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

POLYBROMINATED DIPHENYL ETHERS (PBDEs)

June 2011

Edmund G. Brown Jr.
Governor
State of California

Linda Adams
Acting Secretary for Environmental Protection
California Environmental Protection Agency

George V. Alexeeff, Ph.D.
Acting Director
Office of Environmental Health Hazard Assessment

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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
Gail Krowech, Ph.D.
Martha Sandy, Ph.D.
Jianming Yang, Ph.D.

Final Reviewers
Anna Fan, Ph.D.
Melanie Marty, Ph.D.
Allan Hirsch

FOREWORD

In 2008, OEHHA published fish contaminant goals (FCGs) and advisory tissue levels (ATLs) for seven common fish contaminants (chlordane, DDTs, dieldrin, methylmercury, PCBs, selenium, and toxaphene) (Klasing and Brodberg, 2008). This report extends the process described in that report to developing an FCG and ATLs for polybrominated diphenyl ethers (PBDEs), emerging environmental contaminants that can accumulate in fish.

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

DEVELOPMENT OF FISH CONTAMINANT GOALS AND ADVISORY TISSUE LEVELS FOR COMMON CONTAMINANTS IN CALIFORNIA SPORT FISH: POLYBROMINATED DIPHENYL ETHERS (PBDEs)

INTRODUCTION

In 2008, OEHHA published fish contaminant goals (FCGs) and advisory tissue levels (ATLs) for seven common fish contaminants (chlordane, DDTs, dieldrin, methylmercury, PCBs, selenium, and toxaphene) (Klasing and Brodberg, 2008). FCGs and ATLs were developed using non-cancer and cancer reference levels available from OEHHA, U.S. EPA and other sources. Polybrominated diphenyl ethers (PBDEs) are emerging environmental contaminants that can accumulate in fish. Recent research has led to the development of non-cancer and cancer reference levels by U.S. EPA. These values are used by OEHHA in this report to develop an FCG and ATLs for PBDEs.

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. They 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 reference dose (RfD) for non-carcinogens or to a risk level greater than 1×10^{-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.

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 RfD for non-carcinogens or to a risk level greater than 1×10^{-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 confer 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 PBDEs 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.

PBDEs are a class of flame retardants used in consumers goods such as couches, mattresses, carpet padding, textiles, televisions, computers, cell phones, car seats, stereos, and dashboards (Betts, 2008; Leijs et al., 2008). PBDEs are structurally related to polychlorinated biphenyls (PCBs), common environmentally persistent contaminants with well-established adverse human health effects, and have the chemical formula $C_{12}H_{(0-9)}Br_{(1-10)}O$, where the sum of H and Br atoms always equals ten (Birnbaum and Cohen Hubal, 2006; Gill, 2004). There are 209 possible PBDE congeners in ten homolog groups (mono- to decabromodiphenyl ethers), but only approximately 30 congeners are commonly detected in environmental samples (Mizukawa et al., 2009).

PBDEs have been produced commercially in three mixtures: pentabromodiphenyl ether (pentaBDE), comprised of tetra-, penta-, and hexaBDE congeners; octabromodiphenyl ether (octaBDE), comprised of nona-to hexaBDE congeners; and decabromodiphenyl ether (decaBDE), comprised almost solely of the single decaBDE congener (BDE-209) with a small amount of nonaBDE (ATSDR, 2004). Tetra- and penta-congeners are generally referred to as "lower brominated" PBDEs (e.g., ATSDR, 2004), while those with six or more bromines are considered "higher brominated" PBDEs. However, use of the terms "lower" and "higher" PBDEs is not consistent in the literature and may be relative, at times, rather than quantitative.

PBDEs were first produced in the 1970s (ATSDR, 2004). By 1990, PBDE production volume exceeded the maximum annual PCB production (Vonderheide et al., 2008). In 1999, approximately half of the total global tonnage of the three mixtures, and 97.5% of the tonnage of penta-BDE, was used in North America (Hale et al., 2003). At that time, penta-BDE was used primarily as a flame retardant in polyurethane foam (Hale et al., 2003), octa-BDE was used largely in electronic casings, and deca-BDE was used in textiles, electronic equipment and construction materials (U.S. EPA, 2009). PBDEs are added rather than covalently bonded to product materials, as is the case with reactive flame retardants. As a consequence, they can leach during use and disposal, thus increasing their potential for human exposure (Costa et al., 2008; Daniels et al., 2010; de Wit, 2002; Sjodin et al., 2003; Vonderheide et al., 2008).

With the realization that PBDEs were accumulating in the environment and human tissues, penta- and octa-BDEs were banned in Europe in 2004; the use of deca-BDE was banned in Sweden in 2006, effective in 2007 (Lorber, 2008). The U.S. manufacturer of penta- and octa-BDE mixtures voluntarily stopped production in 2004 (Betts, 2008; Birnbaum and Cohen Hubal, 2006). California banned the manufacture, process or distribution in commerce of products containing more than 0.1% penta- or octaBDEs in 2006. The California Environmental Protection Agency (Cal/EPA) formed the Cal/EPA PBDE Workgroup in 2005 to propose steps to further reduce continuing exposures to PBDEs after the ban was implemented (Cal/EPA, 2006). U.S. EPA recently announced that the two U.S. producers and largest U.S. importer of decaBDE will phase out production, importation, and sales of decaBDE for most uses by the end of 2012 and all uses by the end of 2013 (U.S. EPA, 2010a).

EXPOSURE SOURCES

Similar to PCBs, PBDEs are lipophilic, environmentally persistent (Costa et al., 2008; Darnerud et al., 2001) and can bioaccumulate and biomagnify in the terrestrial and aquatic food webs (U.S. EPA, 2010b). PBDEs are found in indoor and outdoor air, water, sediment, soil and biota; lower brominated forms are reported to be transported worldwide, including to the arctic environment (Wolkers et al., 2004; ATSDR, 2004; Costa, 2008). In soils, debromination of higher brominated congeners to form lower brominated forms may occur via photolysis; metabolic transformation can result in debromination of higher brominated congeners in fish, birds, and mammals (U.S. EPA, 2010b).

The predominant source of PBDE exposure in the U.S. appears to be ingestion of house dust and not food (Jones-Otazo et al., 2005; Lorber, 2008; U.S. EPA 2010b). Based on published reports of PBDE levels in various environmental media, Lorber (2008) estimated that 82% of total PBDE exposure in adult U.S. residents was derived from house dust, while approximately 17% came from food sources. In that assessment, water and air accounted for less than 2% of total PBDE exposure, combined. Similarly, an exposure assessment conducted by

Johnson-Restrepo and Kannan (2009) estimated that 56-77% of total PBDE exposure for U.S. toddlers, children, teenagers, and adults resulted from ingestion and dermal absorption of house dust. Infants were estimated to acquire about 91% of their total PBDE exposure from breast milk consumption. Differences in PBDE concentrations in house dust may account for the significantly higher PBDE body burdens in North Americans compared to Europeans (Lorber, 2008; Harrad et al., 2006; Roosens et al., 2009). This disparity may be the result of stricter fire safety standards in California, which may have also led to increased use of flame-retardant products in other parts of the United States and Canada (Petreas et al., 2003; see: Windham et al., 2010). Quiros-Alcala et al. (2011) found that maximum concentrations of BDE-47 and -99 in house dust collected from low-income California households were the highest reported at that time.

Although fish often contain higher PBDE concentrations than other foods, because of relatively low fish consumption rates in typical U.S. consumers, fish are generally not the largest contributor to dietary PBDE exposure in this country (Schecter et al., 2006a; Wu et al., 2007). This may be different for frequent fish consumers or residents of other countries where fish consumption is higher (Darnerud et al., 2006; Frederiksen et al., 2009; Kiviranta et al., 2004; Ohta et al., 2002; Schecter et al., 2006a; Spliethoff et al. 2008; Voorspoels et al., 2007; Wu et al., 2007; Uemura et al., 2010). Whole blood concentrations of most lower (≤ six bromine atoms), but not higher, brominated PBDEs were positively associated with plasma concentrations of the biological markers of fish consumption, eicosapentaenoic and docosahexaenoic acids, in a study of the general Japanese population (Uemura et al., 2010). This relationship may not be evident in a population with lower fish consumption rates.

Fish have been shown to absorb PBDEs from their food (Burreau et al., 2000; Stapleton et al., 2004). Although biomagnification of PBDEs in the aquatic food chain has been reported, particularly tri-, tetra- and pentaBDEs (Bragigand et al., 2006; Burreau et al., 1999; 2006; Johnson-Restrepo et al., 2005a; Mizukawa et al., 2009; Shaw et al., 2009; Tomy et al., 2004; U.S. EPA, 2010b; Yu et al. 2009), study results have not been consistent (see Yu et al., 2009). Determination of congener availability, half-lives and biomagnification factors in fish are complicated by *in vivo* PBDE debromination (Tomy et al., 2004; Stapleton et al., 2004). As has been shown in human tissues, PBDE concentrations in fish have also increased exponentially in the last few decades, with doubling times estimated to be as short as two years (Johnson-Restrepo et al., 2005a). PBDE levels in Lake Ontario lake trout, for example, increased 315-fold between 1978 and 1998 (Luross et al. 2000).

Studies of PBDE concentrations in fish are numerous and difficult to compare because different congeners have been analyzed and reported on a different basis (wet weight versus lipid normalized), fish have been analyzed as whole bodies or fillets, and it is often not clear whether fish were analyzed with skin or

without. Organic contaminant levels are known to vary greatly in different tissues of the same fish (see, for example, MSRP and U.S. EPA [2007]), so consistency in sample preparation and analysis is imperative for interpretation. Most studies indicate that BDE-47 and -99 are the predominant congeners found in fish, although BDE-183 and -209 are often not analyzed (U.S. EPA, 2010b). As is the case with human body burdens (see below), several studies have shown that PBDE levels in North American fish are higher than in European fish (Ackerman et al., 2008; Hites, 2004; Schecter et al., 2004). Johnson and Olson (2001) reported highly variable concentrations of six PBDE congeners (BDE-47, 99, 100, 153, and 154 [hexa]) in freshwater fish collected from water bodies in Washington State. Total PBDE levels ranged from 1.4 ppb wet weight in whole rainbow trout collected from areas considered "background" to 1,250 ppb wet weight in whole mountain whitefish collected from a watershed draining an urban area. BDE-47 and 99 comprised the majority of PBDEs measured. Similarly, in multiple species of freshwater fish collected from various Virginia watersheds, the sum of six tetra-to-hexaBDE congeners in fish fillets ranged from <5 to 57,000 ppb lipid (Hale et al., 2000; 2001). PBDE levels were significantly positively correlated with fish length and also tended to be higher in piscivorous fish. Dodder et al. (2002) found that the sum of PBDEs (BDE-47, 99, 100, 153, 154, 190 [hepta], and 209) in composites of bluegill and white crappie collected from a possibly contaminated lake averaged 65 ppb wet weight (2,400 ppb lipid) compared to 6.9 ppb wet weight (300 ppb lipid) in bluegill and white crappie collected from a "background" site. Congener profiles were different in fish between the two sites, with much higher levels of hexa-BDEs (BDE-153 and 154) in fish collected from the water body near a known source of PBDEs. BDE-209 was the most prevalent congener in sediment in the more contaminated lake, often by an order of magnitude or more, but was below detection limits (1.3 to 1.4 ppb wet weight) in fish from the lake. The authors concluded that PBDE bioavailability decreases with increasing bromination for hepta- and higher congeners (Dodder et al. 2002) although, as noted above, bioavailability estimates may be confounded by *in vivo* debromination.

Studies on PBDE levels in farmed versus wild fish are also inconsistent. Staskal et al. (2008), for example, reported that the sum of 43 PBDEs was higher in wild-caught catfish fillets from southern Mississippi than in farm-raised catfish fillets from the same area. Hites et al. (2004) found that the sum of 43 PBDE congeners was higher in farmed than wild salmon, whereas Shaw et al. (2008) reported no difference in the sum of nine PBDE congeners analyzed in farmed and wild salmon. Differences in overall study results may reflect variability in types and sources of PBDEs in the local environment and food sources of the farmed and wild fish. In contrast to what is typically found for persistent organic pollutants, Shaw et al. (2008) reported that PBDE concentrations were not lower, and were sometimes higher, in skin-off versus skin-on salmon fillets. The authors speculated that PBDEs may preferentially accumulate in muscle lipids compared to skin lipids. However, Bayen et al. (2005) found that the sum of BDE-47, -99 and -100 ranged from 2.5-7.6 ng/g ww in raw salmon muscle tissue

and 4.1-11.5 ng/g ww for raw salmon skin. PBDE levels in cooked salmon were 25 to 51% lower than in raw salmon, depending on the method of cooking and whether they were cooked with or without skin. Broiling reduced total PBDEs in a study in catfish, rainbow trout and salmon (Schecter et al. 2006b); however, Perello et al. (2009) found that PBDEs levels were reduced after cooking in sardines and tuna, but increased in hake, depending on cooking method.

TOXICOKINETICS

Although it is clear from body burden studies (see below) that many PBDE congeners are absorbed and distributed to various tissues, few studies investigating absorption, metabolism, or excretion of PBDEs in humans were located. U.S. EPA recently reviewed published toxicokinetic studies for four BDE congeners (47, 99, 153, and 209) (IRIS, 2008a,b,c,d). Animal studies indicate that PBDE toxicokinetics are species-, gender-, age-, dose-, and congener-dependent (Kuriyama et al., 2007; Costa et al., 2008). In general, lower brominated BDEs are well absorbed by the oral route, while decaBDE is poorly absorbed (ATSDR, 2004). It is not known whether the relatively higher prevalence of pentaBDEs in human tissues (and other biota) reflects debromination of higher brominated BDEs or differences in toxicokinetics or environmental persistence or exposure (Staskal et al., 2006).

PBDEs were first identified as an emerging persistent organic pollutant through a Swedish breast milk monitoring program (Noren and Meironyte, 1998, 2000; Hooper and McDonald, 2000). Over a 25 year period, total PBDE concentrations in Swedish breast milk increased exponentially, doubling approximately every five years and averaging 4 ppb lipid by 1997 (Noren and Meironyte, 1998, 2000). Since those reports, numerous studies have identified PBDEs in human breast milk throughout the world (e.g., Guvenius et al., 2003; Ingelido et al., 2007; Inoue et al., 2006; Jaraczewska et al., 2006; Li et al., 2008; Polder et al., 2008). In the United States, Schecter et al. (2003) found that breast milk total PBDE levels ranged from 6.2 to 419 ppb lipid (mean: 73.9 ppb lipid) in 47 nursing mothers (Schecter et al. 2003). TetraBDE-47 was the major congener detected, accounting for more than 50% of the sum of PBDEs. PBDE breast milk levels in this cohort were approximately 10-100 times those reported in Europe. In a subsequent study in the Pacific Northwest, total PBDE levels in breast milk of 40 first-time mothers averaged 96 ppb lipid, with 10% of the samples exceeding 250 ppb lipid (She et al., 2007). Daniels et al. (2010) investigated PBDE levels in nursing mothers from North Carolina at three (n=304) and twelve (n=83) months post-partum between 2004 and 2006. The sum of PBDEs 28, 47, 99, 100, and 153 ranged from 1 to 2,010 ppb lipid and was positively associated with high pre-pregnancy maternal body mass index and negatively associated with maternal age. BDE-47 was the congener detected in the highest concentration; BDE-209 was not detected in this study.

Along with their accumulation in breast milk, PBDEs have been reported in other human tissues with concentrations increasing an estimated 100-fold since the early years of their use (Hites, 2004). In the United States, Sjogin et al. (2004) found a significant positive correlation between total PBDE levels and collection year for pooled serum samples from the southeastern United States and Seattle, Washington, over the years 1985 to 2002. As was the case with breast milk, more than 50% of serum total PBDEs consisted of BDE-47. In another comparative study, analysis of serum samples from 100 U.S. residents archived since 1973 found all tested congeners below detection limits of 0.01-1.0 ppb lipid (Schecter et al., 2005). In contrast, in 2003, serum and whole blood total PBDE levels in pooled samples of 100 U.S. residents were 61.8 and 79.7 ppb lipid, respectively. BDE-47 comprised approximately 50% of the 13 congeners tested while BDE-153 and BDE-99 were the second and third most prevalent congeners, depending on blood compartment. PBDE levels in the 2003 study were highly variable, with total whole blood PBDE levels in 39 individuals ranging from 4.6 to 365.5 ppb lipid (Schecter et al., 2005).

Analysis of 10 tri- to heptaBDE congener concentrations in serum of 2,062 individuals aged 12 years and older in the 2003-2004 National Health and Nutrition Examination Survey (NHANES) showed that BDE-47 had the highest frequency of detection and highest concentration of any congener, with a geometric mean of 20.5 ppb lipid and a 95th percentile of 291 ppb lipid (Sjodin et al., 2008). The highest total PBDE concentration in any individual from NHANES was 3,680 ppb lipid (Sjodin et al., 2008). Although BDE-209 was not included in NHANES 2003-2004, because an earlier study had shown that the concentration of this congener in serum was low (~2 ppb lipid) (Sjodin et al., 2008), some studies have shown clear evidence that this congener can accumulate in human tissues (Frederisksen et al., 2009). In a study of a California family of four, for example, Fischer et al. (2006) found that serum BDE-209 concentrations in a five-year-old child and toddler neared or exceeded concentrations of BDE-47, and were higher than other tested congeners. Ninety days later, however, BDE-209 levels had dropped approximately ten-fold in all family members. BDE-209 concentrations in the children ranged from 2-to-15-fold higher than in the mother and father, regardless of timing. The authors suggested that the short half-life (approximately 15 days; Thuresson et al., 2006) and presumed reduction in exposure over the duration of the study accounted for the difference in BDE-209 levels over time. In a survey of serum and breast milk in residents of a PBDE production area in China, Jin et al. (2009) found that BDE-209 levels were higher than the other seven congeners measured, while Wu et al. (2010) found that BDE-209 was also the predominant congener in umbilical cord samples from e-waste recycling and control areas in China. In a survey of non-occupationally exposed 15 to 74 year olds in Japan, Uemura et al. (2010) found that, of the 14 congeners analyzed, BDE-209 was the most abundant congener in whole blood.

Toms et al. (2009) measured serum PBDEs in individuals from 17 different age groups (neonates to >60-year-olds), in an effort to determine the time and

concentrations at which levels peak in the Australian population. Results showed that concentrations of the sum of BDE-47, -99, -100, and -153 were higher in children two to five years of age, peaking at 2.6 to 3 years of age, and lowest in adults over 31 years of age. BDE-47 was the predominant congener detected, averaging 47% of the total of sum of the four congeners. The authors suggested that young children either have higher PBDE exposures and/or decreased elimination rates.

A small study of PBDE levels in human breast adipose tissue and harbor seal blubber from the San Francisco Bay area showed mean total PBDE concentrations of 86 and 1,730 ppb lipid, respectively (She et al., 2002). PBDE concentrations in harbor seals had increased nearly 100-fold over the previous ten-year period. Johnson-Restrepo et al. (2005a) found relatively high average PBDE concentrations in adipose tissue of 52 individuals from New York who had undergone liposuction. Concentrations of 11 PBDE congeners ranged from 17 to 9630 ppb lipid, with a mean of 399 ppb lipid, and were similar to concentrations of PCBs found in the same population.

Human studies have shown that PBDEs cross the placenta and accumulate in the fetus. Similar levels of six congeners (BDE-47, -99, -100, -153, -154, and -183) were found in maternal and cord serum samples from 12 maternal-fetal pairs in Indiana at the time of delivery (Mazdai et al., 2003). As was the case with other studies, BDE-47 accounted for approximately 50% of total PBDEs. The authors noted that PBDE levels were approximately 20 to100 times greater than those reported in similar studies conducted in Sweden and Norway (Guvenius et al., 2003; Thomsen et al., 2002). In 11 stillborn U.S. fetuses or newborn infants who died prior to being formula-fed or nursed, Schecter et al. (2007) found the sum of 13 PBDE congeners in liver ranged from 4 to 98.5 ppb lipid. BDE-47 was the most predominant congener identified while BDE-209 did not surpass detection limits in any samples. Guvenius et al. (2003) reported that lower brominated PBDE concentrations were similar in maternal and cord blood compartments while higher brominated PBDEs were higher in maternal blood than cord blood, suggesting that larger compounds may not transverse the placenta as easily as smaller ones. Animal studies also confirm placental transfer of PBDEs. In one study, Kuriyama et al. (2007) administered a single oral dose of BDE-99 to pregnant Wistar rats on gestational day (GD) 6. On postnatal day (PND) 1, the study found that BDE-99 concentrations in liver were 2.5-fold higher in offspring than in dams.

PBDE half-lives appear to be dependent on the degree of bromination. Apparent half-lives of deca- to hepta- congeners, for example, have been modeled by examining serum levels in occupationally exposed workers prior to, during, and at the end of a vacation period compared to non-occupationally exposed workers (Thuresson et al., 2006). Congener half-lives were inversely related to degree of bromination, with BDE-209 having an estimated half-life of 15 days and likely undergoing metabolic transformation to nona- and octa-BDEs. Half-lives were 18

to 39 days and 72 to 91 days for nona- and octa-BDEs, respectively. BDE-209 rapidly increased in serum after a one day re-exposure period. The apparent half-lives of lower or medium brominated congeners such as BDE-153 (hexa) were longer than the one-month study period. Jakobsson et al. (2003) studied Swedish workers occupationally exposed to various BDEs and compared them to non-occupationally exposed workers. BDE-209 had an estimated half-life of 14 days, while half-lives for nona-, octa-, hepta-, and hexa-BDEs ranged from 17-35 days, 37-84 days, 111 days, and 271-677 days, respectively. On the other hand, Geyer et al. (2004) estimated the terminal elimination half-lives for lower brominated PBDEs in non-occupationally exposed adults based on daily intakes and total body burdens under steady state conditions. Estimates ranged from 1.8 to 6.5 years for BDE-47, -99, -100, -154, and -153, and generally increased with increasing degree of bromination.

TOXICITY

The toxicity of PBDEs has been reviewed by numerous authors (e.g., Darnerud et al., 2001; Hardy, 2002; McDonald, 2002; Branchi et al., 2003; Darnerud, 2003; ATSDR, 2004; Birnbaum and Staskal, 2004; Gill, 2004; McDonald, 2005; Birnbaum and Cohen Hubal, 2006; Cal/EPA, 2006; Betts, 2008; Costa et al., 2008; Darnerud, 2008; IRIS, 2008a,b,c,d; Legler, 2008; Vonderheide et al., 2008; Dingemans et al. 2011). Toxicity testing has been conducted on individual congeners and congener mixtures. Acute toxicity in laboratory animals is low, with oral LD_{50} values ranging from 0.5 to >28 g/kg, depending on species, route of exposure and congener (Darnerud, 2003). Of the homolog groups tested, decaBDE has lower acute and repeated-dose toxicity than penta- or octaBDEs (ATSDR, 2004). This is likely because of lower absorption and higher metabolism and excretion rates of decaBDE (Darnerud, 2003; ATSDR, 2004). PBDE critical effects include developmental neurotoxicity, endocrine disruption, fetal toxicity, and morphological changes to thyroid, liver and kidney, depending on homolog group (Darnerud, 2003; ATSDR, 2004; see, for example, Norris et al., 1975). The following is a summary of evidence for PBDE effects on specific toxic end points. Key studies used to derive reference doses and a cancer slope factor are discussed in greater detail later.

Neurodevelopmental Toxicity

As noted, neurodevelopmental effects have been found for all BDE congeners tested and are considered the adverse effects of greatest concern. Of the four BDE congeners for which U.S. EPA has developed a reference dose (RfD) (BDE-47, -99, -153, and -209; see later discussion), all are based on neurobehavioral endpoints in animals (IRIS, 2008e,f,g,h).

Limited epidemiological evidence is available in humans suggesting an association between PBDE exposure and results of subsequent tests of neurodevelopment. In a preliminary study of motor, cognitive and behavioral

abilities in children at 5-6 years of age in the Netherlands, Roze et al. (2009) found that prenatal PBDE exposure (as evidenced by maternal serum levels at 35 weeks gestation) was associated with poorer outcomes in some tests and improved outcomes in others. The authors speculated that these inconsistencies may have been the result of multiple statistical analyses or the effect of other chemicals, some of which may not have been analyzed (e.g., methylmercury). In a prospective cohort study of children born in New York City in 2001 or 2002, higher levels of BDE-47, -99, and/or -100 in cord blood were associated with reduced indices of neurodevelopment as measured by the Psychomotor Development Index or Mental Development Index at 12-48 months and 72 months (Herbstman et al., 2010). In a study of a subset (n = 482) of the Spanish Menorca birth cohort, Gascon et al. (2011) evaluated PBDE levels in cord blood (n = 88) and serum levels at age four (n = 244). PBDE exposure was considered relatively low in that area and only BDE-47 levels were consistently above detection limits. When analyzed as a dichotomous variable (above and below the level of quantification), postnatal BDE-47 exposure was positively associated with an increased risk of attention deficit, but not hyperactivity, disorder, as well as with a higher risk of poor social competence symptoms. Thyroid hormone levels and other measures of neurodevelopment were not affected by postnatal BDE-47 exposure in this study.

Numerous studies in animals have evaluated the effects of PBDE congeners on neurobehavioral endpoints. Male NMRI mice exposed to a single oral dose of 8 mg/kg body weight BDE-99 at 3 or 10 days of age had significant alterations in spontaneous motor behavior when tested as adults (four months of age). These changes were not seen in mice exposed on postnatal day 19, indicating that there is a critical window of developmental susceptibility (Eriksson et al. 2002). Cheng et al. (2009) gavaged Sprague-Dawley rats with 2.0 mg/kg-day BDE-99 from GD 6 to PND 21. Delayed development of two types of reflexes during the postnatal period as well as impaired memory and learning at adolescence was seen in exposed animals. As noted by the authors, the mean concentration of BDE-99 in adipose tissue of adolescent rats in this study was only approximately two-fold higher than the maximum BDE-99 concentration reported in human adipose tissue by Johnson-Restrepo et al. (2005a). Kuriyama et al. (2005) gavaged pregnant Wistar rats with a single oral dose of 60 or 300 µg/kg BDE-99 or a vehicle control on GD 6. At PND 36, male and female rats showed increased spontaneous locomotor activity in all parameters tested at the 300 µg/kg dose. At PND 71, total locomotor activity and time of activity were increased in both the low- and higher-dose groups.

Male NMRI mice exposed to a single oral dose of 0.45, 0.8 or 9.0 mg/kg body weight BDE-153 on PND 10 had dose- and time-dependent decrements in spontaneous behavior at 2, 4 and 6 months of age and in learning and memory (based on the Morris water maze test) at 6 months of age (Viberg et al. 2003a).

Male NMRI mice gavaged with a single oral dose of 20.1 mg/kg body weight BDE-209 on postnatal day 3 had time-dependent alterations in spontaneous behavior at 2-, 4-, and 6-months of age, with adverse effects increasing with increasing age (Viberg et al., 2003b). These results were not seen at lower doses or when animals were dosed on PND 10 or 19. Rice et al. (2007) dosed male and female C57BL6/J inbred mice pups with 0, 6 or 20 mg BDE-209/kg bodyweight from PND 2-15. Animals were evaluated for developmental milestones and various functional observational behaviors (on PNDs 14- 20), and adult locomotor activity. High-dose BDE-209 exposure resulted in slowed acquisition of palpebral reflex in males and females on PND 14, reduced forelimb grip in males on PND 16, and changes in locomotor activity in young adults. Low-dose pups showed increased struggling during handling on PND 20. Other measured variables were not affected by treatment. In a chronic exposure study, Xing et al. (2009) exposed Wistar rats to 20 µmol/kg body weight BDE-209 for varying time periods (at least 19 days) between the beginning of gestation and 20 day post-weaning. As adults, the animals showed impaired synaptic plasticity. Synaptic plasticity is considered a key neurological element for learning and memory (Xing et al., 2009).

In a comparative study, different higher brominated PBDE congeners (BDE-183, -203, and -209) were shown to have varying abilities to cause neurodevelopmental effects (Viberg et al., 2006). Based on tests of spontaneous behavior and the Morris water maze, the authors found that BDE-203 was a more potent developmental neurotoxin than BDE-183 or -206.

Endocrine Disruption and other Reproductive Effects

Considerable research has been conducted on the endocrine disruption potential of PBDEs because of their structural likeness to thyroid hormones and known endocrine disruptors such as PCBs (Vonderheide et al., 2008). Thyroid hormones play a crucial role in neurodevelopment (ATSDR, 2004), which, as noted, is considered the primary critical effect. Several observational studies on the effects of PBDE exposure on thyroid hormones have been conducted in humans. In an early study, Hagmar et al. (2001) evaluated plasma persistent organic pollutant concentrations and thyroid and reproductive hormone levels in 110 adult men who consumed differing amounts of fatty fish from the Baltic Sea. BDE-47 was the only PBDE analyzed and showed a high positive correlation with Baltic Sea fatty fish consumption (see Sjodin et al., 2000). Plasma BDE-47 was negatively associated with thyroid stimulating hormone (TSH; thyrotropin), but only accounted for approximately 10% of the variance in TSH levels. Other thyroid hormones were not associated with BDE-47 levels. Turyk et al. (2008) evaluated multiple measures of thyroid function in a cohort of 405 adult male Great Lakes sport fish consumers. Serum thyroglobulin antibodies and thyroxine (T_4) levels were positively associated with serum levels of the sum of eight BDE congeners, while serum triiodothyronine (T_3) and TSH levels were negatively associated with serum PBDEs. Bloom et al. (2008) found no association

between PBDE exposure and thyroid hormone levels in New York fishers; however, the authors noted that small sample size may have been a limiting factor.

Yuan et al. (2008) found that serum PBDE (lipid-adjusted) and TSH levels were elevated in 23 Chinese adult male and females occupationally exposed to PBDEs compared to 26 demographically-similar controls (congeners not specified). In a small study of pregnant woman residing near an electronic waste recycling site in China, cord whole blood levels (not lipid-adjusted) of polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs), PCBs, and six PBDE congeners were elevated compared to referents (Zhang et al., 2010). However, only PCDD/Fs and PCBs, not PBDEs, were statistically (negatively) associated with maternal serum T_4 levels taken at 16 weeks gestation. T_3 and TSH levels were not associated with contaminant concentrations. The authors speculated that small sample size may have limited the ability to detect potential PBDE effects. Lipid-adjusted cord serum PBDE concentrations (BDE-47, -100, or 153) among babies born by spontaneous unassisted vaginal delivery in Baltimore, Maryland, were negatively associated with total and free T_4 levels, although these trends were generally not significant (Herbstman et al., 2008). Chevrier et al. (2010) found that serum concentrations of BDE-28, -47, -99, -100, and -153 and the sum of those congeners were negatively associated with TSH levels in pregnant women at 27 weeks gestation. Free and total T_4 levels were not related to PBDE concentrations.

In a small preliminary study, Meeker et al. (2009) reported that BDE-47, -99 and -100 concentrations in house dust were positively associated with free T_4 in U.S. men from infertile couples. Total T_3 and TSH levels were not related to PBDE exposures. In the same study, Meeker et al. (2009) also evaluated other serum hormones in men and their relationship to household dust PBDE levels, including testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin, inhibin B, sex hormone binding globulin (SHBG), and the free androgen index (FAI; the molar ratio of total testosterone to SHBG). Of these, FSH, LH and FAI were negatively associated with PBDE levels in house dust, while inhibin B and SHBG were positively associated with such exposure. In a study of 52 men recruited from a fertility clinic, Abdelouahab et al. (2011) evaluated associations between serum BDE-47, -99, -100, and -153 and serum TSH, total T_3, total T_4, free T_3, free T_4, and various measures of sperm quality. Serum concentrations of BDE-47, -99 and the sum of the four congeners were negatively associated with serum total T4 and grade A sperm motility. Serum BDE-100 concentration was also associated with reduced Grade A sperm motility. In prospective case-cohort or nested case-control studies conducted in Danish and Finnish neonates, respectively, the sum of seven PBDE congeners and five individual PBDE congeners in breast milk were positively associated with cryptorchidism. A similar positive association was found between the sum of seven PBDEs in breast milk and increased serum LH in the infants at 3 months of age. Other hormones (FSH, SHBG and testosterone) were not related to

breast milk PBDE concentrations. Placenta PBDE concentrations, on the other hand, were not associated with cryptorchidism or measured hormone levels (Main et al., 2007).

Harley et al. (2010) evaluated the association between maternal PBDE levels and fecundability in 223 pregnant, predominantly Mexican immigrants living in a low-income agricultural community in California. Ten BDE congeners were measured, but statistical analyses were only conducted for the four that were detected in at least 75% of the population (BDE-47, -99, -100, and -153). Results showed that, for every 10-fold increase in the concentrations of maternal serum BDE-100, and -153, the odds of achieving pregnancy in each month declined 40 and 50%, respectively (Harley et al., 2010). An approximately 30% reduction in the odds of achieving pregnancy was found for each 10-fold increase in the concentration of the sum of BDE-47, -99, -100, and -153. Menstrual cycle irregularities were not associated with serum PBDEs in this population. In a much smaller study (n=20) of a cohort of healthy pregnant Taiwanese women, Chao et al. (2007) found that PBDEs in breast milk, especially BDE-47, -99, -100, and -209, were associated with various adverse birth outcomes, including lower birth weight and length, head and chest circumference, and body mass index (BMI; Quetelet's index). Menstrual irregularities associated with PBDE exposure were also seen, but these were no longer significant after controlling for maternal age, pre-pregnant BMI and parity. The authors noted that PBDE concentrations in breast milk in this population were approximately 20 times lower than those reported for American women by Schecter et al. (2003).

Various adverse effects on the thyroid have been reported in mice and rats following exposure to different PBDE congeners or congener mixes in numerous studies, particularly reduced T_4 levels in developing animals (e.g., Hallgren et al., 2001; Hallgren and Darnerud, 2002; Zhou et al. 2002; Ellis-Hutchings et al., 2006; Darnerud et al., 2007; Kuriyama et al., 2007; Rice et al., 2007; Richardson et al., 2008; Dunnick and Nyska, 2009). This is in contrast to several human studies in adults (see above), which have generally shown a positive relationship between PBDE exposure and T_4 (see discussion in Meeker et al., 2009). In studies with DE-71 (a commercial penta-PBDE mixture that includes BDE-47, -99, -100, and -153), Szabo et al. (2009) identified multiple, complex mechanisms that may be responsible for the hypothyroxinemic effect of PBDEs in rats, although polybrominated dibenzodioxins/furans (PBDD/Fs) present in DE-71 complicate interpretation. Anti-androgenic activity has also been shown following exposure to relatively high doses (30 mg/kg and above) of DE-71 in adult and peri-pubertal male rats (e.g., Stoker et al., 2004; Stoker et al., 2005). Effects included delayed puberty, reduced androgen-stimulated reproductive tract growth, and increased LH levels, depending on dose.

Experiments conducted in the same laboratory have shown adverse endocrine and reproductive effects in male and female rats at doses lower than those causing adverse effects in the study used to develop the RfD for BDE-99. U.S.

EPA reviewed two of these papers during the RfD development process, but chose another study for multiple reasons (IRIS, 2008b; see RfD discussion below). Kuriyama et al. (2005) gavaged pregnant Wistar rats with a single oral dose of 60 or 300 µg/kg BDE-99 or a vehicle control on GD 6. In adult male offspring, relative testis weights were decreased compared to controls in the higher-dose group, while relative epididymis weights, sperm and spermatid counts, and daily sperm production were reduced compared to controls in both dose groups. Using the same treatment protocol, Talsness et al. (2005) evaluated reproductive endpoints in F1 female offspring. Adverse effects at the time of estrus included electron microscopic alterations in ovarian mitochondria and the uterus and vagina. A dose-related increase in resorption rates in mated F1 rats compared to concurrent and historical controls was also reported. In a subsequent paper, also using the same treatment protocol, Kuriyama et al. (2007) found reduced T_4 levels in dams at PND 1 at both dose levels; T_4 was reduced in high-dose pups at PND 22. The authors noted that the average lipid-based BDE-99 concentration in adipose tissue of rats in this study was 4.5-fold lower for the 60 µg/kg group and 1.4-fold higher for the 300 µg/kg group than the highest lipid-based concentration of BDE-99 in adipose tissue of U.S. residents reported in Johnson-Restrepo et al. (2005a). In further work, offspring of primiparous Wistar rats administered 0, 140 or 700 µg/kg BDE-47 on GD 6 showed a significant reduction of secondary and tertiary follicles in the 700 µg/kg group and a non-significant ($p<0.06$) reduction of secondary follicles in the 140 µg/kg group on PND 38 (Talsness et al., 2008). Estradiol concentrations were reduced in the higher-dose group at the same time period. Electron microscopic evaluation of ovaries and thyroid of F1 females at PND 100 showed numerous ultrastructural abnormalities in both dose groups.

Liver Toxicity and Other Adverse Effects

Dunnick et al. (2009) evaluated the liver toxicity of DE-71 in a 13-week study in F344/N rats and B6C3F1 mice. Increased liver weights were seen at doses of 5 mg/kg-day and above in rats and 50 mg/kg-day and above in female mice. Other hepatic signs, such as increased hepatic cytochrome P-450 and hepatocyte hypertrophy occurred at doses of 50 mg/kg-day, or above. PentaBDE (in a formulation similar to commercial DE-71) was found to alter heme biosynthesis in a 28-day study of adult female Wistar rats, as evidenced by an increase in hepatic delta-aminolevulinic acid synthase (ALA-S) activity, increased urinary and hepatic porphyrin concentrations, and increased 24-hour porphyrin excretion (Bruchajzer, 2010).   The LOAEL in this experiment was determined to be 2 mg/kg-day, based on increased urinary excretion of hexacarboxyporphyrins, tetracarboxyporphyrins and total porphyrins compared to the vehicle controls.

Concomitant Exposures

Fish may potentially contain multiple contaminants. Because of the structural similarity between PBDEs and certain other bioaccumulative contaminants that

may be found in fish, such as PCBs and PBBs (polybrominated biphenyls), there is concern that their toxicities may be additive (Cal/EPA, 2006; McDonald, 2005). Eriksson et al. (2006) dosed ten-day-old male NMRI mice with single oral doses of either low or high levels of BDE-99 (0.8 or 8.0 mg/kg body weight) or low or high levels of PCB-52 (0.4 or 4.0 mg/kg body weight). In tests on eight animals per treatment, randomly selected from three to four litters, mice showed impaired spontaneous motor behavior at four and six months of age at the higher, but not lower, doses of the individual chemicals. However, when given a single combined oral dose of low level BDE-99 + low level PCB-52 (0.8 and 0.4 mg/kg body weight, respectively), spontaneous motor behavior impairment was greater than when mice were given the high dose of PCB-52 alone (Eriksson et al. 2006). He et al. (2010) found a synergistic effect of BDE-47 and PCB-153 on neurobehavioral deficits, as measured by the place navigation experiment of the Morris water maze test. Latency periods were increased in two-month-old Sprague-Dawley rats following oral dosing with 10 mg/kg BDE-47 and 5 mg/kg PCB-153 on PND 10 compared to either chemical alone. In another study, concomitant exposure to methylmercury (MeHg) and PBDEs enhanced the developmental neurotoxicity of both compounds in a synergistic way (Fischer et al., 2008). In tests on eight animals per treatment, randomly selected from three to four litters, male NMRI mice orally gavaged with 0.8 mg/kg BDE-99 and 0.4 mg/kg MeHg on PND 10 showed greater deficits in neurobehavioral tests of habituation, learning, memory, and spontaneous activity over the next two to six months compared to rats treated with either chemical alone.

Carcinogenicity

The National Toxicology Program is currently evaluating the toxicity of the penta-BDE mixture (DE-71) in two-year gavage studies in mice and rats of both sexes (see: http://ntp.niehs.nih.gov/index.cfm?objectid=BD73BA18-123F-7908-7BD4AEF6AB4318BF). A prior study evaluated the carcinogenicity of BDE-209 in male and female mice and rats (NTP, 1986; see discussion in the derivation section below). Based on those results, the International Agency for Research on Cancer (IARC) found limited evidence of the carcinogenicity of decaBDE in experimental animals, with an overall evaluation of "not classifiable as to its carcinogenicity to humans (Group 3)" (IARC, 1999). U.S. EPA has listed BDE-209 as having "suggestive evidence of carcinogenic potential" based on increased incidence of neoplastic nodules or carcinomas, combined, in male rat livers (NTP, 1986; IRIS, 2008d; see discussion below). U.S. EPA has determined that there is "inadequate information to assess the carcinogenic potential" of BDEs-47, -99, or -153.

DERIVATION OF A REFERENCE DOSE AND CANCER SLOPE FACTOR FOR PBDEs

U.S. EPA prepared assessments to identify an RfD or cancer slope factor (CSF) for the four PBDE congeners that are most prevalent in the environment and

human tissues: tetraBDE-47, pentaBDE-99, hexaBDE-153, and decaBDE-209 (IRIS, 2008e-h). Of these, two (BDE-47 and BDE-99) are known to accumulate in fish and have the lowest RfDs (i.e., are considered the most toxic). A cancer slope factor has only been developed for BDE-209. The following discussion will be limited to the derivation of the RfDs for BDE-47 and BDE-99 and the CSF for BDE-209.

The U.S. EPA RfD for these compounds has been derived from animal data, as relevant data in humans are inadequate. The RfD for BDE-47 is 1×10^{-4} mg/kg-day (IRIS, 2008e), based on a study that administered single oral doses at two levels to 10-day-old male NMRI mice (Eriksson et al. 2001). This was considered the only BDE-47 study useful for conducting a dose-response assessment (IRIS, 2008a). Mice were gavaged with 0 (vehicle only), 0.7 or 10.5 mg BDE-47/kg body weight on postnatal day 10 and then 8 to 18 mice per treatment group were subjected to neurobehavioral tests at two and four months of age (Eriksson et al., 2001). In tests of spontaneous motor activity at two months of age, spontaneous locomotion (horizontal), rearing (vertical) and total activity were decreased ($p<0.05$, $p<0.01$ and $p<0.01$, respectively) in the 10.5 mg/kg body weight group compared to vehicle controls in the first 20 minutes of the test but not in the second 20 minutes of the test. In contrast, spontaneous locomotion, rearing and total activity were increased ($p<0.01$) in mice dosed with 10.5 mg/kg BDE-47 compared to vehicle controls in the third 20 minutes of the test. Results at 4 months of age were similar, and all changes were significant at the $p<0.01$ level. The habituation capability (i.e., the ratio between performance in spontaneous motor behavior at 40-60 minutes and 0-20 minutes at two and four months of age compared to controls) for all three spontaneous behaviors decreased ($p<0.001$) with age in the 10.5 mg/kg group compared to vehicle controls, indicating that treated mice did not habituate to the decreasing novelty of test conditions over time as did control mice. Performance in the Morris water-maze test did not differ among treatments. The NOAEL and LOAEL values were determined to be 0.7 and 10.5 mg/kg, respectively, based on changes in spontaneous motor behavior and decreased habituation capability (IRIS, 2008e). To develop the RfD, a benchmark dose (BMD) approach was applied using habituation ratios for total activity as the point of departure. The benchmark response (BMR) was considered to be a change in mean equivalent to one standard deviation from the control mean. The 95% lower confidence limit of the BMD (reported as the $BMDL_{1SD}$, where SD equals the standard deviation) was determined to be 0.35 mg/kg (IRIS, 2008e). To the $BDML_{1SD}$, an uncertainty factor of three thousand (ten for interspecies variability, ten for intrahuman variability, three for extrapolation from a single-dose duration to chronic exposure duration, and ten for a deficient database) was applied to the $BDML_{1SD}$ to develop the RfD (IRIS, 2008e).

The principal study used to develop the RfD for BDE-99 was a study that administered single oral doses at five levels to 10-day-old male and female C57/Bl mice (Viberg et al., 2004). Mice were gavaged with 0 (vehicle only), 0.4,

0.8, 4.0, 8.0, or 16 mg BDE-99/kg body weight on postnatal day 10 and then a total of eight mice were subjected to the same neurobehavioral tests of spontaneous locomotion, rearing and total activity described in Eriksson et al. (2001), above, at two, five and eight months of age. Results for BDE-99 were similar to those for BDE-47, with spontaneous behaviors generally decreased compared to vehicle controls in male and female mice at doses of 0.8 mg/kg and above in the first 20 minutes of the test but increased at doses of 0.8 mg/kg and above compared to vehicle controls in the third 20 minutes of the test at two, five and eight months of age. Habituation capability at eight months of age compared to two months of age was decreased compared to controls for locomotion control in male mice exposed to 16 mg/kg and in female mice exposed to 4.0 or 16 mg/kg BDE-99. The NOAEL and LOAEL were determined to be 0.4 and 0.8 mg/kg, respectively, based on changes in spontaneous motor behavior and decreases in habituation capability for locomotion and rearing in male and female mice (IRIS, 2008f). The RfD was developed using the BMD approach using rearing habituation in 8-month-old mice as the point of departure. The BMD_{1SD} was 0.41 mg/kg and the $BDML_{1SD}$ was 0.29 mg/kg. To the $BDML_{1SD}$, an uncertainty factor of three thousand (ten for interspecies variability, ten for intrahuman variability, three for extrapolation from a single-dose duration to lifetime exposure duration, and ten for a deficient database) was applied to the $BDML_{1SD}$ to develop the RfD of 1×10^{-4} mg/kg-day (IRIS, 2008f). U.S. EPA chose this study to develop the RfD for BDE-99, even though other studies had a lower LOAEL, because "1) several different dose levels of BDE-99 were employed, 2) quantitative dose-response data were available with which to conduct benchmark dose modeling, 3) good model fits were obtained in subsequent BMD modeling, 4) a clear NOAEL was identified from this study, and 5) the results of this study are supported by several other studies in mice and rats" (IRIS, 2008b). This is the same value as the RfD determined for BDE-47.

Studies to assess the carcinogenicity of PBDEs in humans are not available. In 2008, U.S. EPA developed a CSF for BDE-209 using two-year feeding studies in male and female F344/N rats and B6C3F1 mice (IRIS, 2008h; NTP, 1986). Male rats were fed 0, 1,120, or 2,240 mg/kg-day deca-BDE and female rats were fed 0, 1,200, or 2,550 mg/kg-day deca-BDE. Male mice were fed 0, 3,200, or 6,650 mg/kg-day deca-BDE and female mice were fed 0, 3,760, or 7,780 mg/kg-day deca-BDE. The point of departure for calculating the CSF of the most sensitive endpoint (neoplastic nodules or carcinomas, combined, in male rat livers) was the LED_{12} (the 95% lower confidence limit of the dose associated with a 12% extra cancer risk) of 178 mg/kg-day. Dividing this into the slope of the linear extrapolation from the LED_{12} (0.12) gives a CSF of 0.0007 $(mg/kg-day)^{-1}$ (IRIS, 2008h). In 2006, for the purposes of screening analyses, the Cal/EPA PBDE Workgroup derived an upper bound cancer potency for deca-BDE of 0.00108 mg/kg-day using the same data. With the exception of the interspecies scaling factor applied (U.S. EPA used a body weight $(bw)^{3/4}$ scaling factor whereas the Cal/EPA PBDE Workgroup used a $(bw)^{2/3}$ scaling factor), these two values are in agreement.

In the IRIS document, U.S. EPA noted that NTP has changed histopathological terminology since the 1986 NTP study. The former "neoplastic nodule" is not completely equivalent to the currently defined "hepatocellular adenoma." It is possible that some lesions previously identified as "neoplastic nodules" may now be classified as benign hepatocellular adenomas (Wolf and Mann, 2005; see IRIS, 2008h for discussion). Consequently, U.S. EPA concluded that "the derivation of a cancer slope factor based on increased incidence of neoplastic nodules could result in an overestimation of risk. Overall, the risk presented is considered a plausible upper bound."

In summary, the non-cancer and cancer critical values used to evaluate the PBDEs in fish for the development of an FCG and ATLs are **$1x10^{-4}$ mg/kg-day (oral RfD) and 0.0007 (mg/kg-day)$^{-1}$ (CSF)**, respectively; derived by the U.S. EPA (IRIS 2008e,f,h). The FCG and ATLs for PBDEs are presented in Tables 1 and 2, respectively.

For fish consumption advisories, these values will be compared to the sum of analyzed PBDE congeners. There are currently 27 congeners analyzed in fish by the Department of Fish and Game Water Pollution Control Laboratory, including nine congeners that are most relevant on an environmental, bioaccumulation, and toxicological basis. These are BDE-28, -47, -99, -100, -153, -154, -183, -190, and -209. Non-detects will be given the value of one-half of the method detection limit (MDL) or zero depending on the data set(s).

Table 1. Fish Contaminant Goals (FCGs) for PBDEs Based on Cancer and Non-Cancer Risk* Using an 8-Ounce/Week (prior to cooking) Consumption Rate (32 g/day)**	FCGs (ppb, wet weight)
PBDE Cancer Slope Factor 7×10^{-4} **(mg/kg/day)$^{-1}$**	10000
PBDE Reference Dose 1×10^{-4} **(mg/kg-day)**	**310**

*The most health protective Fish Contaminant Goal for PBDEs (cancer slope factor- versus reference dose-derived) 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.

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.

Table 2. Advisory Tissue Levels (ATLs) for PBDEs Based on 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
PBDEs	≤100	>100-210	>210-630	>630

*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).

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.

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