissue Levels (ATLs), which are chemical levels in fish[3] tissue that are considered acceptable, based on chemical toxicity, for a range of consumption rates. ATLs also incorporate consideration of health benefits associated with including fish in the diet (OEHHA, 2008), one of the differences between ATLs and other chemical evaluations conducted by OEHHA, for instance the development of "no significant risk levels" and "maximum allowable dose levels" for chemicals listed under Proposition 65.

In 2008, OEHHA published ATLs for seven common fish contaminants (chlordane, dichlorodiphenyltrichloroethane [DDT] and its metabolites, dieldrin, methylmercury, polychlorinated biphenyls [PCBs], selenium, and toxaphene) (OEHHA, 2008). In 2011, OEHHA published ATLs for polybrominated diphenyl ethers (PBDEs) (OEHHA, 2011). Cadmium is another common environmental contaminant that can accumulate in finfish and shellfish. This report provides ATLs for cadmium, based on an existing toxicity analysis by OEHHA under the Public Health Goal program (OEHHA, 2006).

[1] Sport-harvested fish includes all finfish and shellfish caught from California waters for non-commercial purposes (e.g., recreational, tribal/cultural, and subsistence practices).
[2] The California Department of Fish and Wildlife's inland and ocean sport fishing regulations can be found online at: https://wildlife.ca.gov/Fishing/Inland and https://wildlife.ca.gov/Fishing/Ocean, respectively.
[3] The term "fish" as used in this document includes finfish and shellfish, except when specified.

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## EXECUTIVE SUMMARY

This report presents Advisory Tissue Levels (ATLs) for cadmium in California sport-harvested[4] finfish and shellfish. The ATLs were developed with consideration of both the unique health benefits associated with fish[5] consumption and the fact that fish can be a significant exposure pathway for several contaminants of concern. The ATLs developed in this report will be used to develop health advisories for sport-harvested finfish and shellfish based on cadmium tissue levels.

Food is the predominant oral cadmium exposure source for people. Cereals and breads, leafy vegetables, and potatoes are the primary contributors to the average total cadmium intake for the US population (Kim et al., 2019). These foods are a greater source of cadmium than finfish and shellfish for many people, especially those who seldom or never consume fish. However, individuals who frequently consume fish, especially shellfish, may have an increased cadmium burden. This may pose health risks.

ATLs are based on toxicity determinations that indicate an acceptable amount of a chemical that can be consumed without significant risk of harmful effects, taking health benefits into account. For exposure to cadmium from sport-harvested finfish and shellfish, OEHHA developed a reference value based on the risk assessment for cadmium in drinking water developed by the Public Health Goal (PHG) program (OEHHA, 2006). That value is based on studies of kidney toxicity[6] in humans due to oral cadmium exposure. Because the ATL is based on the most sensitive endpoint for cadmium (i.e., kidney toxicity), the reference value developed by OEHHA for the Fish Advisory Program is assumed to be protective against the other adverse effects from oral exposure to cadmium, including developmental toxicity.

OEHHA developed cadmium ATLs (*see table below*) for all populations based on 4-ounce and 8-ounce serving sizes. The ATLs were developed for 4-ounce sizes for two reasons: (1) bivalve shellfish, such as mussels and oysters, typically accumulate cadmium to a greater extent than finfish or other shellfish species (Olmedo et al., 2013), and (2) they are typically consumed in smaller quantities during a single eating occasion than other types of finfish and shellfish (Tran et al., 2013). OEHHA also developed a second set of ATLs based on an 8-ounce serving size for use in issuing fish advisories for crustaceans and finfish.

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[4] Sport-harvested fish includes all finfish and shellfish caught from California waters for non-commercial purposes (e.g., recreational, tribal/cultural, and subsistence practices).
[5] The term “fish” as used in this document includes finfish and shellfish, except when specified.
[6] Throughout this document, “toxicity” refers to non-cancer toxicity; in some cases, the document specifically refers to “kidney toxicity”. Kidney toxicity is synonymous with “renal” toxicity.

OEHHA determined that different sets of ATLs for cadmium should be developed for the following populations: (1) pregnant individuals (sensitive population), and (2) non-pregnant individuals (general population). OEHHA developed advice for the sensitive population on a meal-per-week rather than a meal-per-month basis. This approach can be especially protective during pregnancy when exposure to higher amounts of cadmium over a short period of time can disrupt placental development, increasing the risk of harm to the fetus. For the general population, OEHHA includes one and two meal-per-month frequency categories. This allows for meals with higher amounts of cadmium to be eaten, but less frequently—monthly rather than weekly. This considers the fact that many individuals in the US may only occasionally consume higher-cadmium-containing bivalve shellfish, such as oysters. Weekly advice is also provided, which allows more meals containing cadmium, but a lower amount per meal. The risk for cadmium toxicity in the general population is largely a function of total body burden over time.

EXECUTIVE SUMMARY TABLE. ADVISORY TISSUE LEVELS FOR CADMIUM: 4- AND 8-OUNCE SERVING SIZES

| Consumption Frequency Categories (4- or 8-ounce servings per week or month)[a,b] and ATLs (in ppb)[c] for Pregnant and Non-Pregnant Individuals | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Population Group** | **Serving Size (ounces)** | **Servings per Week** | | | | | | | **Servings per Month** | | |
| | | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 2 | 1 | No consumption |
| **Pregnant Individuals** | **4** | ≤39 | >39–46 | >46–55 | >55–69 | >69–92 | >92–140 | >140–280 | n/a | n/a | >280 |
| | **8** | ≤20 | >20–23 | >23–28 | >28–34 | >34–46 | >46–69 | >69–140 | n/a | n/a | >140 |
| **Non-pregnant Individuals** | **4** | ≤39 | >39–46 | >46–55 | >55–69 | >69–92 | >92–180 | >180–550 | >550–1,100 | >1,100 – 2,200 | >2,200 |
| | **8** | ≤20 | >20–23 | >23–28 | >28–34 | >34–46 | >46–92 | >92–280 | >280 –550 | >550–1,100 | >1,100 |

[a] Serving sizes (prior to cooking, wet weight) are based on an average 160-pound person. Individuals weighing less than 160 pounds should eat proportionately smaller amounts. OEHHA fish advisories provide guidance about serving sizes for children that consider their relatively smaller body size.

[b] OEHHA will typically use a 4-ounce serving size for developing advice for bivalves and an 8-ounce size for crustaceans and finfish.

[c] ppb = parts per billion

n/a = not applicable

## ADVISORY TISSUE LEVELS FOR CADMIUM IN CALIFORNIA SPORT-HARVESTED FINFISH AND SHELLFISH

### *INTRODUCTION*

This document establishes Advisory Tissue Levels (ATLs) for cadmium. ATLs, are contaminant concentrations in sport-harvested fish[7] that, taking into account the health benefits associated with eating fish,[8] pose no significant health risk[9] to the individuals consuming them in the quantities shown over a lifetime. ATLs are developed using the specific methodology and for the limited purposes described below. They are not intended to apply to finfish and shellfish that are sold commercially. ATLs provide recommended consumption frequencies (i.e., meals per week or month) for a specified contaminant in finfish and shellfish.

This adds to the existing ATLs published by the Office of Environmental Health Hazard Assessment (OEHHA). OEHHA previously published Fish Contaminant Goals (FCGs) and ATLs for polybrominated diphenyl ethers (PBDEs) in 2011 and FCGs and ATLs for seven other common fish contaminants (chlordane, DDTs,[10] dieldrin, methylmercury, polychlorinated biphenyls [PCBs], selenium, and toxaphene) in 2008 (OEHHA, 2008 and 2011).

FCGs are estimates of contaminant levels in fish that pose no significant health risk to individuals consuming sport-harvested fish at a standard consumption rate of eight ounces per week (equivalent to 227 grams [g] or ~32 g/day if averaged over 7 days), prior to cooking, over a lifetime. ATLs present no significant health risk to individuals consuming sport-harvested fish in the quantities shown over a lifetime by maintaining risk within acceptable toxicity benchmarks (e.g., hazard quotient for non-cancer endpoint). These thresholds differ from FCGs because ATLs were developed with the recognition that there are unique health benefits associated with fish consumption and the advisory process should promote the overall health of the fish consumer. Both FCGs and ATLs discourage consumption of fish in amounts that should not be eaten because of contaminant concentrations. But because ATLs balance the health benefits and risks

[7] Sport-harvested fish includes all finfish and shellfish caught from California waters for non-commercial purposes (e.g., recreational, tribal/cultural, and subsistence practices).
[8] The term “fish” as used in this document includes finfish and shellfish, except when specified.
[9] The term “no significant health risk” used in this document, other OEHHA risk assessments (e.g., Drinking Water Public Health Goals), and by other scientific agencies (e.g., Centers for Disease Control and Prevention Agency for Toxic Substances and Disease Registry), describes the negligible risk for adverse health effects associated with a specific chemical when exposed at levels (e.g., toxicity reference value) that are unlikely to cause harm over a specific time period (e.g., single eating occasion). This is distinct from a “no significant risk level” (NSRL) safe harbor level established for a listed carcinogen under Proposition 65.
[10] Dichlorodiphenyltrichloroethane (DDT) and its metabolites, dichlorodiphenyldichloroethane (DDD) and dichlorodiphenyldichloroethylene (DDE)

associated with sport-harvested fish consumption (whereas FCGs[11] consider only risk), they serve as the foundation for developing OEHHA fish consumption advisories. The general process and calculations used to develop the FCGs and ATLs are discussed in detail in OEHHA (2008).

In general, OEHHA develops ATLs using non-cancer reference values and cancer slope factors developed internally, or that are available from the US Environmental Protection Agency (US EPA) or other authoritative sources. A reference value based on the critical effect, typically the most sensitive endpoint, is treated as protective against other adverse effects (e.g., liver or reproductive toxicity) because those effects are expected to be observed at higher exposure levels than the critical effect, via the same route of exposure. As discussed below, OEHHA determined that it was appropriate to develop ATLs for cadmium based on a non-cancer critical effect (i.e., kidney toxicity). To develop ATLs for cadmium, OEHHA reviewed reference values from various authoritative sources with respect to methodology, scientific rationale, and supporting documents.

OEHHA has derived two oral reference values for cadmium. Pursuant to Proposition 65, OEHHA developed a single-day Maximum Allowable Dose Level (MADL) for cadmium based on developmental toxicity. OEHHA also developed a reference value based on the critical effect of kidney toxicity[12] in the 2006 cadmium Public Health Goal (PHG) (OEHHA, 2006). OEHHA modified the reference value from the PHG to establish the acceptable daily dose via fish consumption, or "$ADD_{fish.}$" This value represents an estimate of the maximum average daily dose of cadmium from fish that can be consumed for a lifetime without adverse effects (e.g., kidney or developmental toxicity).

OEHHA is issuing ATLs to provide cadmium-based consumption advice for sport-harvested finfish and shellfish. Although applicable to other sport-harvested finfish and shellfish species, the cadmium ATLs were developed primarily for bivalve shellfish, such as clams, oysters, scallops, and mussels, with the recognition that cadmium accumulates in these species to a higher extent than in other types of finfish or shellfish (Lakshmanan, 1988; Olmedo et al., 2013; Silva de Araújo et al., 2016; Djedjibegovic et al., 2020). Based on analyses of the US Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES) dietary data that account for both serving size (i.e., amount per meal or eating occasion) and meal frequency, bivalve shellfish are usually consumed less frequently, and in a smaller quantity per eating occasion, than finfish (Tran et al., 2013). OEHHA thus included a 4-ounce meal

[11] Calculated FCG value for cadmium has a maximum hazard quotient of ~1, and is equivalent to the maximum ATL value for the sensitive (pregnant) population at the one meal per week frequency (i.e., 280 ppb, 4-ounce serving [Table 1]; 140 ppb, 8-ounce serving size [Table 2]).
[12] Throughout this document, "toxicity" refers to non-cancer toxicity; in some cases, the document specifically refers to "kidney toxicity". Kidney toxicity is synonymous with "renal" toxicity.

size when developing the ATLs for cadmium in addition to the 8-ounce meal size that was used for other contaminants (see OEHHA, 2008 and 2011). Additional meal frequency categories of one or two meals per month were included for non-pregnant consumers.

## *CADMIUM EXPOSURE SOURCES*

Cadmium is a metal naturally occurring in the earth's crust but rarely found in its elemental form (EFSA, 2009a; IARC, 2012). Food is the predominant oral cadmium exposure source for humans in the general population (ATSDR, 2012; EFSA, 2009a; Olsson et al., 2002; WHO, 1992). However, exposure via inhalation is a major contributing source among cigarette smokers and workers in occupational settings where cadmium aerosols are released (ATSDR, 2012; Bernard et al., 1979; EFSA, 2009a; Morrow, 2010; WHO, 1992).

Ionized cadmium typically forms complexes with organic and inorganic substances (ATSDR, 2012; Cullen and Maldonado, 2013; Schaefer et al., 2020) and moves easily from soil to plants (Hajeb et al., 2014), depending on factors such as soil pH, organic matter, temperature (Roberts, 2014; Ismael et al., 2019), and plant species (Clemens et al., 2013). Its mobility within environmental media is enhanced with increased soil salinity (Roberts, 2014) and acidity in terrestrial (Ismael et al., 2019) and aquatic environments (Cullen and Maldonado, 2013; McLaughlin et al., 1999; Roberts, 2014; Schaefer et al., 2020). Acidic conditions favor the release of the more toxic, soluble ionic form of cadmium ($Cd^{2+}$) from these organic complexes (Meng et al., 2018). This form more readily binds to sulfur-containing proteins (e.g., metallothionein) and accumulates in plant (Ismael et al., 2019) and animal tissues (ATSDR, 2012; Hajeb et al., 2014; Ismael et al., 2019; WHO, 1992). Shi et al. (2016) observed that increased cadmium accumulation in bivalves correlated with overall seawater acidification.

Based on NHANES 2007-2012 data, the primary food groups contributing to the average total cadmium intake for individuals in the United States aged two years and older were cereals and bread (34%), leafy vegetables (20%), and potatoes (11%) (Kim et al., 2019). In terms of exposure, when averaged over the entire population, finfish and shellfish contribute less than 1% of total dietary cadmium (Kim et al., 2019). However, individuals who regularly consume shellfish can have an increased cadmium burden, so it is important to develop advice for this population. For frequent consumers in particular, bivalve shellfish can be a significant contributor to their overall cadmium burden.

Cadmium exposure from shellfish and other seafood for an individual is dependent on the amount and type of seafood consumed (e.g., finfish versus shellfish, including bivalves) (Olmedo et al., 2013), and where the seafood was harvested (Copes et al., 2008; Kruzynski, 2002 and 2004).

Bivalves are known to bioaccumulate cadmium, particularly because of their higher metallothionein (MT) levels compared to many other finfish and shellfish species (Copes et al., 2008; EFSA, 2009a; FOC, 2010; Pacific Shellfish Institute et al., 2008; Shi et al., 2016; WHO, 1992). Finfish and non-bivalve shellfish, including crab, lobster, and shrimp, can also accumulate cadmium, though usually to a lesser degree than bivalves (Ju et al., 2012; Lakshmanan, 1988; Olmedo et al., 2013). Frequently consuming finfish and shellfish with high cadmium levels may considerably increase total dietary cadmium exposure.

Cadmium concentrates in the internal organs (e.g., liver, kidneys) of humans and animals, including the digestive organs of finfish and shellfish (Cao et al., 2012; Cogun et al., 2017; de Conto Cinier et al., 1999; Morrow et al., 2001 and 2010; Widmeyer and Bendell-Young, 2008), through binding to cysteine-rich low molecular weight proteins, like MT (ATSDR, 2012; Clemens et al., 2013; Hajeb et al., 2014; Nordberg and Nordberg, 2022; WHO, 1992). Limiting consumption to only the fillet or "meat," as recommended by OEHHA, may significantly reduce an individual's potential cadmium exposure from finfish and some crustaceans (e.g., crab or lobster). However, the edible portions of bivalve shellfish typically include both the meat and viscera; thus, consumers may be exposed to considerably more cadmium from consuming whole bivalve shellfish compared to consuming a similar portion of a finfish fillet or crab/lobster body or meat.

## *CADMIUM TOXICITY*

OEHHA conducted an extensive literature search to identify human or animal studies on the toxic effects of cadmium following oral exposure. In addition to targeted searches executed in scientific databases (e.g., PubMed), OEHHA also reviewed OEHHA programmatic risk assessments for oral cadmium exposure, reference lists of included literature search papers, and systematic reviews conducted by authoritative bodies, particularly the US Food and Drug Administration (US FDA). These resources were evaluated to determine the most appropriate health effect to serve as the basis for and establish a suitable oral toxicity reference value for calculating the cadmium ATLs.

Cadmium has numerous adverse effects on a variety of organs (Nordberg et al., 2018) and is classified as carcinogenic to humans (IARC, 2012). Exposure to cadmium and cadmium compounds is known to cause human lung cancer following inhalation exposures. Inhalation of cadmium has also been positively associated with kidney and prostate cancer (IARC, 2012; OEHHA, 2006).

For ingestion, OEHHA concluded in the 2006 PHG report for cadmium (pg. 60) that, "While cadmium has been identified as a human carcinogen, the available studies are not sufficient to characterize the carcinogenic risk associated with oral exposure to this metal." In the absence of this evidence and the lack of a

suitable oral cancer slope factor or other cancer value to develop ATLs based on a cancer endpoint, OEHHA only evaluated non-cancer toxicity for the ATL.

Cadmium's primary and most extensively studied target of toxicity following chronic oral exposure is the kidney (ATSDR, 2012; Bernard, 2008; EFSA, 2009a; Elinder et al., 1985; Jakubowski et al., 1987; Nordberg et al., 2018). The most sensitive toxicity endpoint is proximal renal tubular injury as evidenced by urinary excretion of specific low molecular weight proteins, such as beta-2 microglobulin (B2M) (ATSDR, 2012; EFSA, 2009a and 2009b; Nordberg et al., 2018; Piscator, 1984; US EPA, 1989). Cadmium-induced kidney toxicity is a function of body burden (i.e., how much of the metal is accumulated in the body, specifically the kidney) (Nordberg et al., 2018). Factors that affect the body burden of a chemical include exposure, absorption, and half-life (10 – 30 years for cadmium; Elinder et al., 1976; Jarup and Akesson, 2009).

Cadmium-related toxicity from chronic oral exposure is closely linked with MT levels, an important low molecular weight protein that facilitates metal storage (e.g., zinc, iron) and detoxification (Nordberg and Nordberg, 2022; Sabolic et al., 2010; Zlotkin and Cherian, 1988). Cadmium has a high affinity for MT and readily forms complexes with it for uptake into MT-rich depots, including the liver, kidneys, and placenta (Cherian, 1979; Kippler et al., 2010; Sabolic et al., 2010). Exposure to heavy metals like cadmium induces MT synthesis as a detoxification mechanism in these common targets of cadmium-induced toxicity (Habeebu et al., 2000; Nordberg and Nordberg., 2022; Sabolic et al., 2010). The role of MT in mitigating toxicity has been demonstrated in rodent studies, where repeated exposure to cadmium via the subcutaneous route induced increased synthesis of MT, with subsequent sequestration of cadmium in an inert form, resulting in reduced kidney toxicity (Liu et al., 1998 and 1999; Nordberg et al., 1994; Nordberg and Nordberg, 2022). However, when the total amount of cadmium accumulated in the kidney exceeds the amount of MT available for binding, renal damage can occur (Nordberg and Nordberg, 2022). Thus, available MT serves a critical protective function in reducing cadmium-induced kidney toxicity from chronic oral exposure (Liu et al., 1999).

Older (> ~50 years of age), peri- and postmenopausal women represent the population in which the clinical syndrome of cadmium-induced kidney toxicity (e.g., proximal tubule damage, elevated proteinuria) is most prevalent (Akesson et al., 2005). Cadmium-associated decreases in bone mineral density attributed to dietary exposure have also been reported for this population at urinary cadmium concentrations similar to those associated with early indications of kidney toxicity (Engstrom et al., 2011 and 2012; Nordberg et al., 2018). However, available studies examining adverse bone effects at relatively low estimated dietary exposure levels, such as those more typically reported for the US and European populations, are limited and interrogating these dose-response relationships in the lower ranges is confounded by factors such as nutritional

deficiencies factors and tissue-level toxicodynamics (Nordberg et al., 2018). Women are more likely to incur a greater cadmium body burden on a per weight basis over the life span due to sex-specific physiological states (e.g., pregnancy) that may enhance cadmium absorption during periods of dynamic change (Berglund et al.; 1994; Buchet et al., 1990; Elinder et al., 1976; Nishijo et al., 2004). Higher total body burden contributes to an increased risk for cadmium-related kidney toxicity later in life, particularly in multiparous[13] women (Akesson et al., 2002; ATSDR, 2012).

Oral exposure to cadmium during pregnancy may present health concerns beyond those associated with total accumulation over the lifespan, including elevated risk of harm to the fetus through potential disruption of placental development (Jacobo-Estrada et al., 2017). Cadmium may accumulate in the placenta, kidneys, and other tissues during pregnancy (Baranowska, 1995; Kippler et al., 2010; Leazer et al., 2002; Stasenko et al., 2010). Degradation of cytotrophoblastic cells critical for placental membrane formation, changes in the gene expression of metal transporter proteins (e.g., zinc transporters) in the placenta, and disruption of calcium binding proteins associated with placental cell proliferation have been observed in cadmium-treated pregnant animal and cell culture studies (Caserta et al., 2013; Espart et al., 2018; Geng et al., 2019; Liu et al., 2016; Nakamura et al., 2012; Wang et al., 2016, Zhou et al., 2016).

During pregnancy, the upregulation of gastrointestinal metal transport mechanisms to meet increased metabolic demands, coupled with other physiological changes, contributes to enhanced gastrointestinal absorption of essential nutrients (e.g., calcium, iron, and zinc) and other metals, including cadmium (Gao et al., 2015; Leazer et al., 2002). Absorption can be further increased when iron deficiency-related anemia accompanies pregnancy (Akesson et al., 2002; Mikolic et al., 2016). Increased cadmium absorption and retention has been observed in pregnant animals when compared to similarly exposed (via the oral route), non-pregnant controls (Leazer et al., 2002; Mikolic et al., 2016).

Cadmium-induced changes in placental formation and transport processes may also impact important developmental endpoints (e.g., fetal weight or length) by upregulating metal-binding proteins (e.g., MT) that detoxify but also by forming complexes with trace metals (e.g., zinc and copper) that are critical for fetal growth and development (Espart et al., 2018; Geng et al., 2019; Torreblanca et al., 1992; Zhang et al. 2016; Zhou et al., 2016). The ability of cadmium to “trade places” with essential metals (Espart et al., 2018) is an occurrence known as molecular and ionic mimicry (Bridges and Zalups, 2005) that may increase the risk for cadmium toxicity during early development. For these reasons, OEHHA

[13] Women who have given birth to more than one child.

designated pregnant individuals as the “sensitive population” for the cadmium ATL (see *Designation of Population Groups* section).

Cadmium can be excreted in the breast milk of previously exposed women (ATSDR, 2012). Though some studies report associations with early life cadmium exposure and adverse developmental impacts in younger children (e.g., 2 – 10 years of age), these findings were observed predominantly in children with some prenatal cadmium exposure (Gardner et al., 2013; Gustin et al., 2018; Ma et al., 2021; Sanders et al., 2015). Since the release of the OEHHA PHG for cadmium, newer studies have been published that investigate developmental toxicity in humans from oral exposures. Exposure of the fetus (*in utero*) or young children (via the oral route) during critical windows of development is linked to aberrations including preterm birth, low birth weight, disrupted postnatal growth (i.e., low-for-age weight and height), neurobehavioral and learning challenges (e.g., motor dysfunction, cognitive delay), and immune dysfunction (Chandravanshi et al., 2021; Cheng et al., 2016; Ciesielski et al., 2012; Gardner et al., 2013; Gustin et al., 2018; Ma et al., 2021; Salpietro et al; 2002; Sanders et al., 2015; Yang et al., 2016; Zeng et al., 2020; Zheng et al., 2016). Adverse neurobehavioral and cognitive effects associated with dietary cadmium exposure during childhood have been reported for populations in regions with historical environmental cadmium contamination and/or where high-cadmium foods (e.g., rice) are a dietary staple (Kippler et al., 2012). While these studies indicate potential adverse effects in children, the effects occurred at exposures higher than those that result in initial kidney toxicity.

During OEHHA’s toxicological review of cadmium, US FDA released two reviews that evaluated oral cadmium exposure and related adverse health effects. The first was a scoping review of dietary cadmium-associated health effects in infants and children exposed directly (i.e., by ingestion) or indirectly, (e.g., by exposure during pregnancy or lactation), in part to support FDA’s Closer to Zero Initiative, which seeks to restrict dietary exposure of these populations to toxic elements to the lowest levels possible (Flannery et al., 2022). Flannery and colleagues characterized the overall availability and scope (e.g., physiological systems and health effects evaluated) but not the quality of data reported for oral cadmium exposure-related health effects in infants and children. Based on the available literature, the studies evaluated were organized into three primary system-based categories as nervous, cardiovascular, and urinary impacts.

Studies that evaluated developmental endpoints and described adverse findings predominantly represented nervous system and anthropometric measure (e.g., birth weight) effects, including potential negative associations with cadmium exposure and decrements in full-scale IQ, attention, and birth weight (Flannery et al., 2022). Additionally, US FDA identified that cadmium exposure during pregnancy may present concerns for potential adverse birth outcomes, including at estimated oral exposure levels reported for US adult females (i.e., based on

maternal cadmium blood and urine concentrations) (Flannery et al., 2022). US FDA submitted that the availability of and/or consistency in reported findings from studies assessing cardiovascular and urinary endpoints, including kidney toxicity, were insufficient to appropriately characterize these dose-response relationships in infants and children at this time. Flannery et al. determined that most of the available data for oral cadmium-related health effects in infants and children suggest that these impacts are associated with exposure levels above those typically reported for US children (Flannery et al., 2022). OEHHA developed similar interpretations following its toxicology review of the selected primary literature, whereby non-kidney adverse health effects, including potential developmental impacts in infants and children, were reported at levels higher than those associated with the critical effect of kidney toxicity. US FDA identified several potentially significant limitations that may present data suitability challenges with evaluating oral cadmium dose-response relationships in these populations (Flannery et al., 2022). US FDA estimated that overall, these suggestive findings require more investigation and currently available data remain sparse for evaluating multiple potential health effects in infants and children.

US FDA also conducted a systematic review of oral cadmium exposure-related health effects (Schaefer et al., 2022). Schaefer and colleagues identified a select set of epidemiological (N=2) and toxicological (N=3) studies of sufficient quality (low risk of bias) to appropriately characterize oral dose-response relationships and establish the basis for deriving an oral toxicity reference value based on two critical effects, reduced bone mineral density and renal tubular degeneration (i.e., kidney toxicity). US FDA evaluated the merit and scope of several published literature reviews conducted by US and European authoritative/scientific bodies, including EFSA (2009b), JECFA (2011), ATSDR (2012), and ANSES (2017),[14] to inform the design and approach for this systematic review.

Based on this systematic approach to evaluating oral cadmium exposure-related health effects, US FDA released a companion publication describing the oral toxicological reference value (TRV), represented by a range of values to account for uncertainty (i.e., 0.21 – 0.36 micrograms cadmium per kilogram body weight per day), intended for use in food-related human health assessments (Schaefer et al., 2023). The TRV range was based on data from adult females, identified by Schaefer et al. (2023) as the more sensitive population characterized by increased gastrointestinal absorption over the lifespan when compared to men, particularly during pregnancy or in women with decreased bodily stores of iron. Using the reverse dosimetry physiologically based pharmacokinetic (PBPK)

[14] EFSA: European Food Safety Authority (2009b), JECFA: Joint Food and Agriculture Organization of the United Nations and the World Health Organization Expert Committee on Food Additives (2011), ATSDR: Agency for Toxic Substances and Disease Registry (2012), and ANSES: French Agency for Food, Environmental and occupational Health and Safety (2017)

model described by Pouillot et al. (2022), US FDA estimated a point of departure based on data from two critical epidemiological studies that incorporated bone and kidney endpoints, applied to US population focused NHANES body weight and urinary creatinine ranges (Schaefer et al., 2023). Similarly, OEHHA developed the PHG oral cadmium reference value, which was adapted for the $ADD_{fish}$, with recognition that the human adult female is the more sensitive receptor for kidney toxicity associated with oral cadmium exposure (OEHHA, 2006).

US FDA (2023) also developed a second TRV range (0.63 – 1.8 micrograms cadmium per kilogram body weight per day) using benchmark dose (BMD) analysis to estimate points of departure for bone and kidney endpoints based on high quality animal studies identified by Schaefer and colleagues (2022). BMD analyses produced similar results to the first TRV range, and further contributed to the weight of evidence that supported the cadmium TRV range informed by the epidemiological studies. US FDA noted that the human-based TRV range is comparable to the cadmium oral reference values established by ANSES and EFSA (EFSA, 2009b; ANSES, 2017; Schaefer et al., 2023). For comparison, the OEHHA $ADD_{fish}$ reference value (i.e., 0.063 micrograms cadmium per kilogram body weight per day) developed for the cadmium ATLs is about 3 to 6 times less than the lower and upper range values of the US FDA TRV, respectively, and about 6 times less than the ANSES and EFSA oral cadmium reference values (values based on kidney toxicity). This shows that the overall range of OEHHA ATLs for the pregnant population is relatively close to the US FDA TRV range, albeit OEHHA's range is based on a more health-protective reference value ($ADD_{fish}$). Thus, the ATL range values based on the $ADD_{fish}$ reference value calculated for each of the meal frequency categories (i.e., 1 – 7 meals per week) for the pregnant population are consistent with the US FDA oral cadmium TRV range for food-based human health assessments (see Tables 1 and 2, Schaefer et al., 2023).

OEHHA critically reviewed the relevant new studies and key health effect assessments, including those conducted by authoritative bodies, that were published after OEHHA's 2006 cadmium PHG. OEHHA determined that the studies of kidney toxicity used in the PHG were of comparable quality and sensitivity to the more recently published studies. OEHHA concluded that the no-observed-adverse-effect level (19 µg cadmium/day) established in the 2006 PHG based on the estimated oral cadmium intake associated with a given body burden and an assumed absorbed fraction (10%) in the sensitive receptor (i.e., women), in combination with the uncertainty factor (5) to account for toxicokinetic differences, was suitable for determining an acceptable oral exposure value (OEHHA, 2006). When the toxicokinetic uncertainty factor (5) is excluded from the $ADD_{fish}$ calculation, the resulting value of 0.32 µg/kg-d is well within the US FDA TRV range (0.21 – 0.36 µg/kg-d) that was derived using a systematic review and PBPK model approach (Schaefer et al., 2023). Thus, the $ADD_{fish}$, that

incorporates the uncertainty factor for toxicokinetic differences is sufficiently health protective for all populations, particularly pregnant individuals.

### *CADMIUM AND OEHHA REFERENCE VALUES*

OEHHA develops program-specific toxicity reference values[15] for chemicals that pose potential adverse human health effects. Reference values for the same chemical may differ among OEHHA programs (for example, the PHG program, the Fish Advisory Program, and Proposition 65) based on consideration of many factors, including regulatory requirements (e.g., specific uncertainty factors), exposure route (e.g., inhalation vs. oral), critical endpoints (e.g., cancer vs. non-cancer; developmental or reproductive vs. other organ-specific toxicity), or the incorporation of modifying factors (e.g., health benefits of fish consumption). OEHHA evaluated oral cadmium reference values developed by external authoritative/scientific bodies (e.g., ATSDR, EFSA, US FDA) as well as internal OEHHA scientific programs (e.g., Proposition 65, PHG program). Ultimately, the OEHHA cadmium reference value used for the development of these ATLs is adopted from the PHG for cadmium in drinking water (OEHHA, 2006).

The OEHHA Fish Advisory Program considers non-cancer and cancer effects independently when developing FCG and ATL values for fish tissue contaminants. OEHHA ATLs for a specific chemical are developed based on the non-cancer (e.g., reference dose or equivalent) or cancer (e.g., cancer potency or slope factor) critical value, as appropriate (OEHHA, 2008 and 2011). There is no oral cancer slope factor for cadmium. As noted above, OEHHA concluded in establishing the PHG that the available studies were not sufficient to characterize the carcinogenic risk associated with oral exposure (see *Cadmium Toxicity* section).

Cadmium is also listed under Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code [HSC] 25249.5 et seq.), for developmental and male reproductive toxicity. A Proposition 65 maximum allowable dose level[16] (MADL) is a safe harbor level at or below which no consumer warning is required. The MADL for cadmium was derived from a lowest-observable-effect level (LOEL) based on adverse developmental effects, including decreased postnatal weight gain and altered locomotor activity, observed in the offspring of Wistar rats following exposure to cadmium in drinking water during pregnancy (Ali et al., 1986; OEHHA, 2001). The LOEL (0.7 mg/kg-day[17]) was divided by 10 to establish a no-observable-effect level (NOEL) of 0.07

[15] A toxicity reference value represents the level of a chemical at which an exposure occurs via a specific route (e.g., oral) for a defined duration (e.g., consuming a single meal) that is unlikely to be associated with adverse health effects.
[16] Level of exposure below which a Proposition 65 warning is not required for that listed chemical.
[17] mg/kg-day = milligram per kilogram body weight per day

mg/kg-day. Per the Proposition 65 statute and regulations (HSC 25249.10(c); Cal. Code of Regs., Title 27, sections 25801 and 25803), the NOEL was converted to a milligram per day dose and divided by 1,000 to establish the MADL[18] for the oral route of exposure of 4.1 micrograms in a single day (µg/day) (OEHHA, 2001). Proposition 65 can list chemicals as either carcinogens or reproductive toxicants or both. In deriving its safe harbor values (i.e., no significant risk level [NSRL] and MADL), Proposition 65 uses the most sensitive study for cancer or a reproductive toxicity endpoint. If the most sensitive endpoint for that chemical is a non-cancer or non-developmental/reproductive toxicity effect (e.g., kidney, liver toxicity), that endpoint is considered in the hazard identification process but is not necessarily examined in the seminal study for the NSRL/MADL. By contrast, ATLs focus on the most sensitive endpoint known as the critical effect, either cancer or non-cancer, and consider adverse biological effects in all organ systems (e.g., reproductive, developmental, and kidney, among others).

The $ADD_{fish}$ used to calculate the cadmium ATLs for non-cancer risk was developed based on an adaptation of the toxicity reference value[19] (i.e., $ADD_{fish}$, see *Derivation* section) for the same critical effect (kidney toxicity) cited as the basis for the PHG (OEHHA, 2006). That value is 0.063 micrograms per kilogram body weight per day (µg/kg-day), as explained further below.

The Proposition 65 MADL for cadmium via the oral route is 4.1 µg/day, which on a per body weight basis (0.07 µg/kg-day) is similar to the $ADD_{fish}$ (0.063 µg/kg-day) based on kidney (i.e., renal) toxicity in humans. This similarity suggests that the ATL for kidney toxicity will also be protective against adverse developmental effects. It is important to recognize, however, that ATLs and MADLs use separate methodologies. They serve different purposes, incorporate different uncertainty factors, and cannot be applied interchangeably. The Proposition 65 MADL for oral cadmium exposure is set by OEHHA without consideration of any benefits associated with a specific food, is a single-day level rather than a multi-day average, and applies to consumer products throughout the state. The cadmium ATLs take into account the benefits of fish consumption, are issued by OEHHA to develop weekly or monthly consumption advice, and apply to individual species of sport-harvested finfish and shellfish in specific water bodies. Furthermore,

[18] For detailed information on the derivation of the MADL, refer to OEHHA's MADL for Reproductive Toxicity for Cadmium (Oral Route) (OEHHA, 2001), available at: https://oehha.ca.gov/proposition-65/general-info/current-proposition-65-no-significant-risk-levels-nsrls-maximum.

[19] The $ADD_{fish}$ used to calculate the ATLs for cadmium is for non-cancer effects only and is based on the Acceptable Daily Dose for the cadmium PHG, which contains an uncertainty factor of 10 to account for potential carcinogenicity via the oral route. OEHHA develops ATL values for cancer endpoints only when an appropriate cancer slope factor is available, which is not the case for ingested cadmium. Therefore, the uncertainty factor of 10 for potential cancer risk that was used in the PHG was excluded from the $ADD_{fish}$.

Proposition 65 is a consumer right-to-know law that reflects the responsibilities of businesses towards their customers. In contrast, these cadmium ATLs provide consumption advice to individuals who catch their own sport-harvested finfish and shellfish.

## *DERIVATION OF CADMIUM ATLs*

### DESIGNATION OF POPULATION GROUPS

OEHHA has established different ATLs for separate population groups, based on their unique susceptibilities to contaminant-related adverse effects (see, e.g., mercury discussion in OEHHA, 2008). For cadmium, OEHHA determined that pregnant populations should be separately addressed based on physiological changes that occur during pregnancy (see *Cadmium Toxicity* section). These changes may increase cadmium absorption and retention, particularly in the placenta and kidney, and pose an elevated risk of harm to the fetus through cadmium-induced disruption of placental formation and transport processes if exposed to an inadvisably high amount of cadmium over a brief period (e.g., consuming a higher cadmium-containing meal). ATLs for cadmium were therefore developed for (1) pregnant individuals, referred to as the sensitive population, and (2) the general population (non-pregnant individuals) (See Tables 1 – 2).

OEHHA considered factors that influence susceptibility to cadmium-induced toxicity when determining the population groups:

1) Pregnant Individuals
   To minimize the exposure of pregnant individuals to higher amounts of cadmium on a single eating occasion, OEHHA used the typical weekly meal frequencies, in contrast to those recommended for the general population (see below). This practice accounts for enhanced cadmium absorption and retention because of physiological changes that occur during pregnancy. Minimizing acute exposure to higher amounts of cadmium during pregnancy reduces the risk of dysregulation of placental formation and transport processes that are critical to fetal developmental pathways (e.g., zinc-mediated).

2) General Population (Non-Pregnant Individuals including Children 1 – 17 years of age)
   OEHHA provided additional meal frequency options for non-pregnant people, because they are not susceptible to the same risks associated with exposure during pregnancy. This allows for occasional, less-frequent consumption of species with higher levels of cadmium. As discussed above, the risk for cadmium toxicity in the general population is largely a

function of total body burden over time. This contrasts with the elevated risk of acute exposure for the sensitive population, pregnant women and the developing embryo/fetus.

As shown in Table 1 below, pregnant individuals are advised not to consume bivalve shellfish at the 4-ounce serving size when the cadmium concentration meets or exceeds 280 parts per billion (ppb). For the general population the "no consumption" concentration is 2,200 ppb. Table 2 shows cadmium concentrations for 8-ounce servings, which are half of those concentrations shown in Table 1 because of the doubling of the serving size (i.e., 8-ounce versus 4-ounce).

### HAZARD QUOTIENT

Hazard Quotient (HQ) is defined by the US EPA as the ratio of "exposure to a substance and the level at which no adverse effects are expected (calculated as the exposure divided by the appropriate chronic or acute value). A hazard quotient less than or equal to 1.0 indicates that adverse noncancer effects are not likely to occur, and thus can be considered to have negligible hazard." (US EPA, 2020). To incorporate the unique health benefits associated with fish consumption, OEHHA modified the base consumption rate of 32 g/day in the ATL equation (shown below) to calculate the maximum HQ value for each meal frequency category (see discussion in the *Appendix: Hazard Quotients Used in Advisory Tissue Level Calculations)*. OEHHA's analysis determined that the *average* exposure over the course of a week for the general population would be equivalent to the reference value[20] (e.g., $ADD_{fish}$) and have a calculated average HQ value of ~1. However, because pregnancy represents a limited window of elevated risk for cadmium toxicity via disruption of placental development and function, OEHHA determined that a *maximum* HQ value of 1 should be maintained during pregnancy for this chemical. This minimizes risk during a critical window of exposure while still allowing for the benefits of fish consumption to accrue over much of the lifespan. (See discussion on pg. 57 of OEHHA, 2008, and the *Appendix: Hazard Quotients Used in Advisory Tissue Level Calculations* for a detailed explanation about hazard quotients for ATLs and the rationale for modification and calculation of the base consumption rate.)

### SERVING SIZE AND MEAL FREQUENCY

The standard serving size typically used in OEHHA's advisories is eight ounces. One 8-ounce serving (prior to cooking) per week is consistent with the US

[20] Approach maintains an average HQ of ~1 across the entire range of potential exposures for any meal frequency category, but does not exceed an HQ of 2 (2 times the reference value or ADD) or ~1.5 (1.5 times the reference value or ADD) at the one or two meals per week frequency categories, respectively.

Dietary Guidelines recommendation for minimum weekly fish consumption (USDA/USDHHS, 2020). In its advisories, OEHHA recommends smaller serving sizes for children, proportional to the individual's body weight.

OEHHA also evaluated whether to calculate cadmium ATLs for a smaller serving size (i.e., less than 8-ounces). A smaller portion reflects practices among US consumers who report eating shellfish in smaller amounts than finfish (Tran et al., 2013; Razzaghi and Tinker, 2014). To estimate bivalve molluscan shellfish consumption in US women (including pregnant women) and children, OEHHA analyzed NHANES data, using the US EPA Food Commodity Intake Database-What We Eat in America (FCID-WWEIA) calculation tool.[21] Food frequency questionnaire consumption data from NHANES recall surveys among bivalve molluscan shellfish-eating US subpopulations (women 16 – 49 years and children 1 – 5 years) for a given 30-day period[22] were examined to estimate the 90$^{th}$ percentile bivalve molluscan shellfish consumption rate. Bivalve molluscan species include clams, mussels, oysters, and scallops. Seventeen percent of the 843 women surveyed (all: N=141; pregnant: N=17) reported consuming bivalve molluscan shellfish during the 30-day survey period. Parents and caregivers of children 1 - 5 years old (N=40 children, all shellfish consumers) were also questioned about bivalve molluscan shellfish consumption in young children, specifically clams, mussels, oysters, and scallops.

Among surveyed consumers of bivalve molluscan shellfish,[23] the 90$^{th}$ percentile consumption rates of these shellfish species for young children (1 – 5 years), all women (independent of pregnancy status, 16 – 49 years), non-pregnant women (16 – 49 years), and pregnant women (16 – 49 years) were 1.3, 2.4, 1.8, and 3.3 ounces/week, respectively. OEHHA ultimately determined that the cadmium ATLs should also be calculated for a 4-ounce serving size (Table 1), with the recognition that this amount is slightly more than the quantity reported at the 90$^{th}$ percentile consumption of bivalves among adult female bivalve molluscan shellfish consumers. Notably, the 4-ounce portion (uncooked, ~ 110 g) is also the serving size recommended by US EPA and FDA for finfish or shellfish (US FDA/EPA, 2021), and is based on the FDA reference amount customarily

[21] NHANES Food Commodity Intake Database-What We Eat in America Calculator (2005-2010), available at http://fcid.foodrisk.org/percentiles.

[22] NHANES Food Commodity Intake Database-What We Eat in America Food Frequency Questionnaire (2003-2004). Available at https://www.ars.usda.gov/northeast-area/beltsville-md-bhnrc/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/wweianhanes-overview/.

[23] NHANES applies the term "molluscan shellfish" used by the United States Department of Agriculture to describe clams, mussels, oysters, and scallops, and to differentiate from other types of shellfish (e.g., crustaceans). OEHHA includes the term "bivalve" to distinguish these molluscan species from non-bivalve mollusks, such as octopus and squid.

consumed (RACC) per eating occasion for uncooked finfish and shellfish (US FDA 21 CFR 21 §101.12).

In accordance with standard OEHHA practice, cadmium ATLs were also calculated for an 8-ounce serving size (Table 2). OEHHA uses this serving size to develop advice for crustaceans and finfish, which are typically eaten in larger amounts than bivalves. As previously stated, cadmium accumulates largely in the internal organs (e.g., kidney, liver; viscera or "guts") of finfish and shellfish. Thus, OEHHA recommends that consumers should remove and discard the internal organs prior to cooking and limit consumption to only the fillet (finfish) or the "meat" (crustaceans) to significantly reduce an individual's potential cadmium exposure. However, the edible portions of bivalve shellfish typically include both the meat and viscera; thus, these species routinely have higher levels of cadmium than those commonly found in similar "meat" portions of finfish and crustaceans.

OEHHA calculates ATLs with serving frequencies of one to seven servings per week. Because bivalve shellfish usually are not consumed as frequently as finfish and some crustaceans, particularly among US women (Razzaghi and Tinker, 2014; Tran et al., 2013), OEHHA added serving frequency options fewer than one serving per week for the general population group for the cadmium ATLs for bivalve shellfish.

Establishing consumption categories less frequent than one serving per week for the general population (defined as non-pregnant individuals) is reasonable in the case of cadmium because cadmium-induced adverse effects are largely a function of total body burden over time (e.g., accumulation over decades) (ATSDR, 2012; Nordberg et al., 2018), and are shaped by the chemical-specific factors that influence cadmium absorption and retention kinetics (e.g., long half-life, poor oral absorption). Thus, the general population could consume a serving containing a higher amount of cadmium less frequently (versus consuming multiple servings containing less cadmium more frequently) while remaining within a health-protective range (i.e., the ATLs). This approach would allow for some consumption of higher-cadmium species but still limit total cadmium exposure over a given period. As explained below, this does not apply to exposure during pregnancy.

### *DERIVATION OF A REFERENCE VALUE FOR FISH CONSUMPTION*

Based on the toxicity studies reviewed in OEHHA's 2006 PHG, increased excretion of urinary proteins indicative of renal injury (i.e., kidney toxicity) is not seen when urinary cadmium does not exceed 1 microgram Cd per gram creatinine (µg Cd/g creatinine) (OEHHA, 2006). OEHHA used a toxicokinetic model to estimate that a long-term (50 year) oral cadmium intake of 19 µg/day or

less would not lead to an exceedance of this urinary cadmium to creatinine ratio. OEHHA considered this value to represent a no-observed-adverse-effect level, or NOAEL, for kidney toxicity. The calculation of the $ADD_{fish}$ from this NOAEL to protect against kidney toxicity and other effects was conducted as follows:

$$ADD_{fish} = \frac{NOAEL}{BW \times UF}$$

where,

$ADD_{fish}$ = reference value for fish advisories, in µg/kg-day
NOAEL = no-observed-adverse-effect level, 19 µg cadmium (Cd)/day
BW = adult female body weight, 60 kg
UF = the uncertainty factor of 5.

OEHHA used the intraspecies uncertainty factor of five from the PHG assessment to address "the uncertainties due to limited information on the toxicokinetics of cadmium, particularly in women" (OEHHA, 2006).[24]

Therefore, the $ADD_{fish}$ = 19 µg / (60 kg[25] x 5)

= **0.063 µg Cd/kg-day** or **0.000063 mg Cd/kg-day.**

Thus, OEHHA used the $ADD_{fish}$ value of $6.3 \times 10^{-5}$ mg/kg-day to develop the ATLs for cadmium. OEHHA did not incorporate a relative source contribution approach because diet is the major source of oral cadmium exposure in humans (OEHHA, 2006), and shellfish consumption varies considerably within the U.S. population (Kim et al., 2019).

The general equation for developing ATLs for a non-cancer endpoint is the following (OEHHA, 2008):

Tissue concentration (ppb) =

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

Where,

RfD = Chemical specific reference dose or other reference value (e.g., $ADD_{fish}$)

[24] OEHHA did not include the PHG's carcinogenesis uncertainty factor of ten (OEHHA, 2006) because the ATL is not based on a cancer endpoint.
[25] PHG Program default body weight value for adult females, the presumed sensitive receptor, used to derive the ADD for cadmium (OEHHA, 2006). The 60 kg value was retained in the calculation to develop the $ADD_{fish}$ reference value for cadmium.

BW = Body weight of consumer (70 kg[26])
CR = Consumption Rate as the daily amount of fish consumed (see Table A3)
CRF = Cooking Reduction Factor, typically 1 for non-organic chemicals or 0.7 for organic chemicals, in skin-off fillet or meat (see discussion in OEHHA, 2008)

[26] OEHHA Fish Advisory Program default body weight value for US adults recommended in several risk assessment guidelines and used historically in several US EPA risk assessments. (OEHHA, 2008, U.S. EPA, 2011). The use of a lower default body weight for risk assessment calculations (e.g., 70 kg versus 80 kg) results in lower allowable contaminant concentrations in fish and shellfish.

TABLE 1. ADVISORY TISSUE LEVELS FOR CADMIUM: 4-OUNCE SERVING SIZE (TYPICALLY USED FOR BIVALVE ADVISORIES)

| Consumption Frequency Categories (4-ounce servings per week or month)[a] and ATLs (in ppb)[b] for Pregnant and Non-Pregnant Individuals | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Population Group** | **Serving Size (ounces)** | **Servings per Week** | | | | | | | **Servings per Month** | | |
| | | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 2 | 1 | No consumption |
| **Pregnant Individuals** | **4** | ≤39 | >39–46 | >46–55 | >55–69 | >69–92 | >92–140 | >140–280 | n/a | n/a | >280 |
| **Non-pregnant Individuals** | **4** | ≤39 | >39–46 | >46–55 | >55–69 | >69–92 | >92–180 | >180–550 | >550–1,100 | >1,100–2,200 | >2,200 |

[a] Serving size (prior to cooking, wet weight) are based on an average 160-pound person. Individuals weighing less than 160 pounds should eat proportionately smaller amounts. OEHHA fish advisories provide guidance about serving sizes for children that considers their relatively smaller body size.

[b] ppb = parts per billion

n/a = not applicable

ATL values are rounded based on laboratory reporting of three significant digits in results, where the third reported digit is uncertain (estimated). Values are rounded to the second digit, which is certain.

TABLE 2. ADVISORY TISSUE LEVELS FOR CADMIUM: 8-OUNCE SERVING SIZE (TYPICALLY USED FOR CRUSTACEAN AND FINFISH ADVISORIES)

| Consumption Frequency Categories (8-ounce servings per week or month)[a] and ATLs (in ppb)[b] for Pregnant and Non-Pregnant Individuals | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Population Group** | **Serving Size (ounces)** | **Servings per Week** | | | | | | | **Servings per Month** | | |
| | | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 2 | 1 | No consumption |
| **Pregnant Individuals** | **8** | ≤20 | >20–23 | >23–28 | >28–34 | >34–46 | >46–69 | >69–140 | n/a | n/a | >140 |
| **Non-pregnant Individuals** | **8** | ≤20 | >20–23 | >23–28 | >28–34 | >34–46 | >46–92 | >92–280 | >280–550 | >550–1,100 | >1,100 |

[a] Serving size (prior to cooking, wet weight) consumed by an average 160-pound person. Individuals weighing less than 160 pounds should eat proportionately smaller amounts. OEHHA fish advisories provide guidance about serving sizes for children that considers their relatively smaller body size.

[b] ppb = parts per billion

n/a = not applicable

ATL values are rounded based on laboratory reporting of three significant digits in results, where the third reported digit is uncertain (estimated). Values are rounded to the second digit, which is certain.

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## APPENDIX: HAZARD QUOTIENTS USED IN ADVISORY TISSUE LEVEL CALCULATIONS

A Hazard Quotient (HQ) is defined by the US EPA as the ratio of:

> exposure to a substance and the level at which no adverse effects are expected (calculated as the exposure divided by the appropriate chronic or acute value). A hazard quotient less than or equal to 1.0 indicates that adverse non-cancer effects are not likely to occur, and thus can be considered to have negligible hazard (US EPA, 2020).

Standard risk assessment guidelines generally recommend limiting non-cancer exposures to no more than the reference dose (RfD) or equivalent (i.e., toxicity reference value such as an acceptable daily dose [ADD]), which results in an HQ that does not exceed 1.

The following discussion is largely adapted from the advisory tissue levels for non-cancer risk (hazard) discussion in the OEHHA (2008) ATL technical report. OEHHA has historically developed chemical-specific Fish Contaminant Goals (FCGs) for non-cancer effects using a *maximum* HQ of 1 at the base consumption rate of 32 grams per day (g/day) (OEHHA, 2008 and 2011). FCGs do not consider the health benefits associated with fish consumption. Advisory Tissue Levels (ATLs) are designed to incorporate the unique health benefits associated with fish consumption and balance the risks by using an *average* HQ of 1. To achieve this for chemical-specific ATLs developed for non-cancer effects, OEHHA typically modifies the base consumption rate of 32 g/day in the ATL equation (shown below) to specify the maximum HQ value for the one and two meal frequency categories (see Table A1). Each meal frequency category encompasses a range of fish contaminant levels.

Sportfish consumers over time will be exposed to a range of HQs when 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 to set the cutoff for each meal frequency (i.e., 32, 64, and 96 g/day for one, two, and three servings per week, respectively) leads to an actual average HQ for fish consumers, over a multiple week basis, of less than 1. This is because most sportfish consumed in accordance with each meal frequency category will usually have a lower contaminant level than the maximum contaminant level used to set the cutoff (see *Advisory Tissue Levels, Non-Cancer Risk* section in OEHHA, 2008). If the cutoffs are adjusted so that 1 and 2 meals per week corresponds to HQs of 2 and 1.5, respectively – yielding an *average* HQ of 1 over several weeks – then sportfish consumers can safely eat more fish and gain greater health benefits without incurring significant non-cancer hazards.

As an example, US 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, to balance the risks and benefits of fish consumption and simplify communication (US EPA, 2004). US 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 typically incorporates 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 (~ 224 g) 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 (Thus, 32 g/day x 0.5 = 16 g/day). Following the example of US EPA in their national advisory (see paragraph above), OEHHA also uses a 16 g/day 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 uses a consumption rate of 48 g/day (approximately 1.5 servings per week, thus, 32 g/day x 1.5 = 48 g/day) to compute the ATLs for the two servings per week category for non-cancer hazard.

Because consumers are less likely to accrue additional benefits as consumption increases beyond two servings per week, OEHHA does not adjust the consumption rate beyond this category. Thus, a base consumption rate of 32 g/day multiplied by the number of servings per week is applied, resulting in a calculated rate of 96, 128, 160, 192, and 224 g/day to determine the ATLs for three, four, five, six, and seven servings per week, as is typically done for cancer risk (OEHHA, 2008). Because of these adjustments, the average HQ, over the entire range of potential exposures, remains less than 1. OEHHA typically regards this average HQ approach as appropriate to balance the risks and benefits of fish consumption when considering non-cancer hazard for most chemicals.

Using the RfD or other reference value for each chemical, and consumption rates of 16, 48, 96, 128, 160, 192, and 224 g/day in the above equation, will yield seven numbers that are the cutoff values for one, two, three, four, five, six, and seven servings per week, respectively, for non-cancer hazard. OEHHA’s analysis determined that for most chemicals for which non-cancer ATLs are developed,

the *average* exposure over the course of a week for sportfish consumers would be equivalent to the reference value[27] (e.g., RfD for mercury, $ADD_{fish}$ for cadmium) for each respective chemical and have a calculated average HQ value of ~ 1 (OEHHA, 2008).

### *Non-Cancer Risk (Hazard) Fish Contaminant Goal (FCG) Calculations (Maximum HQ of ~ 1)*

The following general equation can be used to calculate Fish Contaminant Goals (µg/kg or ppb) at which the consumption exposure from a chemical with a non-cancer effect is equal to the reference value for that chemical at any consumption level (OEHHA, 2008).

Tissue concentration (ppb) =

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

Where,

RfD = Chemical specific reference dose or other reference value
BW = Body weight of consumer (70 kg[28])
CR = Consumption Rate as the daily amount of fish consumed (see Table A3)
CRF = Cooking Reduction Factor, typically 1 for inorganic chemicals or 0.7 for organic chemicals, in skin-off fillet or meat (OEHHA, 2008)

*Case Example: Mercury FCG*

The FCG for mercury is calculated using a consumption rate of one, 8-ounce serving per week (32 g/day) for women aged 18 to 49 years and children aged 1 to 17 years (i.e., identified by OEHHA as the sensitive population for mercury; OEHHA, 2008):

[27] Approach maintains an average HQ of ~ 1 across the entire range of potential exposures for any meal frequency category, but does not exceed an HQ of 2 (2 times the reference value [ADD]) or ~ 1.5 (1.5 times the reference value or ADD) at the one or two meals per week frequency categories, respectively.
[28] OEHHA Fish Advisory Program default body weight value for US adults (OEHHA, 2008).

Tissue concentration (ppb) = 220[29] ppb (FCG for mercury)

$$\frac{(1\times10^{-4}\ \text{mg/kg-day})(70\ \text{kg BW})(1000\ \mu\text{g/mg})}{(0.032\ \text{kg/day})(1)} = 219\ \mu\text{g/kg or ppb}$$

RfD = $1\times10^{-4}$ mg/kg-day (US EPA IRIS, 2001)
BW = 70 kg
CR = 0.032 kg/day
CRF = 1 for inorganic chemicals (e.g., metals)

### *Non-Cancer Risk (Hazard) Advisory Tissue Level (ATL) Calculations (Average HQ of ~ 1)*

The same general equation is used to calculate ATLs (µg/kg or ppb) and the consumption rate modified to incorporate an "average HQ" concept (OEHHA, 2008). Consumption of two servings of fish per month would be equivalent to 0.5 servings per week, or 16 g/day, as described above with the US EPA national advisory example. The level of exposure to a chemical with a non-cancer effect ranges from equal to double the reference value for that chemical at the one serving per week consumption frequency (i.e., 16 g/day, HQ ~ 2), approximately 1.5 times the reference value at the two servings per week frequency (i.e., 48 g/day, HQ ~ 1.5), and equal to the reference value for that chemical at three servings or more per week (i.e., 32 g/day x number of servings/week = g/day consumption rate, HQ ~ 1), as shown in tables A1 – A2.

Tissue concentration (ppb) =

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

Where,

RfD = Chemical specific reference dose or other reference value
BW = Body weight of consumer (70 kg[30])
CR = Consumption Rate as the daily amount of fish consumed
CRF = Cooking Reduction Factor, typically 1 for inorganic chemicals or 0.7 for organic chemicals, in skin-off fillet or meat

[29] Value is rounded based on laboratory reporting of three significant digits in results, where the third digit is uncertain (estimated). Calculated FCG and ATL values are rounded to the second digit, which is certain (OEHHA, 2008).
[30] OEHHA Fish Advisory Program default body weight value for US adults (OEHHA, 2008).

*Case Example: Mercury*

The ATL for mercury is calculated using a consumption rate of one, 8-ounce serving per week and a maximum HQ of ~ 2 (16 g/day) for women aged 18 to 49 years and children aged 1 to 17 years (i.e., sensitive population for mercury per OEHHA, 2008).

Tissue concentration (ppb) = 440[31] ppb (ATL for mercury)

$$\frac{(1\times10^{-4}\ \text{mg/kg-day})(70\ \text{kg BW})(1000\ \mu\text{g/mg})}{(0.016\ \text{kg/day})(1)} = 438\ \mu\text{g/kg or ppb}$$

RfD = $1\times10^{-4}$ mg/kg-day (US EPA IRIS, 2001)
BW = 70 kg
CR = 0.016 kg/day
CRF = 1 for inorganic chemicals (e.g., metals)

[31] Value is rounded based on laboratory reporting of three significant digits in results, where the third digit is uncertain (estimated). Calculated FCG and ATL values are rounded to the second digit, which is certain (OEHHA, 2008).

TABLE A1. TYPICAL CONSUMPTION RATES FOR NON-CANCER ATL CALCULATIONS: 8-OUNCE SERVING

| Consumption rates (in grams/day, wet weight) used to calculate ATL values for each frequency category | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Population Group** | **Serving Size ounces (grams)** | **Servings per Week** | | | | | | |
| | | 7 | 6 | 5 | 4 | 3 | 2 | 1 |
| **All Populations** | **8** (224 g) | 224[a] | 192[a] | 160[a] | 128[a] | 96[a] | 48[b] | 16[c] |

[a] Maximum HQ of 1

[b] Maximum HQ of ~ 1.5

[c] Maximum HQ of ~ 2

TABLE A2. TYPICAL MAXIMUM HAZARD QUOTIENT VALUES FOR NON-CANCER ATLS AT EACH MEAL FREQUENCY CATEGORY

| Maximum Hazard Quotient | | | | | | | |
|---|---|---|---|---|---|---|---|
| **All Populations** | **Servings per Week** | | | | | | |
| | 7 | 6 | 5 | 4 | 3 | 2 | 1 |
| **Maximum Hazard Quotient** | 1 | 1 | 1 | 1 | 1 | 1.5 | 2 |

## *Cadmium: Non-Cancer Risk (Hazard) ATL Calculations*

OEHHA may establish different ATLs for separate population groups, when appropriate, based on their unique susceptibilities to contaminant-related adverse effects (see mercury discussion in OEHHA, 2008). In the case of cadmium, pregnancy represents a limited window of elevated toxicity risk via disruption of placental development and function, as described in the *Cadmium Toxicity* section. Thus, OEHHA developed cadmium ATLs for two population groups: pregnant individuals and non-pregnant individuals, including children. OEHHA determined that cadmium ATLs should also be calculated for a 4-ounce serving size and additional meal frequency categories on a per month basis, as described in the *Derivation of Cadmium ATLs* section. The consumption rates used to calculate cadmium ATL values for each meal frequency (i.e., servings per week or per month) and meal size (i.e., 4- or 8-ounce serving) that do not exceed the maximum HQ value permitted for each population group and meal frequency category are shown in Tables A3 – A4.

OEHHA used the same general equation presented above to calculate ATLs for cadmium (µg/kg or ppb). Typically, OEHHA would apply the "average HQ" concept when calculating chemical-specific ATLs for a non-cancer endpoint. However, OEHHA determined that a *maximum* HQ value of ~ 1 should be maintained when developing cadmium ATLs for pregnant individuals (i.e., OEHHA identified as the sensitive population for cadmium ATLs). Thus, an approach consistent with FGCs for a non-cancer endpoint was applied, whereby the consumption rate for each meal frequency category is based on 16 g/day or 32 g/day, for a 4- or 8-ounce serving, respectively (i.e., 16 or 32 g/day x number of servings/week = g/day consumption rate, maximum HQ ~1). This minimizes health effects during a critical exposure window while still allowing for the benefits of fish consumption to accrue over much of the lifespan. For non-pregnant individuals (i.e., OEHHA identified as the general population for cadmium ATLs), the typical "average HQ" approach of modifying the base consumption rate to balance the risks and benefits of fish consumption was applied as described in the *ATL Calculations* section above.

The previously described US EPA national advisory example, which supports the OEHHA rationale for using the average HQ approach to incorporate the benefits of fish consumption, is also applied to the per month basis meal frequency categories for the cadmium ATLs. Specifically, the consumption rates used to calculate the cadmium ATLs for the one serving per week, two servings per month, and one serving per month frequencies are represented by the base consumption rate 32 g/day (8-ounce) or 16 g/day (4-ounce) multiplied by 0.5, 0.25, or 0.125 servings per week, respectively. This approach maintains a maximum HQ of ~2 and incorporates the modified consumption rate resulting in a final calculated consumption rate of 16, 8, or 4 g/day (8-ounce serving) or 8, 4, or

2 g/day (4-ounce serving) for the one serving per week, two servings per month, and one serving per month frequencies, respectively, as shown in Table A3.

*Sensitive Population: Pregnant Individuals (Maximum HQ of ~ 1)*

The cadmium ATLs for the sensitive population (pregnant individuals) calculated at the one, 8-ounce or 4-ounce serving per week frequency, using a 32 or 16 g/day consumption rate, respectively, and permitting a maximum HQ of ~ 1 are shown below.

**8-ounce serving**: Tissue concentration (ppb) = 140[32] ppb (ATL for cadmium)

$$\frac{(6.3\times10^{-5}\ \text{mg/kg-day})(70\ \text{kg BW})(1000\ \mu\text{g/mg})}{(0.032\ \text{kg/day})(1)} = 138\ \mu\text{g/kg or ppb}$$

**4-ounce serving**: Tissue concentration (ppb) = 280[33] ppb (ATL for cadmium)

$$\frac{(6.3\times10^{-5}\ \text{mg/kg-day})(70\ \text{kg BW})(1000\ \mu\text{g/mg})}{(0.016\ \text{kg/day})(1)} = 276\ \mu\text{g/kg or ppb}$$

$Ref_{Value}$ = $6.3\times10^{-5}$ mg/kg-day (OEHHA $ADD_{fish}$)
BW = 70 kg
CR = 0.032 (one 8-ounce serving) or 0.016 kg/day (one 4-ounce serving)
CRF = 1 for inorganic chemicals (e.g., metals) (see OEHHA, 2008)

*General Population: Non-Pregnant Individuals (Average HQ of ~ 1)*

The cadmium ATL for the general population (non-pregnant individuals, including children 1 – 17 years) calculated at the one (8-ounce or 4-ounce) serving per week frequency (using a 16 or 8 g/day consumption rate) and permitting a maximum HQ of ~ 2 are shown below.

**8-ounce serving**: Tissue concentration (ppb) = 280[34] ppb (ATL for cadmium)

$$\frac{(6.3\times10^{-5}\ \text{mg/kg-day})(70\ \text{kg BW})(1000\ \mu\text{g/mg})}{(0.016\ \text{kg/day})(1)} = 276\ \mu\text{g/kg or ppb}$$

[32] Value is rounded based on laboratory reporting of three significant digits in results, where the third digit is uncertain (estimated). Calculated FCG and ATL values are rounded to the second digit, which is certain (OEHHA, 2008).
[33] Ibid.
[34] Ibid.

**4-ounce serving**: Tissue concentration (ppb) = 550[35] ppb (ATL for cadmium)

$$\frac{(6.3\times10^{-5}\ \text{mg/kg-day})(70\ \text{kg BW})(1000\ \mu\text{g/mg})}{(0.008\ \text{kg/day})(1)} = 551\ \mu\text{g/kg or ppb}$$

$Ref_{Value}$ = $6.3\times10^{-5}$ mg/kg-day (OEHHA $ADD_{fish}$)
BW = 70 kg
CR = 0.016 (one, 8-ounce serving) or 0.008 kg/day (one, 4-ounce serving)
CRF = 1 for inorganic chemicals (e.g., metals)

[35] Ibid.

TABLE A3. CONSUMPTION RATES FOR CADMIUM NON-CANCER ATL CALCULATIONS: 4-OUNCE OR 8-OUNCE SERVINGS

| Consumption rates (in grams/day, wet weight) used to calculate ATL values to meet the Maximum Hazard Quotient for each frequency category | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population Group** | **Serving Size ounces (grams)** | **Servings per Week** | | | | | | | **Servings per Month** | |
| | | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 2 | 1 |
| **Pregnant Individuals** | **4** (112 g) | 112[a] | 96[a] | 80[a] | 64[a] | 48[a] | 32[a] | 16[a] | n/a | n/a |
| **Non-pregnant Individuals** | | 112[a] | 96[a] | 80[a] | 64[a] | 48[a] | 24[b] | 8[cd] | 4[cd] | 2[cd] |
| **Pregnant Individuals** | **8** (224 g) | 224[a] | 192[a] | 160[a] | 128[a] | 96[a] | 64[a] | 32[a] | n/a | n/a |
| **Non-pregnant Individuals** | | 224[a] | 192[a] | 160[a] | 128[a] | 96[a] | 48[b] | 16[cd] | 8[cd] | 4[cd] |

n/a = not applicable

[a] Maximum HQ of 1

[b] Maximum HQ of ~ 1.5

[c] Maximum HQ of ~ 2

[d] OEHHA modified base consumption rates of 16 grams/day (for 4-ounce serving) or 32 grams/day (for 8-ounce serving) for non-pregnant individuals at the 1-2 servings/week and 1-2 servings/month categories. This method incorporates an average hazard quotient (HQ) approach to balance the risk and benefits of fish consumption when considering non-cancer risk (see OEHHA, 2008).

TABLE A4. MAXIMUM HAZARD QUOTIENT VALUES FOR CADMIUM NON-CANCER ATLS AT EACH MEAL FREQUENCY CATEGORY

| Maximum Hazard Quotient | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Population Group** | **Servings per Week** | | | | | | | **Servings per Month** | |
| | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 2 | 1 |
| **Pregnant Individuals** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | n/a | n/a |
| **Non-pregnant Individuals** | 1 | 1 | 1 | 1 | 1 | 1.5 | 2 | 2 | 2 |

n/a = not applicable

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