PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

Water Soluble Polychlorinated Biphenyls Expected to be Found in Drinking Water

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PREFACE

Drinking Water Public Health Goals
Pesticide and Environmental Toxicology Branch
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This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that may cause chronic disease shall be based solely on health effects and shall be set at levels that OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.
7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.
8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.

9. In cases where scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the PHG should be set at that threshold.
10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.
11. PHGs adopted by OEHHA shall be reviewed at least once every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations or technical feasibility, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DHS shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By state and federal law, MCLs established by DHS must be at least as stringent as the federal MCL, if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not intended to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR WATER SOLUBLE POLYCHLORINATED BIPHENYLS EXPECTED TO BE FOUND IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal (PHG) of 0.00009 mg/L (0.09 μg/L, or 0.09 ppb) for water-soluble polychlorinated biphenyls (PCBs) expected to be found in drinking water. The PHG is primarily based on carcinogenic effects of the more water-soluble PCBs, as observed in experimental animals. Water-soluble PCBs for the purpose of the PHG are defined as those with 4 or fewer chlorines and with a water solubility of 240 μg/L or more at 25°C.

PCBs are a group of synthetic chlorinated organic chemicals that were first introduced into commercial use as insulating fluids for electric transformers and capacitors. Other applications that were developed included their use in hydraulic fluids, plasticizers, adhesives, paint additives and fire retardants. Production of PCBs in the US was halted in 1977 following concerns over their toxicity and persistence in the environment. The 209 structural variations of PCBs vary by the number and location of chlorine atoms on the basic biphenyl structure. PCBs were produced in the US by the Monsanto Company under the trade name Aroclor. Aroclors are various mixtures of congeners defined by a four-digit number. The first two digits represent the number of carbon atoms (12) while the second two digits give the percentage of chlorine by weight for the congeners in that mixture. In general, PCB persistence and toxicity increases with the degree of chlorination in the mixture (i.e., Aroclor 1260 is more persistent than Aroclor 1248). This PHG document primarily refers to mixtures similar to the Aroclors 1016 and 1242, which contain mostly congeners with 4 or fewer chlorines, because these less-chlorinated and more soluble forms are those most likely to be found in water.

An important toxicity study by Mayes *et al*. (1998) (among others) provides evidence of hepatocarcinogenicity in female rats for four different PCB mixtures (Aroclors 1016, 1242, 1254, and 1260), and also evidence of hepatocarcinogenicity in males for a high dose of one PCB mixture (Aroclor 1260). Such studies as this reveal how cancer potency varies by amount of chlorination in the congener mixture. In development of the PHG, OEHHA followed the recommendations of the United States Environmental Protection Agency (U.S. EPA, 1996b, 1999) draft guidelines for carcinogenic risk assessment, the U.S. EPA guideline on chemical mixtures, and the draft U.S. EPA cancer dose-response assessment for PCBs (U.S. EPA, 1996a). As part of the U.S. EPA PCB guidance document (1999b), U.S. EPA provided 3 cancer potency levels (or tiers) depending on the context of possible environmental exposure to PCBs. Based on this guidance document (1999b), OEHHA selected the slope factor of 0.4 $(mg/kg\text{-}d)^{-1}$ for the mid-potency ranking, which was called the low risk and persistence tier. This tier estimates an exposure due to a mixture of PCBs containing less than 50 percent chlorines (e.g., Aroclor 1242) and the ingestion of water-soluble congeners. The PHG was calculated

assuming a *de minimis* theoretical excess individual cancer risk level of 10^{-6} from exposure to Aroclor 1242 or a similar PCB mixture. The resulting cancer potency estimate is applied for exposure to water-soluble PCB mixtures expected to be found in drinking water.

OEHHA also determined a public health-protective concentration for the non-carcinogenic effects of PCBs. Three sensitive developmental endpoints (neurobehavioral, immunological, and low birth weights) were observed with at least three PCB mixtures. These were a mixture of congeners representative of those found in human breast milk, Aroclor 1016, or Aroclor 1254. Of the three, only the data from Aroclor 1016 and Aroclor 1254 were used to derive a public health-protective concentration for the non-carcinogenic effects because the physical properties of these mixtures render them more relevant to the mixtures likely to be found in water. At the lowest dose evaluated, Aroclor 1016 caused neurobehavioral developmental effects in offspring of rhesus monkeys treated with Aroclor 1016, while Aroclor 1254 caused reproductive/immunological changes in pregnant rhesus monkeys and developmental/immunological changes in infant rhesus monkeys. A geometric mean of the public health protective concentrations estimated from the three sensitive endpoints was calculated. The geometric mean is used in this case to account for varying potencies, mechanisms of action, and distributions of exposures, and would be representative of exposure to a mixture of PCB congeners. The public health-protective concentration for the most sensitive noncancer endpoints (neurobehavioral, 0.187 ppb; developmental, 0.560 ppb; immunological, 0.117 ppb; and reproductive, 0.351 ppb) is 0.3 ppb (0.3 μg/L) with rounding. This public health-protective concentration is only 3-fold higher than the value for the cancer public health-protective concentration. Therefore, the drinking water concentration that is protective against carcinogenic effects is also protective against non-cancer short term and chronic toxicity.

The U.S. EPA Maximum Contaminant Level (MCL) for PCBs in drinking water is 0.5 ppb, as is the California MCL. The U.S. EPA considers PCBs to be "probable human carcinogens" (Group B2), although the MCL is based on a practical quantitation limit, which is also 0.5 ppb.

INTRODUCTION

The purpose of this document is to establish a Public Health Goal (PHG) for water-soluble PCBs expected to be found in drinking water. We evaluated older and newer data on the toxicity of PCBs using the most applicable and up-to-date methodology. Most of the studies used commercial PCB mixtures to demonstrate the physical, chemical, and toxicological properties and effects of PCBs. An increasing number of studies are being undertaken using individual PCB congeners, but there are not yet adequate data from these studies to establish PHGs for individual PCB congeners.

A Maximum Contaminant Level (MCL) of 0.0005 mg/L (0.5 ppb) was established for PCBs in drinking water by the U.S. EPA (U.S. EPA, 1991), and the Maximum Contaminant Level Goal (MCLG) was set as zero. The MCL was based on a Practical Quantitation Limit (PQL) of 0.0005 mg/L, and was associated with a maximum lifetime

individual cancer risk of 1 in 10,000, according to the 1991 analysis. The California Department of Health Services also adopted an MCL of 0.0005 mg/L (DHS, 2002).

U.S. EPA has placed PCBs in Group B2 as a "probable human carcinogen" (IRIS, 2006). Cancer potency estimates for PCB mixtures used by U.S. EPA were based on the tiered approach for discussions of the MCL and MCLG based on 3 different potential patterns of environmental exposure to PCBs. A cancer potency estimate of 2 $(mg/kg\text{-}d)^{-1}$ was adopted for the "high risk and persistence" tier conditions while cancer potency factors of 0.4 and 0.07 $(mg/kg\text{-}d)^{-1}$ were adopted for "low risk and persistence," and "lowest risk and persistence" tier conditions, respectively. OEHHA's Air Toxics Hot Spots Program has adopted similar cancer potency estimates for PCBs for the same risk designations (OEHHA, 2005). Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), PCBs are listed as known to the State of California to cause cancer and reproductive toxicity (OEHHA, 2002). A cancer potency of 7.7 $(mg/kg\text{-}day)^{-1}$ was used to derive a no significant risk level (NSRL) for PCBs of 0.09 μg/day for purposes of Proposition 65.

CHEMICAL PROFILE

Chemical Identity

Polychlorinated biphenyls (PCBs, CAS Registry number 1336-36-3 for all PCBs) are complex mixtures of chlorinated biphenyl congeners. Individually these chemical compounds have the empirical formula $C_{12}H_{10-n}Cl_n$, where *n* (the number of chlorine atoms) is in the range 1-10. PCBs were manufactured by the chlorination of biphenyl using a suitable catalyst (e.g., iron chloride). Theoretically, 209 congeners with different numbers and/or positions of chlorine atoms on the two-phenyl rings are possible. These congeners are referred to by standard chemical nomenclature and are also numbered from 1 to 209 in ascending numerical order based on their chlorine substitution (IUPAC numbering adopted from Ballschmiter and Zell, 1980). PCBs may also contain impurities of polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzodioxins (PCDDs) (ATSDR, 2000). The concentration of individual congeners and impurities in commercial PCB mixtures depends on the manufacturing conditions. In addition, no two descriptions of commercial PCB mixtures even from the same lot or a manufactured product are identical because of the complexity of the mixture and difficulty in separating and identifying all of the congeners (ATSDR, 2000). In a survey of commercially available PCBs, about 130 of the possible 209 individual congeners were found (Safe, 1990).

Physical and Chemical Properties

In general, PCBs are chemically inert, resistant to heat, non-flammable, and have a low vapor pressure and a high dielectric constant (i.e., low electrical conductivity). These properties made them valuable for industrial use (WHO, 1993). Their general stability,

resistance to degradation, and lipophilicity also mean that they persist in the environment and accumulate in organisms.

Physical and chemical properties of two commercial PCB Aroclor mixtures are given in Table 1. These are average properties, which will vary with the congener content of the PCB mixture, and can be more specifically determined or predicted for individual congeners. Several investigators have published physical properties such as solubility, vapor pressure, log K_{ow} value, and Henry's law constant for individual congeners (Dunnivant and Elzerman, 1988; Dunnivant *et al*., 1992; Erickson, 2001; Falconer and Bidleman, 1994; Murphy *et al*., 1987; Sabljic and Gusten, 1989). The relative molecular mass of a monochlorobiphenyl is 188 and that of a completely chlorinated decachlorobiphenyl would be 494 (ATSDR, 2000). The average properties and composition of PCB residues in the environment will change as the residues are subject to partitioning, weathering, and biotransformation.

Table 1. Physical and Chemical Properties of Four Commercial PCB Mixtures*

Property	Aroclor 1016	Aroclor 1242	Aroclor 1254	Aroclor 1260
Molecular weight (ave.)	257.9	266.5	328	375.7
Color	Clear	clear	Light yellow	light yellow
Physical state	Oil	oil	Viscous liquid	sticky resin
Odor	no data	no data	no data	no data
Melting point	no data	no data	no data	no data
Boiling point	325 –356°C	325-366°C	365-390°C	385-420°C
Flash point	170°C	176-180°C	no data	no data
Flammability limits	none to boiling point	none to boiling point	none to boiling point	none to boiling point
Autoignition point	no data	no data	no data	no data
Solubility Water Organic solvents	 0.42 mg/L at 25°C very soluble	 0.24 mg/L at 25°C very soluble	 0.012 mg/L at 25°C very soluble	 0.0027 mg/L at 25°C very soluble
Specific gravity	NA	1.35 at 25°C	NA	1.58 at 25°C
Density	1.37 g/cm^3 at 25°C	1.38 g/cm^3 at 25°C	1.54 g/cm^3 at 25°C	1.62 g/cm^3 at 25°C
Partition coefficients Octanol-water (Log K_{ow}) Soil-organic carbon (K_{oc})	 5.6 no data	 5.6 no data	 6.5 no data	 6.8 no data
Vapor pressure	4x10^{-4} mm Hg at 25°C	4.06x10^{-4} mm Hg at 25°C	7.71x10^{-5} mm Hg at 25°C	4.05x10^{-5} mm Hg at 25°C
Henry's law constant	2.9x10^{-4} atm-M^3/mol	5.2x10^{-4} atm-M^3/mol	2.3x10^{-3} atm-M^3/mol	4.6x10^{-3} atm-M^3/mol
Percent of congeners with	100	75	16	0

Property	Aroclor 1016	Aroclor 1242	Aroclor 1254	Aroclor 1260
$\leq$ 4 chlorines				
Conversion factors				
Air (25°C)	1 mg/m^3 = 0.095 ppm	1 mg/m^3 = 0.092 ppm	1 mg/m^3 = 0.075 ppm	1 mg/m^3 = 0.065 ppm

*Values from ATSDR, 2000; Callahan *et al*., 1979; Erickson, 2001; Monsanto, 1974; and WHO, 1993.

Production and Uses

Commercial production of PCBs in the U.S. began in 1929 and ended in 1977 (ATSDR, 2000). Manufactured products are the primary source of environmental PCBs. Commercial PCB mixtures are referred to by their trade names. Monsanto Corporation produced most PCBs in the U.S. under the trade name Aroclor. A four-digit code was used to distinguish Aroclor mixtures; examples are Aroclor 1242, Aroclor 1248, Aroclor 1254, and Aroclor 1260. The (12) in the first two digits indicated that the parent molecule was biphenyl, and the last two digits indicated the average chlorine content by weight. Thus Aroclor 1242 had an average chlorine content of 42 percent by weight and Aroclor 1260 had an average chlorine content of 60 percent. The amounts of individual congeners vary in each Aroclor depending on the manufacturing conditions for each batch, but in general as the average chlorine content increases, so does the percent of congeners with more chlorine substitutions. The naming of Aroclor 1016 varies from the above system. This is also a PCB mixture developed by Monsanto that contained primarily mono-, di-, tri-, and tetra-chlorinated congeners, yielding an average chlorine content of 41 percent (ATSDR, 2000). Table 1 lists the percent of congeners with 4 or less chlorines for four commercial mixtures. PCBs are no longer produced in the U.S., except under exemption for use as a mounting medium in microscopy, immersion oil in microscopy, optical liquid, and research and development (U.S. EPA, 1990).

Trade names for PCB mixtures produced outside of the U.S. include: Clophen in Germany; Kanechlor in Japan; and Phenoclor in France. Kanechlor 500 has a composition similar to Aroclor 1254, and Clophen A 60 and Phenoclor DP-6 are similar to Aroclor 1260.

Because of their chemical and physical properties, PCBs had a number of industrial uses. Their most frequent uses were as dielectrics in transformers and large capacitors and as heat resistant (cooling) liquids in heat transfer and hydraulic systems (WHO, 1993). They were also used in formulations of lubricating and cutting oils and wax extenders, and as plasticizers in paints, flame retardants, plastics and other compounds. Close to seven million tons were produced in the U.S. from 1930 to 1975 (ATSDR, 2000).

Analytical Methods

PCB residues can be estimated using gas-liquid column chromatography with an electron capture detector (WHO, 1993) to separate and measure them in various media. Residues are typically quantitated as an estimated mass of technical mixture (e.g., Aroclor 1242, Aroclor 1254, etc.) based on analysis of total chromatographic area or characteristic peaks. More recently, using capillary chromatography and synthetic standards, PCB residues can be quantitated as a subset of the occurring PCB congeners. Determinations of environmental PCB residues based on estimating Aroclor values from total chromatographic area or prominent peaks are open to variation. This is due to the subjective assignment of Aroclor speciation and response factors to mixtures in which the congener composition and profiles may be altered by partitioning, weathering, and biotransformation (ATSDR, 2000). Analysis of specific congeners yields a more objective PCB profile, which can be referenced to technical Aroclor profiles or characterized as highly weathered. For specific analytical methods, the reader is referred to ATSDR (2000), Section 7.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

The majority of PCBs released into the environment are man-made. PCBs enter the environment through accidental spills and leakage, volatilization and surface runoff. Over one hundred million pounds of PCBs are estimated to have been released into the environment as a result of human activities (Hutzinger and Veerkamp, 1981). Volcanic eruptions have been identified as a very minor source of natural PCBs (Pereira *et al*., 1980). Once released in the environment, PCBs are stable, very persistent and accumulate in biological organisms. Their environmental fate is determined by their favored partitioning into certain environmental compartments. PCB residues are found chiefly in soil, sediment, and fatty biological tissues. Soils and sediments, especially those with higher organic carbon content, act as sinks for PCBs that adsorb to them. Non-occupational exposure to PCBs is primarily through ingestion of animal protein (fish, poultry, and meat) contaminated with PCBs. Ingestion of contaminated soil by children may also be another route of exposure to humans. Inhalation of contaminated air and ingestion of contaminated water are additional minor sources of human exposure to PCBs.

Air

PCBs already introduced into the environment cycle into the atmosphere and are distributed and deposited worldwide. PCBs volatilize from soil, landfills, and sewage sludge and are released in PCB fires. PCBs also volatilize from water bodies despite low vapor pressures due to their hydrophobicity. Some PCBs are also released into the atmosphere from municipal incinerators where PCBs in contaminated waste are not completely broken down due to inadequate temperatures and their chemical resistance (WHO, 1993). Volatilization of lower chlorinated congeners is greater than higher

chlorinated congeners. Other factors influencing the rate of vaporization are ambient temperature and the characteristics (e.g., carbon content) of particles to which PCBs are adsorbed. PCBs exist in both the gaseous form and adsorbed to airborne particles and aerosols, and are found in rain and snow.

Industrial areas tend to have higher levels of airborne PCBs and measured levels in indoor air are greater than outdoors (U.S. EPA, 1988b). PCBs ranged in air concentration from <0.1 - 10 ng/m^3 in the U.S. in one survey (Baker and Eisenreich, 1990), although occupational exposures would have been higher (WHO, 1993). Non-occupational airborne exposure has been estimated as 100 ng/day via inhalation (ATSDR, 1996) of urban indoor air (5 ng/m^3). However, inhalation is not presently a major human exposure pathway for PCBs.

Soil

PCBs can be deposited on soil via atmospheric deposition, point-source emissions, or direct deposition from accidents, spills, or spreading sewage sludge. PCBs readily adsorb to soils and have a strong affinity to organic carbon in soil. The degree of adsorption of PCB congeners to soils is proportional to their chlorine content. The half-lives of the various PCB congeners in soil and sediment are on the order of months to years (Gan and Berthouex, 1994). Although leaching of PCBs does occur, PCBs are not well mobilized or leached through soils by water because of their hydrophobicity. The major pathways of removal of PCBs from soil are the volatilization and chemical or biological biodegradation pathways. PCB levels in soil are typically <0.1 μg/g, but can be much higher in areas with local contamination. Soil is not a major route of human PCB exposure (U.S. EPA, 1988b; WHO, 1993).

Water

PCBs have a high octanol:water partition coefficient and low solubility in water. Consequently, PCBs in water tend to partition out of the water phase and adsorb to sediment and suspended particles, especially particulate matter with higher organic carbon content. PCB congeners dissolved in water are primarily those with lower chlorine content (≤4 chlorines), while those with higher chlorine content move into the sediment (U.S. EPA, 1988b; WHO, 1993). Water solubility for PCB congeners with chlorine content of 4 or less chlorines (tetrachlorobiphenyls) and for some PCB commercial mixtures primarily composed of these congeners are 240 μg/L at 25 °C or more (Erickson, 2001). PCBs in water are broken down chiefly by photolysis, but also by biodegradation (ATSDR, 1996). Arimoto (1989) estimated residence times of PCBs in water in the Great Lakes of 0.2 -3.3 years depending on the lake. For purposes of the public health-protective concentration, the water-soluble PCBs are those with ≤4 chlorines and with a water solubility of 240 μg/L or more at 25°C.

PCBs residues of 500 ng/L (0.5 ppb) have been detected in surface water. Levels in drinking water and ground water from non-contaminated sources are typically lower, e.g., not detected to 5 ng/L, and seldom exceed 100 ng/L (U.S. EPA, 1988b; WHO, 1993).

Drinking-water exposure at 5 ng/L would be about 10 ng/day for adults consuming 2 L/day of tap water. Miyata *et al*. (1993) estimated that drinking water exposure would be <0.01 percent of dietary PCB exposure. More recently, PCB exposure from drinking water has been suggested to be <200 ng/day, assuming a concentration of <0.1 μg/L PCB and a water consumption rate of 2 L/day (ATSDR, 2000).

The MCL of 0.5 ppb for PCBs in drinking water was the practical quantitation level based on U.S. EPA approved analytical chemistry detection methodology and monitoring requirements (U.S. EPA, 1991). In California, the "detection limit for reporting" is 0.5 ppb, which is equivalent to the MCL. Of the 4,985 drinking-water sources analyzed for PCBs in California from 1984 to 2001, none had reportable PCB levels (DHS, 2002).

Food

Food is an important route of human exposure to environmental (non-occupational) PCBs. PCBs are found in commercial meat, fish, poultry, dairy products, human breast milk, and oils and fats. The more-lipophilic higher-chlorinated congeners tend to accumulate most readily in foods, but the exact congener profile also depends on differential metabolism in the living organism.

The dietary intake of PCBs has declined in recent years, according to the available data. The Food and Drug Administration Market Basket Survey for 1979 (FDA, 1982) estimated adult dietary intake as 0.0133 μg/kg-day (931 ng/day for a 70 kg adult). Adult dietary intake during 1982-1984 was estimated as 35 ng/day (ATSDR, 1996). The estimated dietary intake of PCBs for an adult was 0.027 μg/kg-day in 1978 and 0.0005 μg/kg-day in 1982-1984 (ATSDR, 1996). The latter estimate was based on the 1982-1984 estimate of 35 ng/day for a 70 kg adult. For infants (6-11 months), the decline was from 0.011 μg/kg-day in 1978 to 0.0012 μg/kg-day in 1982-1984 (ATSDR, 1996). Similarly, dietary intake of PCBs for toddlers (2 years of age) declined from 0.099 μg/kg-day in 1978 to 0.0088 μg/kg-day in 1982-1984 (ATSDR, 1996). In more recent years (1992-1997), the intake levels of dietary PCB remained relatively steady: <0.001 μg/kg-day in 1982-1984 for 25 to 30 year old adults compared to <0.002 μg/kg-day in 1997 (ATSDR, 2000). Similarly, the levels for children and older adults remained unchanged up to 1997. In children, the 1997 levels were <0.001, 0.008, 0.003, and 0.003 μg/kg-day for 6-11 months, 2 years, 6 years, and 10 years old, respectively. The difference reported in intake levels may reflect the particular diets that children were given. For example, an infant will receive either breast milk or formula, while an older child will receive a diet that resembles an adult's.

These estimates do not include dietary intake from non-commercial fish and wildlife, some of which have elevated levels of PCBs. PCB levels from 17 ppb to >500 ppb have been found in several sport fish species in San Francisco Bay (SFBRWQCB, 1994). Eating one 8-ounce fish meal a week from San Francisco Bay would result in a PCB exposure between 550 and 16,000 ng/day.

METABOLISM AND PHARMACOKINETICS

Absorption

PCBs are absorbed following oral, dermal and inhalation exposure. PCBs should passively absorb to lipophilic cell membranes. Direct evidence for human gastrointestinal absorption comes from a study in which a volunteer ingested a single dose of a specially prepared ^{13}C-PCB mixture containing 54 percent chlorine (Buhler *et al*., 1988). Blood samples showed that congeners (mainly penta-, hexa- and some heptachlorobiphenyls) were readily absorbed and distributed to the blood. The maximum blood concentration of PCB was reached within two days of dosing. McLachlan (1993) showed that PCBs (penta-, hexa- and heptachlorobiphenyl congeners) in breast milk are readily absorbed by nursing infants and estimated that at least 95 percent of the dose was absorbed. Indirect evidence of human absorption following oral exposure comes from studies of women consuming Great Lakes fish contaminated with PCBs (Schwartz *et al*., 1983). Elevated levels of PCBs were found in the serum and breast milk of these women.

Animal experiments document the gastrointestinal absorption of individual congeners (Albro and Fishbein, 1972) and show that in rats (Tanabe *et al*., 1981) lower chlorinated congeners are absorbed more efficiently (95 percent for dichlorobiphenyls) than higher chlorinated congeners (75 percent for octachlorobiphenyls). Retention of greater than 90 percent was observed following gavage of doses from 5 to 100 mg/kg. Similar results were observed in monkeys administered a single dose of 1.5 or 3.0 g Aroclor 1248/kg by gavage (Allen *et al*., 1974) and in ferrets given 0.05 mg ^{14}C-labeled Aroclor 1254 in the food on days 14 and 35 of gestation (Bleavins *et al*., 1984).

Dermal absorption of PCBs is important for occupationally exposed individuals and for those exposed via skin contact to contaminated soil and water at hazardous waste sites. Schmid *et al*. (1992) used a specially prepared ^{13}C-PCB mixture containing 8 individual congeners (1 tetra-, 3 penta-, 2 hexa- and 2 heptachlorobiphenyls) for experimental dermal exposure of a volunteer human subject. They measured blood plasma levels of congener 153 and estimated that in one experiment about 6 percent of the applied dose was absorbed through the skin. Dermal absorption of PCBs (42 percent and 54 percent chlorine content) across monkey and guinea pig skin has been shown to be approximately 15-34 percent in monkeys and 33 percent (42 percent chlorine) and 56 percent (54 percent chlorine) of the applied radioactivity in the guinea pigs (Wester *et al*., 1983). Wester *et al*. (1990) also reported that the *in vivo* percutaneous absorption of Aroclor 1242 across abdominal skin of monkeys varied between 18 percent (trichlorobenzene) and 20 percent (mineral oil) depending on vehicle used. For Aroclor 1254, very similar percentages were reported (Wester *et al*, 1990). Absorption of PCBs from contaminated soil across skin has also been determined. Wester *et al*. (1993) investigated dermal absorption of Aroclor 1242 and 1254 from soil *in vivo* in rhesus monkey, and *in vitro* in human skin and powdered human stratum corneum. They estimated *in vivo* dermal absorption of Aroclor 1242 as 13.8 ± 2.7 percent (SD), and Aroclor 1254 as 14.1 ± 1.0 percent. *In vitro* experiments with human skin and powdered stratum corneum showed that the Aroclor mixtures partitioned from water into soil and then into skin.

Inhalation absorption is potentially important for occupationally exposed persons. Absorption via this route is not well quantitated in animals or humans. Benthe *et al*. (1972) exposed male rats to an aerosol of a PCB mixture containing 42 percent chlorine (30 g/m^3) for about 2 hours and showed that PCBs were quickly distributed to the liver (~40 μg/g tissue). Since this was a whole-body exposure, the dermal and oral routes may have contributed to the observed absorption. Human absorption via inhalation has been inferred from serum and adipose tissue levels in occupationally exposed workers (Fitzgerald *et al*., 1986; Wolff, 1985).

Distribution

PCBs quickly enter the blood following absorption into the body. The distribution is not route-dependent. Distribution of PCBs is dependent on their biophysical properties and follows their lipid solubility and concentration gradients. PCBs in blood are taken-up into lipoproteins and other plasma proteins (Spindler-Vomachka *et al*., 1984) and distributed throughout the body by the circulatory system. Initially PCBs tend to accumulate in the liver and in muscle tissue, both of which are highly perfused. PCBs have also been detected in the brain, kidney, adrenal, spleen, bone marrow, and testis (Schecter *et al*., 1989; Benthe *et al*., 1972). Over time, PCBs preferentially partition out of the blood and into adipose tissue (Brown and Lawton, 1984). PCBs are also subject to some metabolism, as seen in exposed workers in whom higher levels of congeners with chlorines at the 4 and 4' position were found in serum and adipose tissue than congeners with unsubstituted 3,4 positions on at least one ring (Wolff *et al*., 1982, 1992). Studies in sheep suggest that the lymphatic system may also contribute to PCB distribution (Ziprin *et al*., 1980).

Kuwabara *et al*. (1979) evaluated the distribution of PCBs following oral administration. An increase in total PCB levels in the blood was observed within five hours in human volunteers who consumed a mixture of PCBs in contaminated fish (Kuwabara *et al*., 1979). The blood concentration returned to pre-meal levels in 17 hours as PCBs accumulated in fatty tissues. In occupationally exposed workers, the major congener peaks found in serum and adipose tissues are penta-, hexa-, hepta-, and octachlorobiphenyls (Fait *et al*., 1989). This reflects the elimination of more readily metabolized congeners from tissues and the redistribution of the more persistent congeners at dynamic equilibrium (Matthews and Dedrick, 1984).

Several studies show that PCBs can cross the placental barrier and accumulate in fetuses (Allen and Barsotti, 1976; Takagi *et al*., 1976; Vodicinik and Lech, 1980). PCBs also accumulate in the fat portion of milk in lactating mothers and are passed to suckling offspring (Schwartz *et al*. 1983; Barsotti and van Miller, 1984; Jacobson *et al*., 1984; McLachlan, 1993). This is a potentially important exposure route for young infants.

Metabolism

Microsomal cytochrome P-450 enzymes in the liver metabolize PCBs. In general, metabolism of PCBs seems to reduce toxicity more than it produces activated products

with a major role in PCB toxicity (Hansen, 1999; Safe, 1993). The metabolism of PCB congeners is through formation of arene oxide intermediates, which are potential electrophiles. These highly reactive metabolites can be hydrated to yield trans-dihydrodiols and rearrange to phenols with shifted substituents. The most active P-450 isozymes in metabolizing most PCBs are the P-450 monooxygenases of the 1A and 2B types. PCB metabolites are usually more polar than their parent compounds. Hydroxylated metabolites can be further conjugated with glutathione, and/or glucuronic acid and sulfates prior to elimination (Safe, 1989). Metabolites in addition to phenolic products include sulphur-containing metabolites (Klasson-Wehler *et al*., 1987), trans-dihydrodiols (Norback *et al*., 1976), polyhydroxylated congeners (Koga *et al*., 1989), and methyl ether derivatives (Koga *et al*., 1989; Safe, 1980, 1989; Sipes and Schnellmann, 1987). For a more extensive review of the metabolism, the reader is referred to ATSDR (2000).

The rate of metabolism of a PCB mixture depends on its congener composition since each congener is independently metabolized. The rate of metabolism of individual congeners depends on the number and position of chlorine atoms on the phenyl ring and on the animal species. Considerable variations in metabolite distribution occur among different species when administered a specific PCB congener (Safe, 1980). As the degree of chlorination increases on both phenyl rings, the rate of metabolism decreases (Safe, 1980). Metabolism (hydroxylation) occurs more readily for PCBs with unsubstituted para positions of both biphenyl rings and at carbon atoms that are para to the chloro substituent in the lower chlorinated biphenyls (Safe, 1980).

PCBs are capable of inducing their own metabolism. Some PCBs induce P-450 monooxygenase 2B1 and 2B2 (induced by phenobarbital) and some PCB congeners induce cytochrome P-4501A1 and P-4501A2 (induced by 3-methylcholanthrene) (Kaminsky *et al*., 1981). Another category of PCBs can induce both systems. The metabolism of individual congener is highly dependent on the structure of the substrate and the type of cytochrome P-450 isozyme. Kaminsky *et al*. (1981) showed that the phenobarbital-induced cytochrome P-450 isozymes preferentially metabolize di-ortho-chloro substituted biphenyls. For the 3-methylcholanthrene-induced cytochrome P-450 isozymes, these isozymes primarily metabolize dichlorobiphenyls that do not contain ortho substituents. The oxidation of mono-ortho-chloro substituted dichlorobiphenyls is catalyzed by both P-450 systems.

Experiments in monkeys showed that fetuses accumulated all of the congeners present in a commercial mixture (Aroclor 1016) fed to their mothers, but that only a subset of congeners were found in adults and infants (Barsotti and van Miller, 1984). This suggests that fetal metabolism of PCB mixtures is different than in adults and older infants.

Excretion

The major excretory pathways for PCBs were the fecal and urinary routes. In general, much greater amounts are excreted in the feces than in the urine, independent of route of administration. For nonpolar derivatives, excretion is primarily through the feces while

polar derivatives are preferentially found in the urine. Biliary excretion represents a major source of the PCB compounds found in the feces (Allen *et al*., 1974; Norback *et al*., 1976). In addition to the fecal and urinary routes, some trace amounts of PCBs can be found in exhaled air (Lutz and Dedrick, 1987; Sipes and Schnellmann, 1987).

Another route of PCB excretion is through the mother's milk. Although large amounts of PCBs are excreted in the mother's milk, the composition of the PCBs being excreted in human milk was found to be not identical to that of the original PCB source (Safe *et al*., 1985). PCB accumulation for infants from industrialized countries has been estimated to be 6.8 percent of its lifetime PCB body burden during a nursing period of 6 months (Kimbrough, 1995). Mes *et al*. (1994) showed that the levels in Rhesus monkey infants rise to exceed the levels in mothers during breast-feeding and then decline rapidly about 10 weeks after weaning. An additional 40-50 weeks are needed for the PCB levels in offspring to decline to levels in the mothers and a total of about 100 weeks for the levels in infants to fall to the background level in blood in the control group.

Serum half-lives for PCBs can vary significantly depending on the extent of chlorination, type of substitution, exposure, and person. Individuals exposed to PCB-contaminated rice in the Yu-Cheng incident in Taiwan had elimination half-lives from whole blood ranging from months to years (Chen *et al*., 1982; Ryan *et al*., 1993). For example, a mean elimination half-life of 9.8 months (4.1 to 24.1 months) was reported for 2,3',4,4', 5'-pentachlorobiphenyl, while a mean half-life of 6.7 months (3.3 to 12.1 months) was observed for 2,3,3',4,4'-pentachlorobiphenyl (Chen *et al*, 1982). In this study, Chen *et al*. (1982) observed that tetra- and pentachlorobiphenyls with adjacent unsubstituted carbon atoms in the meta and para positions were rapidly eliminated from blood. The opposite was reported for congeners with the same degree of chlorination but with adjacent unsubstituted ortho-meta positions. Hexa- and heptachlorobiphenyls with adjacent unsubstituted ortho-meta positions were also eliminated slowly.

The serum elimination half-lives for different congeners were also dependent on the exposure and the individual. Serum half-lives varied from 0.3 years to 7.6 years in Rhesus monkeys administered the same congener (Mes *et al*., 1995). In recorded poisonings (work-related or contaminated food), humans have had a variation in serum elimination half-lives for various congeners from 0.6 to 4.6 years (Brown *et al*., 1989).

The extent of chlorination also determines the half-life of the congener. At equilibrium, chlorobiphenyl congeners are eliminated from tissues according to individual kinetic parameters. In rats given six weekly oral doses of PCBs, three general patterns of elimination were observed by Tanabe *et al*. (1981). Congeners with di- and trichlorobiphenyls had elimination half-lives of 1-2 days. The second pattern of elimination observed for another set of congeners, primarily tetrachlorobiphenyls, had 2 elimination constants: one between 2 and 10 days and a second one of $\leq$90 days. The third pattern of elimination was for mostly pentachlorobiphenyl and hexachlorobiphenyl congeners, which had an elimination half-life of > 90 days. A similar pattern also was observed in humans (Wolff *et al*., 1992). For lower chlorinated congeners (tri- and tetrachlorobiphenyls), the whole body elimination half-life ranged from 1 year to 6 years (except for 2,4,4',5- and 2,3',4,4'-tetrachlorobiphenyl, which were much higher). The

whole body elimination half-life ranged from 8 to 24 years for higher chlorinated congeners (penta and above).

One other factor that causes an increase in elimination half-lives is the influence of growth. Growth of the body leads to increases in fat compartments. The increased fat compartment causes a redistribution of the lipophilic congeners, which results in a longer elimination time.

Summary of Absorption, Distribution, Metabolism and Excretion

In both humans and animals, PCBs are absorbed following oral, dermal and inhalation exposure. In general, absorption is more efficient via the oral route compared to the dermal route. Once absorbed, PCBs will tend to accumulate in the lipid-rich tissues due to their lipophilic nature: greater relative levels of PCBs are found in liver, adipose tissue, skin, and breast milk. PCBs are metabolized by the microsomal monooxygenase system, catalyzed by cytochrome P-450, into metabolites that can further be conjugated with glutathione and glucuronic acid. The rate of metabolism is dependent on the number and position of chlorine atoms on the phenyl ring of each congener, and varies across animal species. The major routes of excretion are fecal and urine, with some PCBs and metabolites also being excreted through the mother's milk.

Mechanism of Action

The biological effects observed following the administration of various PCB mixtures differ qualitatively and quantitatively and suggest the possibility of the existence of multiple and diverse mechanisms of action. The mechanisms of toxicity are not clearly understood for all PCBs and are therefore only briefly highlighted in this document. Evidence exists for effects mediated through the Ah receptor and effects involving Ah-receptor-independent mechanisms. For many PCBs, chlorinated dibenzodioxins (PCDD), chlorinated dibenzofuran (PCDF) congeners, and other structurally related halogenated aromatic hydrocarbons, a similar toxic mechanism is suggested based on the similarities in their structures. The proposed mechanism of action for this set of congeners is based on the ability of the compounds to bind to a cellular receptor (Ah receptor) and induce microsomal enzymes (cytochrome P-450-dependent monooxygenases). The proposed mechanism of action for other PCB congeners is based on the induction of microsomal enzymes and estrogenic activity without binding the Ah receptor. Other Ah-receptor-independent mechanisms include altered intracellular calcium homeostasis, alterations in other signal transduction pathways, decreases in brain dopamine levels, and immunological changes.

Ah-Receptor Mediated Effects

Attempts to delineate the structure-receptor binding, structure-induction, and structure-toxicity relationships mediated through the Ah receptor have been made (Bandiera *et al*., 1982; U.S. EPA, 1991; Goldstein and Safe, 1989; Hanneman *et al*., 1996; Hori *et al*.,

1997; Leece *et al*., 1985; Parkinson *et al*., 1980, 1983; Poland *et al*., 1976; Safe, 1984, 1989, 1990, 1993, 1994; Safe *et al*., 1985; Yoshimura *et al*., 1979). The Ah receptor regulates the synthesis of a variety of proteins. Binding of the Ah receptor is thought to initiate the expression of the toxic response. Bandiera *et al*. (1982) estimated the *in vitro* structure-binding relationships for a series of PCB congeners (dioxin-like PCBs) using rat hepatic cytosol preparations. The variable affinity of the congeners was determined to be related to the chlorine substitution pattern. The congeners with the highest affinity were the isostereomers of 2,3,7,8-tetrachlorodibenzodioxin (TCDD), which were unsubstituted or monosubstituted in positions 2 and 2'.

Like the structure-binding relationships, the administration of PCB congeners also resulted in a structure-enzyme induction relationship. In particular, Goldstein and Safe (1989), Leece *et al*. (1985), Parkinson *et al*. (1980), Poland and Glover (1977), Safe (1990), and Yoshimura *et al*. (1979) have studied the induction of hepatic aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin O-deethylase (EROD) in mammalian cell cultures and in laboratory rodents with congeners. Intraperitoneal administrations in male Wistar rats showed that the structure-activity relationships for AHH and EROD inductive potency for a series of congeners were comparable to those reported for the structure-binding relationships (Leece *et al*., 1985). The data suggested a common receptor-mediated mechanism. Sawyer and Safe (1982) provided further support for a common receptor-mediated mechanism of action by demonstrating a linear correlation between AHH induction *in vitro* and *in vivo*.

Structure-toxicity relationships mediated through the Ah receptor were also demonstrated by Leece *et al*. (1985) and Yoshimura *et al*. (1979). Both researchers found structure – dependent changes in ED_{50} values for hepatic microsomal EROD and AHH induction, inhibition of body weight gain, and thymic atrophy following the intraperitoneal administration of several PCB congeners to immature male Wistar rats. Some minor deviations were noted and were postulated to be the result of *in vivo* metabolism. Other researchers have also found a relationship between toxicity and structure. In 1997, Hori *et al*. (1997) reported a link between Ah-receptor responsiveness and inhibition of body weight gain or enzyme level change using two mouse strains (one Ah responsive [C57BL/6] and one non-Ah responsive [DBA/2]) and three PCB congeners. Effects were observed in Ah responsive animals following the administration of 3,3',4,4',5-pentachlorobiphenyl and not in the non-Ah responsive animals or with the other low affinity PCB congener. Franklin *et al*. (1997) and Smith *et al*. (1990a,b) also observed a link between Ah responsiveness and uroporphyria when female F344 rats and female C57BL/6 mice were treated with Aroclor 1254.

Ah-Receptor Independent Effects

Only a small number of PCB congeners in a commercial mixture exhibit Ah receptor-mediated responses. The remaining congeners in a commercial mixture may have a different mechanism and be involved in the elicitation of a toxic response. Some of the congeners whose mechanism of action does not involve the Ah receptor are the di-ortho substituted PCB congeners and those with one or two para chlorines (Connor *et al*., 1995;

Hansen, 1998; Schuetz *et al*., 1998; Seegal *et al*., 1990, 1991b, 1994). Several investigators have found these type of congeners to alter brain cell intracellular calcium homeostasis and related signal transduction pathways (Rao and Banerji, 1993; Kodavianti and Tilson, 1997; Tilson and Kodavanti, 1997, 1998; Tilson *et al*., 1998; Wong and Pessah, 1996, 1997; Wong *et al*., 1997), decrease dopamine levels (Seegal *et al*., 1989, 1990; Shain *et al*., 1991), increase tissue injury related to activation of neutrophils (Brown and Ganey, 1995; Ganey *et al*., 1993; Tithof *et al*., 1995), and inhibit a specific ATPase activity (Maier *et al*., 1994). The reported changes in activity and the detection of some of these PCBs in several brain regions of treated nonhuman primates (*Macaca nemestrina*) led to the proposal of a mechanism of neurotoxicity (Seegal *et al*., 1990).

In addition, some of the tri-ortho substituted non-coplanar congeners also inhibit microsomal calcium release channels (Wong and Pessah, 1996). These alterations and inhibitions may be due to the direct effect on protein kinase C, phospholipases, and/or the ryanodine receptor (Wong and Pessah, 1996).

Effects Involving Ah-receptor Dependent and Independent Mechanisms

PCBs have also been shown to have effects on several systems through Ah-dependent and independent mechanisms. Hori *et al*. (1997) reported liver hypertrophy in Ah-responsive and Ah non-responsive mice following the administration of three PCB congeners with varying affinity for the Ah receptor.

Other changes proposed to occur through Ah-receptor dependent and independent mechanisms include effects on neurodevelopment or reproduction elicited through changes of steroid hormone homeostasis (Arcaro *et al*., 1999; Connor *et al*., 1997; Gierthy *et al*., 1997; Fischer *et al*., 1998; Li and Hansen, 1997; Nesaretam and Dabre, 1997; Seegal *et al*., 1997) or disruption of thyroid hormone levels (Brouwer *et al*., 1998; Hansen, 1998; Li and Hansen, 1996a,b, 1997; Porterfield, 2000). Both direct and indirect estrogenic actions by PCB congeners have been proposed by Waller *et al*. (1995), Jansen *et al*. (1993), and Li *et al*. (1994). Jansen *et al*. (1993) suggested that some PCB congeners might increase gonadotrophin-releasing hormone, affect production and release of luteinizing hormone from the pituitary, or produce effects beyond the receptor for gonadotrophin-releasing hormone.

Immunological effects caused by PCBs have also been reported to occur through Ah-dependent (Harper *et al*., 1993a; Silkworth and Grabsten, 1982) and independent mechanisms (Harper *et al*., 1993a,b; Stack *et al*., 1999). PCB congeners varying in affinity for the Ah receptor were used to evaluate the relationship between immunotoxicity and CYP1A1 induction. The results provided evidence for the existence of the Ah-independent mechanism.

The proposed mechanism for the PCB-induced cancer is through the promotion of oncogenic cells (Cogliano, 1998; Safe, 1994) or through genotoxic mechanisms (Robertsons and Gupta, 2000). Understanding of the involvement of Ah-dependent and independent mechanisms in this effect is incomplete, although the work of several

investigators (Preston *et al*., 1985; Hemming *et al*., 1993; Mayes *et al*., 1998; Silberhorn *et al*., 1990; Safe, 1994; van der Plas *et al*., 1998) provides some experimental evidence.

Summary of Mechanism of Action

In summary, a clear understanding of the toxic mechanism(s) of PCBs is not yet available. The two major mechanisms are implicated for the biological effects observed following the administration of PCBs. Effects mediated through the Ah receptor are associated with PCBs structurally similar to TCDD. For other PCB congeners, the proposed mechanism is based on Ah-receptor-independent effects that include altered intracellular calcium homeostasis, alterations in other signal transduction pathways, decreases in brain dopamine levels, and immunological changes. Overall, qualitative and quantitative differences are observed for the PCBs, which suggests the possible existence of multiple and diverse mechanisms. Because of this, and the fact that congeners found within a commercial mixture have various potencies, the extrapolation methods for calculating the PHG for the PCB commercial mixtures did not rely on one specific mechanism of action.

TOXICOLOGY

Toxicological Effects in Animals

PCB mixtures produce low to moderate acute toxicity in mammalian species, but produce pronounced subacute and chronic toxicity. In addition, as reported for other halogenated aromatic hydrocarbons, PCBs exhibit significant interspecies variability in toxicity. In considering the health effects of PCBs in animals, it is important to consider the isomer and congener composition of the PCBs, potential impurities, the length of exposure, and the species under investigation.

Since the purpose of this document is to establish a PHG for water-soluble PCBs expected to be found in drinking water, the toxicological summaries provided below highlighted studies conducted with the more water-soluble PCB commercial mixtures (e.g., Aroclor 1016, Aroclor 1242, A 30, Kanechlor 300, and to some extent Aroclor 1254). In addition, data from studies on other commercial mixtures (e.g., Aroclor1260), individual congeners, and a PCB mixture simulating the PCBs found in human breast milk are also presented.

Acute Toxicity

A number of studies have been conducted to determine LD_{50} values in experimental animals using commercial Aroclors. The lowest oral (PCBs in vegetable oil) LD_{50} values in rats are between 1 and 2 g/kg (see summary tables in WHO, 1993 and ATSDR, 2000). The LD_{50} for Aroclor 1254 was 1,010 to 1,295 mg/kg, for Aroclor 1242 was 4,250 mg/kg, and for Aroclor 1260 was 1,315 mg/kg. LD_{50} values for Aroclor 1221, 1254, and 1242 in the mink were 750-1,000, 4,000, and >3,000 mg/kg, respectively. Variation in

the LD_{50} values may be related to animal strain, age, sex, formulation, and congener composition.

No inhalation studies were located. Dermal LD_{50} values for rabbits were between 0.8 and 3.16 g/kg. The dermal LD_{50} values for Aroclor 1242 and 1248 ranged between 794 mg/kg and 1,269 mg/kg, for Aroclor 1232 and 1260 ranged between 1,260 and 2,000 mg/kg, and for Aroclor 1221 and 1262 ranged between 1,260 and 3,160 mg/kg (ATSDR, 2000; Fishbein, 1974).

The primary cause of death in these animals was not determined. Effects observed in the oral studies included ulceration of the glandular stomach and duodenum, increased liver weight, and renal tubular damage (Bruckner et al., 1973, 1974; Kimbrough *et al*., 1972). No specific toxic effects (other than death) were reported following acute dermal exposure to PCBs.

Subchronic Toxicity

A summary of the effects observed in animals exposed to commercial PCBs is found in ATSDR (2000) and WHO (1993). The reported effects varied in severity depending upon the isomer and congener composition of the PCB mixture used, presence of potential impurities, the length of exposure, and the species under investigation. Subchronic oral exposures of experimental animals to commercial Aroclor mixtures result in decreases in body weight gain in mice, rats and monkeys (WHO, 1993). Histological changes in the liver, changes in liver weight, and skin lesions are also commonly observed at doses less than 10 mg/kg (ATSDR, 2000). In addition, liver, neurobehavioral, and immunological changes were observed in several animal studies. The neurobehavioral and immunological changes are described separately. Similar changes were noted in rabbits exposed dermally. Table 2 summarizes some of these changes more precisely.

In general, Rhesus monkeys were found to be the most sensitive species, especially for skin and ocular effects. A NOAEL for these effects was not reported. A dose of 0.1 mg/kg-day Aroclor 1248 caused reversible dermal (e.g., facial edema, acne, folliculitis, and alopecia) and ocular changes (e.g., swelling and reddening of eyelids) in monkeys exposed in the feed for 2 months (Barsotti *et al*., 1976). Other changes or effects reported for several commercial PCB mixtures are summarized in Table 2 below. No inhalation studies were found for comparison.

Table 2. Summary of Subchronic Oral Toxicity Studies on Commercial Mixtures of Polychlorinated Biphenyls (ATSDR, 2000)

Test Material	Species (Sex)	Duration	NOAEL (N) or LOAEL (L)	Effect	Reference
Aroclor 1242	Rat (M)	2-6 mo.	0.3 mg/kg-day (L)	Hepatic (increased liver weight)	Bruckner *et al*., 1974
	Mink	247 days	0.9 mg/kg-day (N)	Body weight	Bleavins *et al*., 1980
Aroclor 1248	Rat (M)	20 days	15 mg/kg-day (L)	Hepatic (increased liver weight)	Kato *et al*., 1982
	Rat (M)	20 days	15 mg/kg-day (N)	Endocrine	Kato *et al*., 1982
Aroclor 1254	Rat (F)	5-7 mo.	2.5 mg/kg-day (N)	Hepatic	Byrne *et al*., 1987
	Rat (F)	8 mo.	1.6 mg/kg-day (N)	Hepatic	Kimbrough *et al*., 1972
	Rat (M)	15 wk	0.1 mg/kg-day (N)	Hepatic	Gray *et al*., 1993
	Mouse (M)	6 mo.	0.5 mg/kg-day (N)	Hepatic	Koller, 1977
	Rat (M)	15 wks	1 mg/kg-day (N)	Renal	Gray *et al*., 1993
	Rat (M)	5 wks	0.025 mg/kg-day (N)	Endocrine	Kasza *et al*., 1978
Aroclor 1260	Rat (M)	8 mo.	1.4 mg/kg-day (N)	Hepatic	Kimbrough *et al*., 1972
	Guinea Pig (F)	8 weeks	4 mg/kg-day (N)	Hepatic	Vos & de Roij, 1972
	Guinea Pig (F)	8 weeks	4 mg/kg-day (N)	Renal	Vos & de Roij, 1972
	Rat (M)	120 days	7.1 mg/kg-day (L)	Endocrine (adrenal medulla degenerative change)	Rao & Banerji, 1993
	Guinea Pig (F)	8 weeks	4 mg/kg-day (N)	Endocrine	Vos & de Roij, 1972

F = female; L = LOAEL; M = male; mo. = month; N = NOAEL.

Genetic Toxicity

Commercial PCB mixtures (e.g., Aroclor 1254) are not mutagenic in Ames *Salmonella* assays (Schoeny *et al*., 1979; Schoeny, 1982) or in some assays for chromosomal aberrations in mice and rats (Bruce and Heddle, 1979; Garthoff *et al*., 1977). However, evidence, often using individual congeners, does show that PCBs react to form adducts with cellular macromolecules (protein, RNA and DNA) (Shimada and Sato, 1978; Morales and Matthews, 1979; Wong *et al*, 1979; Narbonne and Daubeze, 1980) and are at least mildly genotoxic (Wong *et al*, 1979; Stadnicki *et al*. 1979). Oakley *et al*. (1996)

and McClean *et al*. (1996) showed that mono-, di- and tri-chlorophenols form DNA adducts *in vitro* following microsomal activation and that additional adducts are formed following oxidation. Guanine (dGp) was found to be the preferred DNA base for adduct formation. Schiestl *et al*. (1997) found that Aroclors 1221 and 1260 at high doses (1000 and 500 mg/kg respectively) induced deletions via intrachromosomal recombination *in vivo* in mouse embryos and *in vitro* in yeast (*Saccharomyces cerevisiae*).

Developmental and Reproductive Toxicity

Reproductive and developmental effects have been observed in several species following administration of commercial mixtures of PCBs (Arnold *et al*., 1995; ATSDR, 2000; Brezner *et al*., 1984; Welsch, 1985). In rats, prolonged estrus, decreased sexual receptivity, and reduced implantation rates in adults or their offspring exposed via gestation and lactation were reported following oral administrations of a mixture of PCBs (i.e., Aroclor 1248, 1254, or 1260). Brezner *et al*. (1984) found a prolonged estrus cycle, decreased sexual receptivity, and transient decrease in body weight gain in Wistar rats after dosing the animals with 10 mg/kg-day Aroclor 1254 by gavage for 4-6 weeks. In ICR mice fed a diet containing a dose of 12.5 mg/kg-day of Aroclor 1254 for 90 days, a decrease of 36 percent in conception rate was reported compared to a lower dose and control animals (Welsch, 1985).

Monkeys and minks were the most sensitive species. Reproductive toxicity in female Rhesus monkeys fed 0.1 mg/kg-day Aroclor 1248 in intermediate-duration studies (Barsotti *et al*., 1976) or as low as 0.02 mg/kg-day Aroclor 1254 for 37 months (Arnold *et al*., 1993a,b, 1995) consisted of decreased fertility (increased incidence of abortions, resorptions, stillbirths) and prolonged menstruation. Lower doses of Aroclor 1248 were not tested. The LOAEL reported by Arnold *et al*. (1995) was 0.02 mg/kg-day Aroclor 1254 for both reduced conception and fetal survival. The NOAEL observed in this study was 0.005 mg Aroclor 1254/kg-day.

In minks, several investigators have reported reproductive failure and associated fetal death following embryo implantation when minks were treated with 0.4 to 1.8 mg/kg-day of Aroclor 1254 or Clophen A50 (Aulerich and Ringer, 1977; Backlin and Bergman, 1995; Backlin *et al*., 1997). No effect on fertility was observed in minks fed a diet containing 0.2 mg/kg-day Aroclor 1254 (Aulerich and Ringer, 1977).

Developmental effects have also been reported. Several authors (Crofton *et al*., 2000; Goldey and Crofton, 1998; Goldey *et al*., 1995; Herr *et al*., 1996; Powers *et al*., 2006; Roegge *et al*., 2000; Roegge *et al*., 2006) reported auditory impairment and decreases in serum T4 and T3 concentrations in pups from pregnant Long Evans rats treated with PCBs. The female rats were treated with 1, 3, or 6 mg/kg of PCB mixture 28 days prior to mating and continuing until the pups were weaned. A brief description of these studies can be found in the Neurotoxicity Section.

However, non-human primates were again the more sensitive species. Barsotti and Van Miller (1984) found reduced birth weights in offspring from Rhesus monkeys treated before mating and during gestation with 0.03 mg/kg-day Aroclor 1016. Low birth weights were also observed by Schantz *et al*. (1989) in offspring of pregnant monkeys

treated with 0.03 mg/kg-day Aroclor 1016. The NOAEL for developmental effects reported for this study was 0.008 mg/kg-day. Other signs of PCB poisoning (i.e., hyperpigmentation) were also reported in the offspring in the studies by Barsotti and Van Miller (1984), and Schantz *et al.* (1989). The reported NOAEL of 0.008 mg Aroclor 1016/kg-day by Schantz *et al*. (1989) was used to calculate the public health-protective concentration.

Arnold *et al*. (1993a,b, 1995) also observed reduced birth weights. In addition, Arnold *et al.* (1995) found some mild clinical manifestations (nail and nailbed changes) of PCB poisoning in the offspring of monkeys treated with 0.005 mg/kg-day or higher of Aroclor 1254. Infant monkeys were exposed through mother's milk for a period of 22 weeks. Nail and nail bed changes included nail bed prominence, elevated nails, and nails folding on themselves. The nail and nail bed changes were similar but more severe in the adult females being treated. In Holzman and Wistar rats, reduced birth weights and postnatal growth were reported following exposure to Aroclor 1254 (Spencer, 1982; Morse *et al*., 1996; Hany *et al*., 1999). Higher doses (e.g., 241 mg/kg-day) must be used to observe any teratogenicity in Aroclor 1254- or PCB 126-treated mice (Haake *et al*., 1987; Zhao *et al*., 1997).

Aroclor 1016 and 1254 cause similar effects (low birth weights and dermal changes) at similar doses in the same species. Both the NOAEL reported by Schantz *et al*. (1989) of 0.008 mg/kg-day and the LOAEL reported by Arnold *et al*. (1993a,b, 1995) of 0.005 mg/kg-day will be considered for calculating the non-cancer public health-protective concentration. The findings by Arnold *et al*. (1993a,b, 1995) were used in the calculation of the non-cancer level due to the fact that 16 percent of the mixture composition would be congeners with 4 or less chlorines and thus may be found in drinking water.

In addition to the reduced birth weights and pigmentation changes reported above, developmental exposures of animals to PCBs have resulted in neurobehavioral effects. These effects are summarized in the Neurotoxicity section of this document.

Immunotoxicity

A number of studies in experimental animals have indicated that PCBs (commercial mixtures, mixtures of congeners, contaminated Great Lakes fish, or single congeners) affect the immune system. For reviews, see Tryphonas (1995a,b), Tryphonas *et al*. (1991b), and ATSDR (2000). The reported effects have included morphological and functional alterations in the immune system. The severity or effect varied with test material (i.e., commercial mixture and/or congener), route of administration, and species tested. As seen in the chronic studies, the non-human primates were found to be the more sensitive species.

Tryphonas *et al*. (1989, 1991a,b) found a dose-related decrease ($p<0.05$) in the anamnestic (IgM and IgE) response to sheep red blood cells (SRBC) in monkeys treated with 5, 20, 40, or 80 μg/kg-day of Aroclor 1254 for 55 months. Other immunomodulatory effects were either transient (alterations in T-cell subsets at 23 months and not at 55 months) or showed dose-related trends (decreasing lymphoproliferative responses to mitogens, increasing natural killer cell activity,

increasing levels of serum thymosin alpha-1, decreasing phagocytic activity of peripheral blood monocytes following activation with phorbol myristate acetate). Arnold *et al*. (1995) also found an exposure-related reduction ($p<0.05$) in antibody level to SRBC and mitogen-induced lymphocyte transformation in the offspring of animals treated by Tryphonas *et al.* (1989, 1991a,b). A NOAEL was not observed in these studies and the LOAEL was determined to be 5 μg/kg-day of Aroclor 1254, which was the lowest dose tested of any congener or commercial mixture in any species. This dose will be used to calculate the non-cancer public health-protective concentration because Aroclor 1254 contains a set of congeners that have the potential to be found in drinking water.

Other commercial mixtures of PCBs and single congeners have also induced both morphological and functional alterations in the immune system. In general, effects have been reported in rats, mice, guinea pigs, or rabbits following oral administration of doses of ≥4 mg/kg-day for intermediate duration of Aroclor 1248, 1260, 1242, 1221, or 1016 and several single congeners (e.g., PCB 28, 72, 105, 118, 126, and 153) (ATSDR, 2000). No generalizations can be made across species for each test material or route of administration. For example, no histological changes in the thymus or spleen were observed in mice or guinea pigs orally treated with Aroclor 1260 (Loose *et al*., 1978a,b; Vos and Notenboom-Ram, 1972). However, histological changes in the thymus, spleen, and lymph nodes were observed in rabbits following dermal administration of 42-44 mg/kg-day of Aroclor 1260 (Vos and Beems, 1971; Vos and Notenboom-Ram, 1972). Similarly, thymic changes were observed in treated Sprague-Dawley rats treated for 13 weeks with some single congeners (PCB 126 153, 28, and 105) at doses of ≥0.74, ≥3,534, ≥3,783, and ≥3,960 μg/kg-day, respectively. No effects were observed with PCB 77 (≤892 ug/kg-day), PCB 118 (≤170 μg/kg-day), or PCB 128 (≤4,125 μg/kg-day) [Chu *et al*., 1994, 1995, 1996a,b, 1998; Lecavalier *et al*., 1997).

Neurotoxicity

Neurobehavioral, neurochemical and auditory effects have been reported in rats, mice, and monkeys treated with commercial PCB mixtures, defined experimental PCB mixtures, or individual congeners. These effects were reviewed by ATSDR (2000).

The neurobehavioral changes consisted of effects on locomotor activity and on higher function while the neurochemical changes were characterized as decreases in dopamine concentrations in different areas of the brain and alterations in serotonin levels. No apparent pattern in locomotor activity changes could be surmised in mice, rats, and monkeys exposed to commercial PCB mixtures and single PCB congeners.

The commercial PCB mixtures evaluated in the neurobehavioral assays were Aroclor 1016, 1242, 1248, 1254, and 1260. Only Aroclor 1254 caused a neurobehavioral change under the conditions tested. In flavor aversion conditioning tests, the reported NOAEL in adult rats for acute and repeated exposure to Aroclor 1254 was 15 or 7.5 mg/kg-day, respectively (Nishida *et al*., 1997). However, Freeman *et al*. (2000) did not find any significant treatment-related effects on a number of comprehensive neurobehavioral endpoints (i.e., functional observational battery, motor activity, and histopathological examination of central and peripheral nervous system). In this study, rats were fed a diet

containing either Aroclor 1016, 1242, 1254, or 1260 for 52 weeks. The NOAELs for Aroclor 1016, 1242, 1254, and 1260 were 14.1, 7.5, 6.9 and 6.1 mg/kg-day, respectively.

Younger animals have been more sensitive to neurobehavioral changes following exposure to various forms of PCBs than adult animals. Effects reported varied with exposure material, age of animal at exposure, age of animal during testing, and species. For example, the offspring of monkeys treated with 0.1 mg/kg-day Aroclor 1248 during pregnancy and for 3 months following birth had hyperlocomotor activity when the offspring were tested at 6 and 12 months of age (Bowman *et al*., 1978). At 44 months of age, however, hypolocomotor activity was observed (Bowman et al., 1981). A similar finding in rats was observed by Schantz *et al.* (1997) using PCB 95. In addition to locomotor activity, effects on higher cognitive functions (i.e., learning, memory, attention) have also been impaired in rats and monkeys exposed during gestation and lactation, and tested after exposure ceased (ATSDR, 2000; Seegal, 2000). In monkeys, long-term administrations of doses of 0.03 mg/kg-day of some PCBs (e.g., Aroclor 1016 and 1248) have impaired the progeny's ability to learn spatial discrimination problems (Schantz *et al*., 1989). Aroclor 1016 did not alter cognitive function in the progeny of animals fed a dose of 0.008 mg/kg-day, but did at 0.03 mg/kg-day, while Aroclor 1248 caused an effect at 0.08 mg/kg-day (Levin *et al*., 1988). The lowest dose tested that demonstrated an effect on cognitive functions was 0.0075 mg/kg-day of a PCB mixture representative of the PCBs typically found in human breast milk (Rice and Hayward, 1997, 1999; Rice, 1997, 1998, 1999). This dose was administered to male monkeys from birth to 20 weeks of age and animals were tested at 3 years of age. The specific effects reported were impaired performance in both nonspatial and spatial discrimination reversal tasks, and inability to inhibit inappropriate responding. Only the NOAEL reported by Schantz *et al*. (1989) of 0.008 mg/kg-day was considered for calculating the non-cancer public health-protective concentration for neurobehavioral changes due to the physical properties of Aroclor 1016, and because it was the most sensitive effect. The findings from Rice (1997, 1998, 1999) and Rice and Hayward (1997, 1999) for a PCB mixture representative of the PCBs typically found in human breast milk was not used since these PCBs would not be expected to be found in drinking water.

Neurochemical effects of PCBs (i.e., changes in dopamine concentrations in different areas of the brain and alterations in serotonin levels) have been also reported in rats, mice, and monkeys exposed to commercial PCB mixtures and to individual PCB congeners. The decrease in dopamine concentrations was observed in various regions of the brain of treated adult animals (rats and monkeys) following exposure to relatively high doses (500 or 1000 mg/kg-day) of commercial PCB mixtures (Aroclor 1254 or 1260) [Seegal *et al*., 1986, 1991a,b]. However, lower doses of Aroclor 1016 did decrease dopamine in a dose dependent manner in monkeys fed Aroclor 1016 for 20 weeks (Seegal *et al*., 1991b). The LOAEL for this study was 0.8 mg/kg-day. Dopamine concentration levels were also decreased in rats being treated with single congeners for 90 days (Chu *et al*., 1994, 1995, 1996a, 1998a,b; Lecavalier *et al*., 1997). The lowest dose where a decrease in dopamine was reported was 0.005, 0.01, and 0.04 mg/kg-day for PCB 128, 153, and 28, respectively.

Perinatal exposure to PCBs has also caused auditory effects. Goldey and Crofton (1998), Goldey *et al*. (1995) and Herr *et al*. (1996) reported a low frequency hearing loss in the offspring of rats treated during pregnancy with Aroclor 1254 at doses of 0, 1, 4, or 8 mg/kg-day. Only the mid and high doses caused the damage. The authors concluded that the auditory alterations were consistent with peripheral auditory dysfunction. Similar findings were later reported in offspring from rats administered PCB 126 during gestation and lactation without evidence of general toxicity (Crofton and Rice, 1999).

The following account describes a small number of recent studies evaluating PCB neurobehavioral effects in animals that were not cited in the recent review by ATSDR (2000).

Roegge *et al*. (2000) exposed pregnant Long Evans rats to Aroclor 1254 (0 or 6 mg/kg-day) from gestation day 6 to weaning at postnatal day 21. Once offspring reached adulthood, one male and one female rat from each litter was tested on a working/reference memory task using a 12-arm radial arm maze (RAM). Roegge *et al*. (2000) found deficits in performance on a spatially mediated task only in male offspring. More recently, Roegge *et al*. (2005) reported a significant reduction in serum T4 and T3 concentrations in the PCB- and PCB plus methylmercury-treated pups on PND 21. Female Long-Evans rats were exposed to 0, 6 mg/kg PCB mixture, 1 mg/kg methylmercury, or the combination of PCB mixture and methylmercury beginning 4 weeks prior to breeding with an unexposed male and continuing until PND 16. The reduction in circulating thyroid hormone concentrations is postulated to have a negative impact on cerebellar development.

Crofton *et al*. (2000) used experimental procedures similar to the study of Roegge *et al*. (2000), with Long-Evans rats treated with 0 or 6 mg/kg Aroclor 1254. However, half of the treated litters and half of the control litters were cross-fostered. Serum thyroid hormone concentrations, liver and brain concentrations of PCBs, body weight, mortality, age of eye opening, auditory startle amplitudes, and auditory threshold for 1 kHz and 40 kHz tones were assessed in offspring at various ages of animals (gestational day 21, postnatal day 3, 7 14, or 21). The authors found that perinatal and postnatal exposure, or postnatal exposure only, caused significant decreases in circulating concentrations of T4, and an approximately 20-dB increase at low frequency (1 kHz). The findings identify a critical window of susceptibility of the peripheral auditory system and the cochlea as the suggested site of action based upon the loss of the outer hair cells on the basilar membrane. More recently, Powers *et al*. (2006) found similar results using the same protocol as above, but animals were exposed to a PCB mixture formulated to model the congener profile of PCBs found in fish consumed by a human population in northeastern Wisconsin.

Gilbert *et al*. (2000) administered either corn oil or 6 mg/kg-day of Aroclor 1254 to pregnant Long Evans rats from gestational day 6 to postnatal day 21. Spatial learning was assessed at three months of age in male and female offspring using the Morris water maze. Male littermates of animals in the behavioral studies were tested electrophysiologically at 5-7 months. The authors found changes in hippocampal long-term potentiation (LTP), a fundamental plasticity process that reflects the neurophysiological and biochemical changes that support learning at the synaptic level.

A decrease in the magnitude of dentate gyrus LTP *in vivo* and an increase in the threshold necessary to induce it were reported in male animals. These findings highlight the effect caused at a specific region of the brain when exposed to PCBs during development.

Altmann *et al*. (2001) exposed pregnant Long Evans rats to 40 mg/kg of a PCB mixture simulating the composition of PCBs in human milk or of Aroclor 1254 via food 50 days prior to mating and terminated at birth of the offspring. The LTP in two brain regions were then measured in offspring at various postnatal periods. In addition, binding of [^{3}H]MK-801 to the N-methyl-D-aspartate (NMDA) receptor ion channel and [^{3}H]muscimol binding to the GABA-A receptor in membrane preparations from the occipital cortex and hippocampus were determined. The authors reported that maternal exposure of rats to PCB mixtures resulted in a reduction of LTP in visual cortical slices of the exposed animals when compared to controls and a reduction in [^{3}H]MK-801 binding sites in the occipital cortex.

Chronic Toxicity

As seen in the subchronic toxicity studies, the reported effects varied in severity depending on the isomer and congener composition of the PCB mixture used, presence of potential impurities, the length of exposure, and the species under investigation. A summary of the effects observed in animals exposed to commercial PCBs is found in ATSDR (2000) and WHO (1993). In general, Rhesus monkeys are the most sensitive species. A NOAEL of 0.04 mg/kg-day was reported for hepatic (increased liver weight) changes and a NOAEL of 0.005 mg/kg-day for dermal (nail and nailbed changes) effects in animals given the commercial Aroclor 1254 mixture in the feed for 72 months (Arnold *et al*., 1993a,b, 1995 and 1997). In this study (Arnold *et al*., 1997), no histological changes were reported in the respiratory, cardiovascular, endocrine, gastrointestinal, hematopoietic, ocular, and renal systems of rhesus monkeys fed doses of 0.005, 0.020, 0.040, or 0.080 mg/kg-day for 72 months. Higher doses of Aroclor 1254 in the feed have resulted in many systemic changes in treated monkeys. Similar effects were observed in rats treated with higher doses (ATSDR, 2000).

No studies were found on chronic exposure to PCBs by inhalation or dermal routes.

Summary of Non-Cancer Effects

PCB mixtures produce low to moderate acute toxicity in mammalian species, but produce pronounced subacute and chronic toxicity. The toxicity exhibited varies among species. The effects reported were immunological, developmental, reproductive, and neurobehavioral toxicity caused by Aroclor 1016, Aroclor 1254, or a mixture of PCBs simulating the content of PCBs found in human breast milk (See Table 3 for list of effects). The neurobehavioral toxic effects consisted of decreased behavioral performance in nonspatial and spatial discrimination reversal tasks of offspring of mothers exposed during pregnancy (Rice, 1997, 1998, 1999; Rice and Hayward, 1997, 1999; Schantz *et al*., 1989). A simulated human breast milk PCB mixture caused these

neurobehavioral effects at a LOAEL of 0.0075 mg/kg-day, while Aroclor 1016 was reported to produce a NOAEL of 0.008 mg/kg-day.

Aroclor 1016 also caused developmental toxicity with a NOAEL of 0.008 mg/kg-day in the offspring of treated Rhesus monkeys (Schantz *et al*., 1989; Barsotti and Miller, 1984; Levin *et al.*, 1988). Low birth weights were reported by Schantz *et al*. (1989) at a LOAEL of 0.03 mg Aroclor 1016/kg-day. Developmental effects were also observed with Aroclor 1254 in Rhesus monkey offspring (Arnold *et al*., 1995) consisting of tarsal gland inflammation, nail lesions, gum recession, and reduced IgM antibody levels to SRBC. The LOAEL for these changes was 0.005 mg Aroclor 1254/kg-day.

Tryphonas *et al*. (1986, 1989, 1991) reported a LOAEL of 0.005 mg/kg-day for the immunological effects caused by Aroclor 1254 in monkeys. The immunological effects (reduced IgM and IgG antibody responses to sheep red blood cells) were obtained following exposure to Aroclor 1254 for up to 55 months. The changes reported in these two articles (both from the same study) were inflammation of tarsal glands, nail lesions, gum recession, and reduced IgM antibody levels to SRBC in infant offspring.

Reproductive effects were observed in female Rhesus monkeys treated with Aroclor 1254 for 37 months (Arnold *et al.*, 1995). The effects reported were decreased fertility and prolonged menstruation. Arnold *et al.* (1995) reported a NOAEL for this effect of 0.005 mg/kg-day.

For the purposes of calculating the non-cancer public health-protective concentration, the most sensitive endpoints at the NOAEL or LOAEL for those PCBs that are considered more water-soluble will be used. In this case, this would be the developmental effects (i.e., low birth weights, neurobehavioral and immunological changes) reported by Schantz *et al*. (1989) for Aroclor 1016, or Arnold *et al*. (1993a,b, 1995) and Tryphonas *et al*. (1989, 1991) for Aroclor 1254.

Carcinogenicity

Multiple lifetime studies in various rat strains have demonstrated the ability of PCB mixtures containing 60 percent chlorine to cause cancers and pre-neoplastic lesions, primarily in the liver. Fewer lifetime studies have been done using PCB mixtures with lower chlorine content and the results vary with the mixture used and the strain tested. Several of the more complete studies are summarized below.

Kimbrough *et al*. (1975) fed groups of 200 female Sherman rats diets containing 0 or 100 ppm (5 mg/kg-d) Aroclor 1260 for about 21 months. Rats were killed and their tissues examined six weeks after cessation of dosing. Hepatocellular carcinomas and neoplastic nodules were diagnosed in 14.1 percent and 84.7 percent of the treated rats and 0.6 percent and none of the controls, respectively. Overall, a significant increase in the incidence of neoplastic liver lesions was observed in the treated rats (92.4 percent) compared to the controls (0.6 percent).

The National Cancer Institute (NCI, 1978) conducted a study using groups of 24 male or female Fischer 344 rats fed diets containing 0, 25, 50, or 100 ppm (about 0, 1.25, 2.5, or 5 mg/kg-day) Aroclor 1254 for 24 months. Hepatocellular carcinomas and unspecified

adenomas were observed in the mid- and high-dose groups but not in the controls. The combined incidence in the high-dose males was 12.5 percent and in females 8.3 percent. This incidence is not statistically significant from matched controls, although a significant trend for increased lymphoma and leukemia was noted for males. A significant trend for liver lesions was demonstrated on reexamination and reevaluation of this data by Ward (1985). Ward (1985) and Morgan *et al*. (1981) also reexamined the gastrointestinal data and found significantly increased gastric metaplasias and adenocarcinomas in the glandular stomach of treated rats.

Schaeffer *et al*. (1984) treated male Wistar rats with 0 or 100 ppm (about 5 mg/kg-day) Clophen A 30 (40-42 percent chlorine) or A 60 (60 percent chlorine) in the diet for 26-27 months. The incidence of liver neoplastic nodules (50 percent) and hepatocellular carcinomas (61 percent) was significantly greater in the A 60 treated animals than controls (4 percent and 2 percent, respectively). The combined incidence of these lesions was 98 percent in the treated males. The incidence of liver neoplastic nodules (40 percent) but not hepatocellular carcinomas (3 percent) was also greater in the A 30 treated males than in controls (4 percent and 2 percent, respectively). The combined incidence of these lesions was significantly greater than in controls in the original evaluation, however, it was not significant following the re-evaluation by Moore *et al*. (1994, see below). A progression was noted from preneoplastic liver lesions (foci of hepatocellular alteration and neoplastic nodules) after 500 days of treatment to hepatocellular carcinomas after 700 days of treatment in rats dying before the end of the study for both mixtures.

Norback and Weltman (1985) treated male and female Sprague-Dawley rats with an estimated average dose of 0 or 3.45 mg/kg-day of Aroclor 1260 in the diet for 24 months. The treatment groups initially contained 70 male or female rats and the control groups 63 rats. The treatment groups were fed 100 ppm (5 mg/kg-day) for 16 months and 50 ppm for 8 months. Rats surviving the 24 months were fed a treatment-free diet for an additional four months before all surviving animals were sacrificed in the 29th month. Partial hepatectomy was performed on two rats per control group and three rats per treatment group at 1, 3, 6, 9, 12, 15, 18 and 24 months. The incidence of liver carcinomas and combined carcinomas and neoplastic nodules in females was 91 and 95 percent, respectively. The incidence of liver carcinomas and combined carcinomas and neoplastic nodules in males was 4 and 15 percent, respectively. The incidence of combined neoplasms in controls was 0 percent in males and 2 percent in females. This demonstrates a significant increase in neoplasms in treated rats and a sex-related effect for Aroclor 1260. A progression of morphological changes from liver lesions to carcinomas was observed in hepatectomy tissue: 3 months, liver foci; 6 months, area changes; 12 months, neoplastic nodules; 15 months, trabecular carcinomas; 24 months, adenocarcinomas.

Moore *et al*. (1994) reevaluated the pathology of all of these studies using more current diagnostic criteria and nomenclature that had recently been adopted by NTP (Maronpot *et al.* 1986). One key difference in the Moore *et al.* (1994) reanalysis was to use the terms hepatocellular hyperplasia and hepatocellular adenoma for lesions that were previously combined under the diagnosis of neoplastic nodule. The change in nomenclature and

diagnostic criteria resulted in a finding of fewer tumors than in the original evaluations. Reevaluation of the pathology data from seven studies (all of the studies discussed above except that of Mayes *et al*., 1998) in which rats were fed PCB mixtures containing different chlorine content shows that, although the same types of liver tumors were found in all studies, the mixtures with 60 percent chlorine content consistently resulted in the highest liver tumor incidence (Moore *et al*., 1994). In the reevaluation, only the 60 percent chlorine mixtures showed a statistically significant increase in tumors; the 42 percent (Clophen A 30) and 54 percent mixtures did not show significant increases. Smith (1997) recalculated the cancer slope factors for these same studies based on the reevaluated pathology and using a cross-species scaling factor of body weight$^{1/3}$ for carcinogenic risk assessment (U.S. EPA, 1996b). The resulting slope factors were lower than prior calculations and the slope factors for the lower chlorinated mixtures were much less than for mixtures with 60 percent chlorine. Smith (1997) concluded that calculating one cancer slope factor from a single "best" study does not appear to adequately describe the range of carcinogenicity of the various technical mixtures.

Mayes *et al*. (1998) treated male and female Sprague-Dawley rats (50/sex/dose) with Aroclors 1016, 1242, 1254, and 1260. These PCB mixtures were administered at two or three dose levels in the diet for 24 months: Aroclor 1016 - 50, 100, 200 ppm; Aroclor 1242 - 50 and 100 ppm; and Aroclors 1254 and 1260 - 25, 50 and 100 ppm; plus 0 ppm control. Increased hepatic and thyroid gland tumors were noted. Treatment-group survival rates were not decreased by these tumors. The incidence of hepatic tumors was sex-dependent. Most hepatic tumors (80 percent) were benign hepatocellular adenomas. Other tumors observed were hepatocellular carcinomas (11 percent), hepatocholangiomas (8 percent), and hepatocholangiocarcinomas (<1 percent). In females the incidence was dependent on the Aroclor mixture as well as the dose. The incidence of hepatocellular adenomas was significantly greater than controls at all dose levels for all Aroclors except the lowest dose (50 ppm) of Aroclor 1016 in females. A reduction in mammary gland tumors compared to controls was seen in females receiving Aroclor 1242, 1254 and 1260 and a statistically significant negative trend was noted for these Aroclors. In males a significant increase in hepatic tumors compared to controls was restricted to the highest dose group receiving Aroclor 1260. A non-dose-related thyroid gland response was also observed in males. Males receiving Aroclors 1242, 1254 and 1260 showed an increase in the incidence of thyroid gland follicular cell adenomas. These tumors were presumed to be a result of a PCB-mediated metabolic mechanism increasing production of thyroid-stimulating hormone (TSH) and producing cell hypertrophy and diffuse hyperplasia in males, which normally have higher circulating levels of TSH and a higher background of this tumor type than females (Hill *et al*., 1987).

Cancer promoting activity has also been demonstrated using certain PCB mixtures; chiefly higher chlorinated PCBs. These PCBs increase the development and incidence of preneoplastic liver lesions and tumors in rats that have first been treated with complete carcinogens that act as initiators. Aroclor 1254 (both the technical product and a formulation purified to remove chlorinated dibenzofurans) administered in the diet (5 mg/kg-day for 18 weeks) promoted a significant increase in hepatocellular carcinomas in male Sprague-Dawley rats that had been initiated for five weeks with N-nitrosodiethylamine (5 mg/kg-day in water) compared to initiated rats not fed PCBs

(Preston *et al*., 1981). Tatematsu *et al*. (1979) also demonstrated the enhanced induction of neoplastic liver nodules following Kanechlor 500 promotion (25 or 50 mg/kg-day in the diet for eight weeks) of male Fischer 344 rats initiated with 2-acetylaminofluorene (10 mg/kg-day in the diet for two weeks).

Summary of Carcinogenicity

Multiple lifetime studies in various rat strains have demonstrated the ability of PCB mixtures to cause cancers and pre-neoplastic lesions, primarily in the liver. Re-evaluation of the carcinogenicity data has been critical in further characterizing some of the unique attributes of PCB mixtures. The above studies provide evidence that the carcinogenicity of all Aroclor mixtures is not equal. Using updated diagnostic criteria and nomenclature for assessing tumor formation, the Moore *et al.* (1994) reevaluation of the pathology data from seven studies found that the mixtures with 60 percent chlorine content consistently resulted in the highest liver tumor incidence. In the reevaluation, only the 60 percent chlorine mixtures showed a statistically significant increase in tumors; the 42 percent (Clophen A 30) and 54 percent mixtures did not show significant increases. The Smith (1997) recalculations of cancer slope factors for these same studies result in lower values than the earlier calculations, with much lower slope factors for the lower chlorinated mixtures compared to mixtures with 60 percent chlorine. All five of the rat data sets discussed above are relevant for calculating cancer slope factors. We conclude that calculations for Kimbrough *et al*. (1975), NCI (1978), Schaeffer *et al*. (1984), and Norback and Weltman (1985) should be based on the Moore *et al*. (1994) reevaluation of these studies, which provide refined cancer slope factors for the various PCB mixtures. These refined cancer slope factors will be used to calculate the public health-protective concentration in drinking water.

Toxicological Effects in Humans

Acute Toxicity

Acute and subacute effects have been reported in studies evaluating worker exposure and accidental poisonings such as the Yusho and Yu-Cheng poisoning incidents (ATSDR, 2000). Some of the effects reported were chloracne, dark brown pigmentation of the skin and lips, swollen eyelids, ocular effects, and swelling and pain in the joints (Fischbein *et al*., 1985; Higuchi, 1976; Hsu *et al*., 1985, 1994; Rogan *et al*., 1988). No clear association exists between PCB exposure and increased risk of cardiovascular disease, respiratory effects, or other systemic changes. Additionally, the effects reported in the poisoning incidents cannot be attributed solely to commercial PCB exposures, but may be due to the victims' co-exposures to polychlorinated dibenzofurans (PCDFs). Several investigators have reported the presence of PCDFs in the serum of exposed individuals (ATSDR, 1994; Ryan *et al*., 1993).

Fitzgerald *et al*. (1989) compared the numbers of deaths, cancers, fetal deaths, and infants with low birth weight or congenital malformations in 482 persons who were potentially

exposed to polychlorinated biphenyls (PCBs), dibenzo-p-dioxins, and dibenzofurans from an electrical transformer fire in a Binghamton, NY office building in 1981 to other matched populations. Exposure-related systemic disorders, e.g., chloracne or peripheral neuropathy, were not diagnosed by personal physicians; however, some persons refused to release their medical records because of ongoing litigation. The rates for the endpoints measured were similar to those expected on the basis of age- and sex-specific rates for upstate New York and other comparison populations. No other studies of acute toxicity are available in humans.

Subchronic and Chronic Toxicity

Health effects due to subchronic and chronic exposure to commercial PCB mixtures have been reported for occupationally exposed workers. These exposures are largely via the inhalation and dermal routes, but probably included some orally ingested PCBs. Respiratory, cardiovascular, hematological, musculoskeletal, and renal effects have been reported in workers exposed to PCBs (ATSDR, 2000). Loss of appetite has been reported in occupationally exposed workers. Both ocular (e.g., edema of upper eyelids, eye discharge) and skin effects (e.g., rashes and chloracne) have been noted in workers exposed more than 5 years. A decrease in serum thyroxine and increase in 17-hydroxycorticosteroids was found in workers exposed an average of 4 years (Emmett *et al.*, 1988). Although changes in hepatic indices (e.g., serum levels of SGTP) have been noted in environmentally exposed individuals (Kreiss *et al*., 1981) comparisons between measurements and serum PCB levels are typically inconclusive.

In a number of occupational exposure studies, an association between PCB exposure and respiratory (e.g., upper respiratory tract or eye irritation, lung function changes), cardiovascular (e.g., increased risk of cardiovascular disease and altered blood pressure), hematological, hepatic effects (e.g., increased serum enzymes, biochemical indices, increased urinary excretion of porphyrins), musculoskeletal effects (i.e., joint and muscle pain), and renal effects on workers has been reported. However clear associations have not been conclusively demonstrated, because of inconsistency, the presence of confounding factors (smoking, exposure to other chemicals), and other limitations such as lack of an appropriate control group (ATSDR, 2000).

Hseih *et al.* (1996) and Yu *et al.* (1997) reported increases in the mortality rate for liver disease in studies of a 1979 episode in Taiwan involving ingestion of rice oil contaminated with PCBs (plus related compounds such as dibenzofurans). Overall mortality, liver cancer, and overall cancer mortality were not increased. Gustavsson and Hogstedt (1997) found an excess increase in mortality due to circulatory diseases in a cohort of 71 male capacitor manufacturing workers with >5 years of high exposure to PCBs and >20 years latency. However, confounding factors such as smoking habits, a well-established risk factor for cardiovascular diseases, were not known or determined for this cohort. Hay and Terrell (1997) also noticed excess deaths due to cardiovascular disease in a cohort of power workers exposed to PCBs in waste transformer oil.

Health effects have also been reported in people exposed to PCBs by ingestion of contaminated fish in several regions of the world (ATSDR, 2000). The changes include

hepatic (enzyme levels, porphyria, and other biochemical indices), thyroid (hormone levels), and skin (pigmentation, chloracne). Dallaire *et al*. (2006) reported that associations existed between concentration of PCB-153 (a marker for PCB exposure) in umbilical cord plasma and the incidences of acute otitis media (AOM) and lower respiratory tract infections (LRTIs) in Inuit children. After reviewing the medical charts of 343 children from 0 to 5 years of age, the PCB-153 plasma concentration in the first quartile of exposure (least exposed) was compared to children in the fourth quartile (most exposed). The authors found rate ratios of 1.25 ($p<0.001$) and 1.40 ($p<0.001$) for AOM and LRTIs, respectively. However, the subjects of both studies had been exposed to a mixture of chemicals in addition to PCBs.

Although the studies may be insufficient, the data do provide evidence of various toxic effects of different PCB mixtures. The effects observed are supported by similar observations in the animal studies, in which many of the changes observed in humans can be observed in animals treated with various commercial mixtures and single congeners. The inconsistent results observed may be due to differences in types of PCB, exposure levels and durations, latency periods, potential sensitive population (children), and differences in cohort sizes in the various studies.

Genetic Toxicity

There are not sufficient data to determine the genotoxic effects of PCBs in humans. Kalina *et al*. (1991) report an increase in chromosome aberrations in workers exposed to PCBs for greater than ten years. However, these workers were also exposed to benzene, which is known to induce chromosome aberrations in humans. Melino *et al*. (1992) observed a small increase in sister chromatid exchanges in men exposed to PCBs following a fire in an electrical station, but interpretation of this result is confounded by the possibility that chlorinated dioxins and/or furans were generated by the fire. One study using Aroclor 1254 for *in vitro* tests of chromosome damage in human lymphocytes showed no effect (Hoopingarner *et al*., 1972), but another using the planar congener 3,4,3',4'-tetrachlorobiphenyl was positive alone and even more potent when mixed with 2,5,2',5'-tetrachlorobiphenyl (Sargent *et al*., 1989).

Reproductive and Developmental Toxicity

Reproductive effects have been reported in people exposed to PCBs following occupational exposures, consumption of contaminated rice oil in the Yusho and Yu-Cheng poisoning incidents, and consumption of contaminated fish (ATSDR 2000). In summary, indications of menstrual disturbances in women, late miscarriages, reduction in the months of lifetime lactation, and effects on male fertility were associated with exposure to PCBs. Although several investigators (Buck *et al*., 1997; Courval *et al*., 1999; Swanson *et al*., 1995) have found no effect with exposure to PCBs, a more recent study (Buck *et al*., 2000) found an association between consumption of contaminated fish for 3-6 years and a reduction in fecundity in females. Earlier, Mendola *et al*. (1997) and Kusuda (1971) had reported a small decrease in length of menstrual cycle or menstrual irregularities in women whose diets contained Great Lakes fish or contaminated rice oil,

respectively. Both studies, however, had limitations (e.g., lack of information on confounders, role of other environmental contaminants).

Developmental effects have also not been clearly demonstrated in humans. Swanson *et al*. (1995) conducted a critical review of the available epidemiological studies regarding exposure to PCBs, reviewing each study on the basis of a defined set of criteria that were considered to be standards in epidemiologic research. After reviewing the strengths and weaknesses of each study, Swanson *et al*. (1995) found 2 occupational studies that had positive findings (i.e., low birth weights), 3 that were suggestive, 3 that were negative, and 31 that were inconclusive. Further, Swanson *et al*. (1995) reported no environmental exposure studies with positive or suggestive findings, 14 that were negative, and 20 that were inconclusive. A similar pattern was reported for these and other studies by ATSDR (2000). The variability in results of these studies may reflect the differences in controlling for confounders and/or the different exposure measures, levels, and substances.

For those studies (Fein *et al*., 1984; Jacobson *et al*., 1990a,b; Patandin *et al*., 1998; Rylander *et al*., 1995) that show an effect, a lower birth weight for infants exposed *in utero* to maternal body burdens of PCBs has been observed. A low birth weight was also common among the children born to mothers exposed to the contaminated rice oil (Funatsu *et al*., 1972; Lan *et al*., 1987; Rogan, 1989; Taki *et al*., 1969; Yamaguchi *et al*., 1971).

Rylander *et* al. (1998) reported that an increase in the risk of a low birth weight was observed at a concentration of PCB-153 (a marker for PCB exposure) of 300 ng/g lipid (adjusted odds ratio of 2.1, with a 95% confidence interval = 1.0-4.7) and at 400 ng/g lipid (odds ratio 2.3, 95% CI = 0.9-5.9). Hertz-Picciotto *et al*. (2005) and Baibergenova *et al*. (2003) also found that higher total in utero PCB exposure was associated with reduced birth weight, head circumference, and weight-for-gestational age in male infants. However, Longnecker *et al*. (2005) reported that maternal levels of PCBs during pregnancy were not associated with preterm birth, low birth weight, or length of gestation. The multivariate-adjusted odds ratio for preterm birth among those with PCB levels of $\geq$ 4 μg/L of total PCBs, compared with those with $\leq$2 μg/L, was 1.1 (95% CI = 0.6-2.2).

Yu *et al.* (2000), in a long-term followup among women who were exposed to the contaminated rice oil in Taiwan (Yu-Cheng disease), reported several apparent effects related to endocrine or reproductive function. These included a higher rate of abnormal menstrual bleeding and a higher frequency of deaths of their offspring during childhood. A higher proportion of these women, compared to controls, had decided to limit childbearing because of their health problems (7% vs. 2%, p = 0.01).

Although no clear association exists between PCB exposure and developmental effects in pregnant women, there is a strong trend indicating that a lower birth weight for infants exposed *in utero* to maternal body burdens of PCBs is observed regardless of the method by which PCB exposure is measured. Unfortunately, the actual exposure levels cannot be determined from the studies reviewed, for use in the determination of a public health-protective concentration for water soluble PCBs found in drinking water.

Immunotoxicity

Immunological changes have been reported in several studies. These studies were reviewed by ATSDR (2000). Alterations (e.g., increased prevalence or susceptibility to infections, decreased total serum IgA and IgM) have been associated with exposure to PCBs following consumption of contaminated fish and other marine foods, consumption of contaminated rice oil (the Yusho and Yu-Cheng poisoning incidents), and occupational exposure. No clear indication exists between PCB exposure and increased risk of immunological toxicity. However, exposures to animals using PCB commercial mixtures, single PCB congeners, and mixtures of PCB congeners simulating the PCB content found in human breast milk or Great Lakes fish have demonstrated the immunotoxicological potential of these agents.

Neurotoxicity

The neurobehavioral effects of PCBs have been extensively investigated in adults and infants. For a review, see ATSDR (2000). The majority of the studies conducted have focused on the possible effects of PCBs on neonates and infants following prenatal and postnatal exposures. In children born to women accidentally exposed to high levels of PCBs (e.g., the Yusho and Yu-Cheng incidents), as well as other polychlorinated aromatic chemicals (e.g., polychlorinated terphenyls, quaterphenyls and dibenzofurans), significant effects on growth, general health, and behavioral and cognitive development of the children were reported (Tilson *et al*., 1990, 1997; Rogan and Gladen, 1992; Sinks *et al*., 1992; Kuratsune *et al*., 1971; Hsu *et al*., 1994). Chen *et al*. (1992, 1994) and Rogan *et al*. (1988) reported that children from the Yu-Cheng incident scored worse than matched controls in different tests and scales assessing cognitive development, emotional or behavioral disorders. To a lower extent, similar findings are reported in several other epidemiological studies conducted in women who consumed contaminated fish (Michigan Mother-Child Study and Oswego Newborn and Infant Development Project) and in the general exposed population (The North Carolina Breast Milk and Formula Project, the Dutch Mother-Child Study, and the German Study [ATSDR, 2000 and references within: Jacobson and Jacobson, 1996, 1997; Jacobson *et al*., 1985, 1990a,b, 1992; Gladen *et al*., 1988; Koopman-Esseboom *et al*., 1996; Patandin *et al*., 1999; Winneke *et al*., 1998]. Observations commonly reported in these studies included motor immaturity and hyporeflexia at birth, lower psychomotor scores between 6 months and 2 years of age, and decreases in cognitive functions at 4 years of age.

In many of the epidemiology studies, a direct correlation between effects and PCB exposure could not be established due to the limitations of the studies. In addition, the effects reported in these studies cannot be attributed entirely to PCBs; the role of the other polychlorinated or environmental agents present in the contaminated rice oil or consumed fish is not known. However, several studies reported significant associations between outcome and level of PCBs in breast milk, serum, or umbilical cord blood.

For adults, PCB exposure during adulthood was associated with impairments in memory and learning. Recently, Schantz *et al*. (2001) found a correlation between higher consumption of contaminated fish and lower scores on several measures of memory and

learning. In victims of the Yusho and Yu-Cheng incidents, reduced motor and sensory nerve conduction velocities have also been observed (Chen *et al*., 1985; Chia and Chu, 1984, 1985; Kuroiwa *et al*., 1969). Some of the workers exposed to PCBs have reported adverse neurobehavioral symptoms, but these have not been clinically confirmed (Emmett *et al*., 1988; Fischbein *et al*., 1979). A recent report suggests an increase in deaths due to neurodegenerative diseases (amyotrophic lateral sclerosis, Parkinson's disease, and dementia) among women exposed to PCBs, but the results suffer from small numbers and a reliance on mortality data rather than incidence (Steenland *et al*., 2006).

Summary of Non-Cancer Toxicity

In the epidemiological studies, general health effects described from the exposure to PCBs include many systemic changes (respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, and ocular), as well as immunological/lymphoreticular, neurobehavioral, reproductive, and developmental effects (ATSDR, 2000). However, the epidemiological and environmental occupational exposure studies have not conclusively demonstrated a direct causal relationship between PCBs and an increased rate of these conditions, in general (Johnson *et al.*, undated). One of the more important limitations is the presence of other polychlorinated contaminants such as polychlorinated dibenzofurans. However, overall, these studies do provide evidence that PCBs may have detrimental effects in humans and the effects are consistent in many respects with those from the animal studies.

Carcinogenicity

Epidemiologic studies following human exposures to higher PCB concentrations as a result of poisoning incidents and occupational exposures present limited evidence for PCB carcinogenicity in humans. Various reports have suggested an association between PCB exposure and cancer of the liver, biliary tract, stomach, breast, intestine, prostate, brain, thyroid, and skin (melanoma) (Bertazzi *et al*., 1987; Brown, 1987; Kimbrough *et al*., 1999; Sinks *et al*., 1992; Svensson *et al*., 1995a,b; Swanson *et al*., 1995, Gustavsson and Hogstedt, 1997; Hoyer *et al.*, 2001; Mallin *et al*., 2004; Prince *et al.*, 2006a,b; Ruder *et al.*, 2006). The increased cancer rates in these studies are relatively weak effects and somewhat inconsistent.

Studies following poisoning incidents in Japan (Yusho) and Taiwan (Yu-Cheng) found liver cancer and skin disorders in humans who accidentally ingested rice oil contaminated with PCBs. Several investigators have suggested that many effects in these poisoning incidents were the result of the formation of polychlorinated dibenzofurans during the heating of this cooking oil (Kashimoto *et al*., 1985; Miyata *et al*., 1985; ATSDR, 2000; Safe, 1994) rather than the direct result of PCB exposure.

Several of the occupational exposure studies involve workers in plants manufacturing large capacitors, which utilized PCBs as a cooling fluid. Occupational exposures were largely via inhalation and dermal exposure and absorption. Bertazzi *et al*. (1987) studied a cohort of workers at a plant in Italy where initially a 54 percent chlorine mixture was

used, and this was later changed to a 42 percent mixture. Both male and female workers were included in the study. Increases in death from gastrointestinal tract cancer noted in males and hematologic cancer in females were not related to exposure duration, latency or year of first exposure. Brown (1987) studied workers at plants in New York and Massachusetts where the Aroclor mixtures used changed from 1254 to 1242 to 1016. Male and female workers (2,588) who were employed at least three months in areas of the plant with high exposure potential were included in the cohort. Although a significant increase in death from liver (2 cases), gall bladder (1 case), and biliary tract (2 cases) cancer was observed, there was no trend related to measures of exposure duration. In addition, the workers were exposed to additional chemicals (e.g., trichloroethylene, toluene, and methyl isobutyl ketone); further compounding the results. Sinks *et al*. (1992) studied a cohort in Indiana of male and female workers employed for at least one day and potentially exposed to first Aroclor 1242 and then 1016. Workers were grouped into five exposure classes based on distance from the highest PCB source. Again, no association was found between potential exposure and an increased risk of death from skin cancer (malignant melanomas). Other studies, including case-control studies measuring PCB levels in serum (Krieger *et al*., 1994) or bone (Scheele *et al*., 1992) also failed to show an association between cancer incidence and PCB level. For review of additional occupational studies, see ATSDR (2000) and Swanson *et al*. (1995).

Nicholson and Landrigan (1994) reported a statistically significant increase in liver/biliary tract/gall bladder (SMR = 285, p = 0.008) after combining the data from three cohort studies (Gustavsson *et al.*, 1986; Brown and Jones, 1981 and Brown, 1987b; Bertazzi *et al.*, 1987). Bosetti et al. (2003) failed to observe any increase in overall or site-specific cancer mortality in their review of six epidemiological studies on worker exposures to PCBs. No clear association between PCB exposure and any cancer rate increases was established in a study where a large cohort was used (Kimbrough *et al*., 1999, 2003).

Several recent reports on the occupational exposure cohorts in capacitor-manufacturing plants update the earlier analyses (Prince *et al.*, 2006a,b; Ruder *et al.*, 2006, Steenland *et al.*, 2006). Increases in various tumor types are significant, but are difficult to interpret. This is summarized by Prince *et al*. (2006a) as follows: "The small numbers of deaths from liver and intestinal cancers, myeloma and nervous system diseases coupled with the lack of an exposure-response relationship with duration of employment preclude drawing definitive conclusions regarding PCB exposure and these causes of death." Other factors that contribute to this inconclusive evidence include inconsistent results, difficulty interpreting co-exposure to other potential carcinogens, limited exposure information, and the small sample sizes in most of the epidemiological studies.

In an environmental exposure study, Svensson *et al*. (1995a) compare two populations of fishers to each other and the general or regional population. One population of fishers (the east coast fishers) had about twice the levels of PCB and dioxins/furans in their blood compared to the other population (the west coast fishers) (Svensson *et al*., 1995b). In addition, the east coast group ate different species of fish that had higher levels of fat content. The authors reported a higher incidence of stomach and squamous cell skin cancers among east coast fishers compared to a regional population and the west coast

population. The incidence of colon cancer in the east coast fishers, however, is decreased. Mortality from multiple myelomas was increased among the east coast fishers compared to the general population and the west coast fishers. However, a marked decrease in mortality from ischemic heart disease (12 percent) was also noted for the east coast fishers. Like the occupational exposure studies, this study does not establish a clear link between the PCB levels and the cancer incidences or mortality due to the possible concurrent exposure to other polychlorinated compounds and other study limitations.

For other cancers, breast and non-Hodgkin's lymphoma, studies have shown no association between environmental exposure to PCBs and risk of breast cancer or non-Hodgkin's lymphoma in the general population (Hoyer *et al.*, 1998; Helzlsouer *et al.*, 1999; Aronson *et al.*, 2000; Negri *et al.*, 2003; Safe, 2004; Rubin *et al.*, 2006). There are, though, some preliminary reports to indicate that particular subgroups of women may be at increased risk for breast cancer following exposure to PCBs, associated with polymorphisms (Moysich *et al.*, 1999; Zhang *et al.*, 2004; Li *et al.*, 2005). The association between PCB exposure and risk among racially and genetically susceptible subgroups warrants further investigation.

Summary of Carcinogenicity

In summary, the human studies evaluating the possible association between PCB exposure and cancer have several methodological limitations. Overall, these studies provide some evidence that PCBs may be carcinogenic in humans, but the data are not adequate to establish definitive conclusions or calculate a cancer potency.

DOSE-RESPONSE ASSESSMENT

As described in the previous sections, PCB exposure is associated with a wide variety of toxic effects in humans and experimental animals. Neurobehavioral toxicity, immunotoxicity, reproductive toxicity, developmental toxicity, and carcinogenic effects have been reported in animals. Although information exists about the adverse effects of PCBs for humans, clear direct evidence is lacking as well as a certainty about the doses at which these effects were seen. Estimated exposure of PCBs to humans in the two rice oil incidents was not clearly established. In some cases, an association between a health effect and concentration of PCBs in sera, tissue, breast milk or estimate of contaminated fish consumption has been reported in the occupational and environmental exposure studies, while in other cases, no association was found. However, these human studies provide supporting evidence that PCBs can cause neurobehavioral effects and are probably carcinogenic in humans.

Noncarcinogenic Effects

The review of animal studies revealed possible neurobehavioral, immunological and reproductive/developmental effects of several of the commercial mixtures in monkeys,

rats, and mice. Table 3 lists the most sensitive effects reported for each of the commercial mixtures. The more sensitive effects were observed with three mixtures: simulated PCB content in human breast milk, Aroclor 1016 and Aroclor 1254. Neurobehavioral effects were observed with the simulated PCB content in human breast milk and with Aroclor 1016, developmental effects with Aroclor 1016 and Aroclor 1254, and reproductive and immunological effects with Aroclor 1254.

Table 3. Summary of Oral Toxicity Studies on Commercial Mixtures of Polychlorinated Biphenyls

Test Material	Species (Sex)	Duration	NOAEL (N) or LOAEL (L)	Effect	Reference
Simulated Human Milk	Monkey (M offspring)	Birth to 20 weeks	0.0075 mg/kg-day (L)	Neurobehavioral developmental (decreased performance in nonspatial and spatial discrimination reversal tasks)	Rice 1997, 1998, 1999; Rice & Hayward, 1997, 1999
Aroclor 1016	Monkey (F)	21.8 mo. (Pmm 12-Ppm 4)	0.008 mg/kg-day (N)	Neurobehavioral developmental (decreased discrimination performance in offspring)	Schantz *et al.*, 1989
	Monkey (F)	21.8mo. (Pmm 12-Ppm 4)	0.008 mg/kg-day (N)	Developmental (low birth weights)	Schantz *et al.*, 1989
	Monkey (F)	87 $\pm$ 9 wk	4.5 mg/kg-day (N)	Developmental (low birth weights)	Barsotti & van Miller, 1984
Aroclor 1221	Mouse (M)	6 mo.	4.9 mg/kg-day (N)	Immunological	Koller, 1977
Aroclor 1242	Mouse (M)	6 mo.	0.5 mg/kg-day (N)	Immunological	Koller, 1977
Aroclor 1248	Monkey (F)	16-21 mo. (Pmm 6-Ppm 3)	0.1 mg/kg-day (L)	Neurobehavioral developmental (impaired learning and hyperactivity in offspring)	Bowman *et al.*, 1978
	Monkey (F)	7 months	0.1 & 0.2 mg/kg-day (L)	Reproductive (0.1 – increased menstrual cycle; 0.2 – reduced conception rate)	Barsotti *et al.*, 1976
	Monkey	18.2 mo. (Pmm 3 – Ppm 3)	0.1 mg/kg-day (L)	Developmental (50% mortality, dermal/ocular effects, degenerative changes in thymus, spleen and lymph nodes)	Allen & Barsotti, 1976
Aroclor	Monkey	37 months	0.04 mg/kg-	Hepatic (decreased serum	Arnold *et al.*,

Test Material	Species (Sex)	Duration	NOAEL (N) or LOAEL (L)	Effect	Reference
1254	(F)		day (L)	cholesterol)	1993a
	Monkey (F)	72 months	0.005 mg/kg-day (L)	Dermal (nail lesion and nail bed changes)	Arnold *et al*., 1995, 1997
	Monkey (F)	37 mo.	0.005 mg/kg-day (N)	Reproductive (decreased fertility, prolonged menstruation)	Arnold *et al*., 1995
	Monkey (F)	23 mo. & 55 mo.	0.005 mg/kg-day (L)	Immunological (reduced IgM and IgG antibody responses to sheep red blood cells)	Tryphonas *et al*., 1989 & 1991
	Monkey	48 mo. (Pmm 37-Ppw 22)	0.005 mg/kg-day (L)	Developmental (inflammation of tarsal glands, nail lesion and nail bed changes, gum recession, and reduced IgM antibody levels to SRBC in infant offspring)	Arnold *et al*., 1995
Aroclor 1260	Rat	24 mo.	1 (M) & 1.4 (F) mg/kg-day (L)	Hepatic (hepatocellular hypertrophy and vacuolization; bile duct hyperplasia)	Mayes *et al*., 1998

Abbreviations: d = days; F = female; Gd= gestational day; L = LOAEL; M = male; mo. = month; N = NOAEL; Pmm = pre-mating month; Ppm = post-parturition month; wk = week.

For the neurobehavioral changes, Rice (1997, 1998, 1999) and Rice and Hayward (1997, 1999) found a LOAEL of 0.0075 mg/kg-day when male infant Rhesus monkeys were treated with a PCB mixture simulating the content of contaminated human breast milk from birth to 20 weeks of age. Neurobehavioral changes were also reported in monkeys treated with a dose of 0.03 mg/kg-day Aroclor 1016; the reported NOAEL was 0.007 mg/kg-day (Schantz *et al*., 1989). The LOAEL reported by Rice (1997, 1998, 1999) and Rice and Hayward (1997, 1999) was used by ATSDR to derive the intermediate exposure duration oral Minimal Risk Level (MRL) of 0.00003 mg/kg-day.

Aroclor 1016 at 0.03 mg/kg-day also caused developmental effects in Rhesus monkeys following an exposure from 12 months prior to mating to 4 months post-parturition (Barsotti and van Miller, 1984; Levin *et al*., 1988; Schantz *et al*., 1989). The reported NOAEL was 0.007 mg/kg-day. A similar dose of Aroclor 1254 (0.005 mg/kg-day) was found to cause immunological, developmental and reproductive effects in Rhesus monkeys (Tryphonas *et al*., 1986, 1989, 1991; Arnold *et al*., 1995). This was the LOAEL for immunological and developmental changes and the NOAEL for reproductive effects. In this study, Rhesus monkeys were treated with Aroclor 1254 for up to 72 months with interval findings given at 23, 38 and 55 months. The immunological changes reported by Tryphonas *et al*. (1989, 1991) were used by U.S. EPA and ATSDR

to derive a similar reference level (0.00005 mg/kg-day) for the non-carcinogenic effect of PCBs. U.S. EPA calculated a Reference Dose (RfD) and ATSDR an MRL.

Carcinogenic Effects

There is evidence that the carcinogenicity of all Aroclor mixtures is not equal. Reevaluation of the pathology data from seven studies (including all of the studies discussed above except the Mayes *et al*., 1998 study) in which rats were fed PCB mixtures containing different chlorine content shows that, although the same types of liver tumors were found in all studies, the mixtures with 60 percent chlorine content consistently resulted in the highest liver tumor incidence (Moore *et al*., 1994). As discussed above in the Animal Carcinogenicity Section, the reevaluation by Moore *et al*. (1994) using updated tumor diagnostic criteria found that only the 60 percent chlorine mixtures showed a statistically significant increase in tumors while the 42 percent (Clophen A 30) and 54 percent mixtures did not show significant increases. Smith (1997) recalculated the cancer slope factors for these same studies based on the reevaluated pathology and concluded that a slope factor from a single "best" study did not appear to adequately describe the range of carcinogenicity of various technical mixtures.

All five of the rat data sets discussed above are relevant for calculating cancer slope factors. We conclude that calculations for Kimbrough *et al*. (1975), NCI (1978), Schaeffer *et al*. (1984), and Norback and Weltman (1985) should be based on the Moore *et al*. (1994) reevaluation of these studies. Combined liver tumors (hepatocellular adenomas and carcinomas) in these studies can be used to calculate cancer slope factors for the technical mixture used in each study. The thyroid tumors observed in some studies are not relevant for dose-response assessment because no dose-response trend was found.

U.S. EPA applied its proposed cancer guidelines (U.S. EPA, 1996b) to calculate cancer slope factors for PCBs based on these studies (U.S. EPA, 1996a). For the Mayes *et al*. (1998) study (U.S. EPA had pre-publication access to this study), it was possible to calculate the dose as a lifetime daily average using weekly body weight measurements and food consumption estimates. For the other studies, default factors for rat weight (350 grams) and food consumption (5 percent of body weight daily) were used to convert the dietary concentration (ppm) to a mg/kg-d dose. The initial dose levels were used without averaging over the study duration for the Kimbrough *et al*. (1975) and Norback and Weltman (1985) studies, although initial dose levels were decreased or discontinued in these studies. U.S. EPA estimates that this might reduce the slope factors by one-third compared to using averaged dose estimates. This will only affect slope factors estimated for Aroclor 1260 mixtures. A linear-quadratic multistage model was fitted to the liver tumor experimental results, and doses were scaled using 3/4 power body weight scaling. These are lifetime studies so no intercurrent mortality scaling was necessary. The calculated cancer potency factors (q_1*), the lower confidence bounds on the dose causing a 10 percent increased incidence of tumors (LED_{10}), and the upper-bounds on the cancer slope factors derived from the LED_{10}sfor these studies are given in Tables 4a and 4b.

Based on the observed 30-fold range in carcinogenic potency for the technical PCB mixtures, U.S. EPA determined that it was not appropriate to select a single potency for all PCB mixtures. They suggest a three-tiered approach to select a cancer slope factor. The tiers are based on potency, environmental processes that increase or decrease risk, and presumed or measured congener content of the PCB mixture being assessed. The upper-bound slope factors recommended (rounded to one significant digit), their derivation and tier (see Table 4b), and their criteria for application are as follows:

Slope factor of 2 mg/k-d:

- highest cancer slope factor for mixtures containing greater than 50 percent chlorines (e.g., Aroclor 1254 and 1260);
- use for food chain exposure, sediment or soil ingestion, dust or aerosol inhalation, dermal exposure when an absorption factor has been applied to reduce the external dose, presence of dioxin-like, tumor-promoting, or persistent congeners, and early-life exposures;

Slope factor of 0.4 mg/kg-d:

- highest cancer slope factor for mixtures containing less than 50 percent chlorines (e.g., Aroclor 1242);
- use for ingestion of water soluble congeners, inhalation of evaporated congeners, dermal exposure when no absorption factor has been applied to reduce the external dose; and

Slope factor of 0.07 mg/kg-d:

- highest cancer slope factor for mixtures containing low proportions of congeners with more than 4 chlorines;
- use when congener analysis verifies that congeners with more than 4 chlorines are less than 0.5 percent of total PCBs.

Table 4a. Cancer Potencies for PCB Mixtures Adapted from U.S. EPA (1996a), Grouped by Study

DATA SET: study/strain/sex	Treatment mixture	q_1* $(mg/kg\text{-}d)^{-1}$	LED_{10} (mg/kg-d)	Upper-bound CSF $(mg/kg\text{-}d)^{-1}$
Mayes *et al*. (1998)				
S-D female	1260	0.56	0.19	0.5
	1254	1.6	0.067	1.5
	1242	0.39	0.27	0.4
	1016	0.073	1.4	0.07
S-D male	1260	0.19	0.55	0.2
*	1254	0.12	0.87	0.1
*	1242	0.061	1.2	0.08
*	1016	0.032	2.5	0.04
Norback & Weltman (1985)				
S-D female	1260	2.3	0.046	2.2
S-D male*	1260	0.20	0.53	0.2
Schaeffer *et al*. (1984)				
Wistar male	A 60	2.2	0.047	2.1
Wistar male*	A 30	0.10	1.0	0.1
NCI (1978)				
Fischer female*	1254	0.17	0.61	0.2
Fischer male	1254	0.19	0.55	0.2
Kimbrough *et al*. (1975)				
Sherman female	1260	1.2	0.091	1.1

*Increase is not significant; values show relative sensitivity of study
S-D: Sprague-Dawley rats

Table 4b. Cancer Potencies for PCB Mixtures Adapted from U.S. EPA (1996b), Grouped by Mixture and U.S. EPA (1996a) Tier.

DATA SET: study/strain/sex	Treatment mixture	q_1* $(mg/kg\text{-}d)^{-1}$	LED_{10} (mg/kg-d)	Upper-bound CSF $(mg/kg\text{-}d)^{-1}$
HIGH RISK AND PERSISTENCE TIER				
Norback & Weltman, S-D female	1260	2.3	0.046	2.2
Kimbrough, Sherman female	1260	1.2	0.091	1.1
Mayes, S-D female	1260	0.56	0.19	0.5
Schaeffer, Wistar male	A 60	2.2	0.047	2.1
Mayes, S-D male	1260	0.19	0.55	0.2
Norback & Weltman, S-D male*	1260	0.20	0.53	0.2
Mayes, S-D female	1254	1.6	0.067	1.5
NCI, Fischer female*	1254	0.17	0.61	0.2
NCI, Fischer male	1254	0.19	0.55	0.2
Mayes, S-D male*	1254	0.12	0.87	0.1
LOW RISK AND PERSISTENCE TIER				
Mayes, S-D female	1242	0.39	0.27	0.4
Schaeffer, Wistar male*	A 30	0.10	1.0	0.1
Mayes, S-D male*	1242	0.061	1.2	0.08
LOWEST RISK AND PERSISTENCE TIER				
Mayes, S-D female	1016	0.073	1.4	0.07
Mayes, S-D male*	1016	0.032	2.5	0.04

*Increase is not significant; values show relative sensitivity of study
S-D: Sprague-Dawley rats

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or non-carcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water and for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses that may result in dermal and inhalation exposures. Exposure could also result from contact with contaminated soil and ingestion of contaminated fish. However, for calculating a public-health protective concentration of water-soluble PCBs expected to be found in drinking water, the calculation for the carcinogenic effects was based on the exposure pathway as recommended by U.S. EPA (1996a). The approach is a tiered approach for mixtures of PCBs with a risk lower than the parent mixture and with a long persistence in the environment. The slope factors were based on rat liver tumor incidence for Aroclors 1260, 1254, 1242, and 1016 from the Mayes *et al*. (1998; ATSDR, 2000) study and for Aroclor 1260 from the Norback and Weltman (1985) study. The highest slope factor (2.0 per $[mg/kg\text{-}day]^{-1}$) is for the high risk and persistence category. An intermediate slope factor (0.4 per $[mg/kg\text{-}day]^{-1}$) is for the low risk and persistence category. The lowest slope factor (0.07 per $[mg/kg\text{-}day]^{-1}$) is for the lowest risk and persistence category. The cancer slope factor for the low risk and persistence tier was considered appropriate for exposure to water soluble PCBs from ingestion of tap water (as drinking water or for preparing foods and beverages), from bathing or showering in contaminated water, and from washing, flushing toilets and other household uses that may result in dermal and inhalation exposures. Likewise, the public-health protective concentration for the non-carcinogenic effects considered several sensitive effects caused by the more water-soluble commercial PCB mixtures that would have a higher likelihood of being found in drinking water. For this calculation, the relative source contribution would take into consideration exposure to water soluble PCBs from ingestion of tap water, bathing/showering, or other household uses that may result in dermal and inhalation exposures, versus total exposure from other sources. Food is expected to be the major exposure source.

Although mechanistic data has led to the use of toxic equivalency risk factors (TEF) and toxic equivalents (TEQ) relative to TCDD as an approach for risk assessment of environmental mixtures for PCBs (Safe, 1990, 1994; Birnbaum and DeVito, 1995; Pohl and Holler, 1995; van den Berg *et al*., 1998; ATSDR, 1998; OEHHA, 2003, 2005), this approach was not used in the calculation of the public-health protective concentration for various reasons. The approach is limited to those congeners that are dioxin-like, which act through the Ah receptor and are coplanar or mono-ortho-coplanar PCBs. In addition, the TEF approach assumes that each component will act in an additive manner through a common Ah-receptor initial mechanism. Non-additive interactions (e.g., antagonistic) between specific PCB congeners and between some PCB congeners and TCDD do exist (Safe, 1998a,b). More specifically, for calculating a drinking water public health goal, no data on the mixture of congeners found in drinking water have been reported. In addition, there were no detections of PCBs (0/4,985 analyses) in California drinking

water supplies in the 1984-2001 sampling period (DHS, 2002). Thus, the use of the TEF approach would exclude the contribution of non TCDD-like congeners and also be inappropriate at this time for calculating a drinking water public health goal.

Noncarcinogenic Effects

The more sensitive effects reported in the animal studies were the immunological, developmental, reproductive, and neurobehavioral toxicity effects caused by Aroclor 1016, Aroclor 1254, or a mixture of PCBs simulating the content of PCBs found in human breast milk (See Table 3 for list of effects). Since the focus of the development of the human health-protective concentration is on water-soluble PCBs expected to be found in drinking water, only the effects observed with the more water-soluble mixtures will be considered in the calculation of the public health-protective concentration. These are Aroclor 1016 and to some extent Aroclor 1254.

A public health-protective concentration was calculated for the developmental effects (low birth weights, immunological and neurobehavioral changes) observed with Aroclor 1016 or 1254. A geometric mean was calculated, and assumed to be representative of an exposure to a mixture of several water-soluble PCB congeners with varying potencies and mechanisms. The uncertainty factors used in these calculations depended on the information reported for each study.

The following general equation was used to calculate the public health-protective concentration (C, in mg/L) for water-soluble PCBs expected to be found in drinking water based on the non-carcinogenic effects:

$$C = \frac{LOAEL/NOAEL \times BW \times RSC}{UF \times W}$$

where,

LOAEL/NOAEL	=	lowest-observed-adverse-effect-level or no-observed-adverse-effect-level for the critical effect;
BW	=	body weight (a default of 70 kg for adults);
RSC	=	relative source contribution (default of 20 percent);
UF	=	uncertainty factors (often, defaults of ten for extrapolations from a LOAEL to a NOAEL, less than lifetime exposures, interspecies extrapolation, and/or interindividual variability, with a maximum combined factor of 3,000);
W	=	A daily adult water consumption rate (2 L/day)

For the developmental/neurobehavioral effects observed with Aroclor 1016, the NOAEL (0.008 mg Aroclor 1016/kg-day) reported by Schantz *et al*. (1989) was used for this

calculation. The uncertainty factors for the calculation from the NOAEL are 3 for less than lifetime exposure, 10 for interspecies extrapolation, and 10 for interindividual variability. The default RSC of 0.2 is considered appropriate because the major source of exposure to PCBs is food, and very little exposure is expected from the drinking water or other uses of tap water. Using the above values and substituting the values for the RSC, appropriate UF, and intake rate into the above equation, the following estimate of the concentration of water-soluble PCBs expected to be found in drinking water protective against the neurobehavioral endpoint observed in the cited studies is derived:

$$C = \frac{8 \times 10^{-3} \text{ mg/kg-d} \times 70 \text{ kg} \times 0.2}{300 \times 2 \text{ L/day}} = 18.7 \times 10^{-5} \text{ mg/L} = 0.19 \text{ ppb} = 187 \text{ ppt}$$

For the developmental/immunological effects observed in infants exposed in utero and treated mothers (nailbed changes/decreased antibody response to SRBC antigen) reported for Aroclor 1254, the LOAEL of 0.005 mg/kg-day (Tryphonas *et al*., 1989, 1991; Arnold *et al*., 1995) in monkeys was used. The uncertainty factors applied for this effect are 3 for extrapolation from relatively mild and reversible effects at this LOAEL, 10 for interindividual variability, and 10 for interspecies extrapolation. Substituting the values for the RSC, appropriate UFs, and intake rate into the above equation, the estimate of the concentration of water-soluble PCBs expected to be found in drinking water protective against the effects observed in the cited study is derived:

$$C = \frac{5 \times 10^{-3} \text{ mg/kg-d} \times 70 \text{ kg} \times 0.2}{300 \times 2 \text{ L/day}} = 11.7 \times 10^{-5} \text{ mg/L} = 0.117 \text{ ppb} = 117 \text{ ppt}$$

For the developmental effects (low birth weights) of Aroclor 1016, the NOAEL of 0.008 mg/kg-day (Schantz *et al*., 1989) in monkeys was used. The uncertainty factors applied for this effect are 10 for interindividual variability and 10 for interspecies extrapolation. Using the NOAEL and substituting the values for the RSC, appropriate UFs, and intake rate into the above equation, the estimate of the concentration of PCB in drinking water protective against the developmental endpoint observed in the cited study is derived:

$$C = \frac{8 \times 10^{-3} \text{ mg/kg-d} \times 70 \text{ kg} \times 0.2}{100 \times 2 \text{ L/day}} = 56 \times 10^{-5} \text{ mg/L} = 0.56 \text{ ppb} = 560 \text{ ppt}$$

For the reproductive effects (decreased fertility, prolonged menstruation) of Aroclor 1254, the NOAEL of 0.005 mg/kg-day (Arnold *et al*., 1995) was used. The uncertainty factors used in this calculation were 10 for interspecies extrapolation and 10 for interindividual variability. Using the NOAEL and substituting the values for the RSC, UF, and intake rate into the above equation, the following estimate of the concentration of water-soluble PCBs expected to be found in drinking water protective against the reproductive toxicity endpoint observed in the cited study is derived:

$$C = \frac{5 \times 10^{-3} \text{ mg/kg-d} \times 70 \text{ kg} \times 0.2}{100 \times 2 \text{ L/day}} = 35.1 \times 10^{-5} \text{ mg/L} = 0.351 \text{ ppb} = 351 \text{ ppt}$$

To derive a public health-protective concentration for the non-carcinogenic effects, acknowledging the minor differences based mainly on application of uncertainty factors, a geometric mean of the calculated public health protective concentrations was taken. The geometric mean would be representative of exposure to a mixture of water-soluble PCB congeners expected to be found in drinking water, which would take into account the varying potencies for these congeners, mechanism(s) of action, and/or varying partitioning rates into various media (such as environmental or human tissues), chemical transformations, and bioaccumulation rates of these mixtures. In addition, the geometric mean would take into consideration differences that may result from extrapolating, for example, the neurobehavioral effects caused by Aroclor 1016 or immunological effects caused by Aroclor 1254. The estimated public health-protective concentrations for the non-carcinogenic endpoints ranged from 117 to 560 parts per trillion (ppt). The geometric mean of the estimates for the four calculations is 30.4×10^{-5} mg/L (0.304 ppb) or 0.30 ppb (0.30 μg/L) with rounding. This public health-protective concentration is higher than the one derived below for cancer. Therefore the drinking water concentration derived below to protect against carcinogenic effects is also protective against non-cancer chronic toxicity.

Carcinogenic Effects

At present, humans are exposed to environmental mixtures of PCBs. Selective partitioning, chemical transformation, and bioaccumulation have modified the composition of these mixtures once the mixtures enter the environment (ATSDR, 2000). These environmental mixtures would then be different from their parent technical mixtures such as those tested in the animal studies. If the true environmental mixture were to be tested, it is likely that a different carcinogenic potency would be obtained compared to the parent mixture. Different media (e.g., soil, water) tend to accumulate a subset of the congeners originally present following PCB contamination. U.S. EPA (1996a) has recommended that the range of cancer potencies (i.e., slope factors) from technical mixtures be used to represent an approximation of the range of altered potencies of environmental mixtures and developed a three-tiered approach for using these potencies in risk assessment. The slope factors were based on rat liver tumor incidence for Aroclors 1260, 1254, 1242, and 1016 from the Mayes *et al*. (1998; ATSDR, 2000) study and for Aroclor 1260 from the Norback and Weltman (1985) study. In the U.S. EPA guidance document, exposure pathway is used as the primary indicator of whether the potency of the contaminating PCB has increased or decreased and a "high or low risk" upper-bound cancer slope factor is recommended. A third "lowest risk" cancer slope factor is recommended only when there are congener data that show that congeners with more than four chlorines make up less than 0.5 percent of the PCB contaminant, and that persistent congeners or those with dioxin-like or tumor-promoting activity are absent.

The risk derived from exposure to environmental mixtures of PCB contaminants in drinking water is likely to be less than from parent PCBs because the higher chlorinated congeners, including those that are lipophilic and most persistent, are reduced in this exposure pathway. Under these circumstances, U.S. EPA recommends a default upper-

bound cancer slope factor from the low risk and persistence tier described above. The cancer slope factor currently proposed by U.S. EPA to be used for the drinking water ingestion risk assessment is 0.4 $(mg/kg\text{-}d)^{-1}$, based on the cancer potency in female Sprague-Dawley rats. We concur with this approach and potency value, in preference to the slightly lower cancer potency value in males (Table 4b).

The following general equation was used to calculate the public health-protective concentration (C, in mg/L) for carcinogenic effects of water-soluble PCBs expected to be found in drinking water:

$$C = \frac{BW \times R}{CSF \times W} = mg/L$$

where,

BW = adult body weight (a default of 70 kg);

R = *de minimis* lifetime excess individual cancer risk (default of 10^{-6});

CSF = cancer slope factor, a potency derived from the lower 95 percent confidence limit on the 10 percent tumor dose (LED_{10}); CSF = $0.1/LED_{10}$; q_1* is the upper 95 percent confidence limit on the cancer potency slope calculated by the LMS model; both potency estimates are converted to human equivalent (in $[mg/kg\text{-}day]^{-1}$) using $BW^{3/4}$ scaling;

W = daily drinking water consumption rate (2 L/day).

Therefore,

$$C = \frac{70\ kg \times 1x10^{-6}}{0.4\ (mg/kg\text{-}d)^{-1} \times 2\ L/day} = 8.8x10^{-5}\ mg/L = 0.088\ ppb = 88\ ppt$$

The calculated value for carcinogenicity can be rounded to one significant figure, considering the uncertainty of the extrapolation. The PHG value for water-soluble PCBs is therefore 0.09 ppb (0.09 μg/L), based on carcinogenic effects. This level should also be adequately protective against all non-cancer effects. However, it should be noted that the geometric mean calculated for non-cancer effects is only about three times higher than the value calculated from the cancer effect.

RISK CHARACTERIZATION

Polychlorinated biphenyls are complex mixtures of chlorinated biphenyl congeners, with the empirical formula of $C_{12}H_{10-n}Cl_n$, where *n* (the number of chlorine atoms) is in the range 1-10. Theoretically, 209 congeners with different numbers and/or positions of chlorine atoms on the two phenyl rings are possible. In general PCBs are chemically inert, resistant to heat, non-flammable, and have a low vapor pressure and a high dielectric constant (i.e., low electrical conductivity). Commercial production of PCBs in

the United States began in 1929 and ended in 1977 (IARC, 1978). The most frequent uses for these chemicals were as dielectrics in transformers and large capacitors and as heat resistant (cooling) liquids in heat transfer and hydraulic systems (WHO, 1993). They were also used in formulations of lubricating and cutting oils and wax extenders, and as plasticizers in paints, flame-retardants, plastics and other compounds. PCBs are no longer produced in the United States, except under exemption for use as a mounting medium in microscopy, immersion oil in microscopy, optical liquid, and research and development (U.S. EPA, 1990).

PCBs enter the environment through accidental spills and leakage, volatilization and surface runoff. Once released in the environment PCBs are stable, very persistent and accumulate in biological organisms. PCB residues are found chiefly in soil, sediment, and fatty biological tissues. Non-occupational exposure to PCBs is primarily through ingestion of animal protein (meat, fish, poultry, dairy products and oils and fats) contaminated with PCBs. Inhalation of contaminated air is also an additional source of human exposure to PCBs. The mixture of PCB isomers available through these different routes may vary. For this reason, the calculation of the public health-protective concentration was based on the effects and properties of the more water-soluble PCBs expected to be found in water. The public health risks of exposure to PCBs can be characterized as follows:

Chronic Health Effects

Typical exposures to water-soluble PCBs in drinking water are not expected to result in any acute health effects, due to the low levels involved. This includes household airborne exposures from showering, flushing toilets, etc. In the epidemiological studies, general health effects described from the exposure to PCBs include many systemic changes (respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, and ocular), immunological/lymphoreticular, neurobehavioral, reproductive, and developmental (ATSDR, 2000). Limited evidence of PCB carcinogenicity in humans has also been reported. However, the epidemiological and environmental occupational exposure studies have not conclusively demonstrated a direct causal effect for an increased rate of human cancers. One of the limitations reported is the presence of other polychlorinated contaminants such as polychlorinated dibenzofurans. Overall, these studies do provide some evidence that PCBs are carcinogenic in humans, including the more water-soluble PCBs. In addition, the trends of effects that are reported in the human studies are corroborated in many cases by the animal studies.

Carcinogenic Effects

In animal studies, oral exposure to PCBs produced increased incidences of hepatic tumors in male and female rats, and thyroid gland tumors only in male rats. However, the thyroid tumors observed were not relevant for dose-response assessment because no dose-response trend was found. The majority of the studies were conducted with a PCB

mixture containing 60 percent chlorine content. Fewer lifetime studies have been done using PCB mixtures with lower chlorine content and the results vary with the mixture used and the animal strain tested. A summary of our evaluation is given below.

- OEHHA considers PCBs to be an animal carcinogen and a probable human carcinogen, including the more water-soluble PCBs.
- Five separate cancer bioassays have shown PCBs to induce tumors at several sites in several strains of rats and mice, in both sexes, by the oral route of exposure.
- The cancer studies in rats consistently show induction of liver tumors by PCB exposures.
- The oral studies in rats were considered adequate for risk assessment of drinking water exposures to PCBs.
- In general, the genotoxicity studies of commercial PCB mixtures have indicated some genotoxic activity at relatively high doses. Further, evidence, often using individual congeners, shows that PCBs form adducts with cellular macromolecules.
- Lack of knowledge of the mode(s) of action of PCBs in causing cancer in rodents and the implication of these processes for human disease is a limitation of this risk assessment.
- The PHG of 0.09 ppb is based primarily on the upper-bound cancer slope factor from the low risk and persistence tier recommended by U.S. EPA.
- The CSFs are upper-bound estimates defined by the 95 percent confidence limit on the ED_{10}. It is theoretically possible that the true value of the cancer potency of PCBs in humans could exceed these values, but that is considered unlikely. It is plausible that the true value of the human cancer potency for PCBs has a lower bound of zero, based on statistical and biological uncertainties.

According to this analysis, the health-protective concentration of water-soluble PCBs in drinking water associated with a one in one million extra lifetime cancer risk is 0.09 ppb. The primary sources of uncertainty in the development of the PHG for water-soluble PCBs in drinking water are also the general issues of uncertainty in any risk assessment, particularly applicability of the rodent carcinogenicity data to low-level human exposures. Additional uncertainties involve the correction factor for less than lifetime exposure in the non-cancer calculations, and issues relating to patterns and amounts of possible human exposure. We acknowledge that a more formal analysis of the uncertainties used in our approach could provide a more rigorous quantitative evaluation and description of the human population risks. However, such an analysis would add even more complexity to this already difficult and complicated analysis. The public-health protective concentration derived here is based on the use of conservative estimates and includes various uncertainties.

The PHG of 0.09 ppb was calculated based on the carcinogenic potency of the more water-soluble PCBs: Aroclor 1016 and to some extent 1254. In calculating the PHG, a *de minimis* theoretical excess individual cancer risk level of 10^{-6} was assumed. The corresponding concentrations for cancer risks of 10^{-5} or 10^{-4} are 0.9 and 9 ppb, respectively.

For PHGs, OEHHA's use of the relative source contribution (RSC) has followed the current U.S. EPA drinking water risk assessment methodology, with a few exceptions. U.S. EPA has treated carcinogens differently from noncarcinogens with respect to the use of RSCs. For approaches that use low-dose extrapolation based on quantitative risk assessment, U.S. EPA does not factor in an RSC. The use of low-dose extrapolation is considered by U.S. EPA to be adequately health-protective without the additional source contributions; in addition, cancer risks are calculated as risks in addition to any background levels, so other exposure sources are irrelevant.

OEHHA has judged for this risk assessment that it is appropriate to calculate cancer potency by low-dose extrapolation from an upper-limit potency estimate. This is an area of uncertainty and scientific discussion, which may overestimate risk but is unlikely to underestimate it. For this risk assessment, the cancer risk assessment calculation produced a *de minimis* health-protective value similar to that for the geometric mean non-cancer value. The PHG would be about the same for either type of endpoint. The final PHG value is judged to be protective of infants, children, the elderly, and other possible sensitive subpopulations.

OTHER REGULATORY STANDARDS

The U.S. EPA's Maximum Contaminant Level (MCL) for PCBs is 0.0005 mg/L (0.5 ppb) and the Maximum Contaminant Level Goal (MCLG) is zero. The MCL is set at the practical quantitation limit for PCBs. This MCL was considered to be associated with a theoretical maximum lifetime excess individual cancer risk of 10^{-4}, which was calculated using an oral q_1* of 7.7 $(mg/kg\text{-}day)^{-1}$. The current California MCL is 0.0005 mg/L (0.5 ppb). Oklahoma, Tennessee, Utah, Wisconsin, and Florida have also adopted an MCL of 0.0005 mg/L. New Hampshire has an MCL of 0.005 μg/L (0.005 ppb) and Kentucky has an MCL of 0.000079 μg/L (0.000079 ppb).

U.S. EPA (1980, and Federal Register, 1980) set ambient water quality criteria for PCBs ingested through water or aquatic organisms of 0.79, 0.079, and 0.0079 ng/L for human health protection against cancer risks at levels of 10^{-5}, 10^{-6}, and 10^{-7}. U.S. EPA promulgated new human health criteria in the final Water Quality Guidance for the Great Lakes System in 1995 (Federal Register, 1995) and removed these criteria in 1997 (Federal Register, 1997). An interim value of 0.0026 ng/L (0.0026 ppt) for both drinking water and non-drinking water uses was calculated at this time for use until U.S. EPA proposes replacement criteria in 1998 (Federal Register, 1997).

The Agency for Toxic Substances and Disease Registry (ATSDR) established a Minimal Risk Level (MRL) of 0.03 μg/kg-day for intermediate-duration oral exposure and 0.02 μg/kg-day for chronic oral exposure. The intermediate oral MRL was based on the LOAEL of 0.0075 mg/kg-day for neurobehavioral effects in infant monkeys given a PCB congener mixture representative of a mixture of PCBs typically found in human breast milk (Rice 1997, 1998, 1999; Rice and Hayward, 1997, 1999). The chronic oral MRL was based on a LOAEL of 0.005 mg/kg-day for immunological effects reported in adult

monkeys treated with Aroclor 1254 for 23 and 55 months (Tryphonas *et al*., 1986, 1989, 1991a). Uncertainty factors of 10 for using a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability were applied.

The Occupational Safety and Health Administration (OSHA) has set transitional permissible exposure levels (PELs) of 0.5 and 1.0 mg/m^3 for Aroclor 1254 and 1242, respectively. The National Institute for Occupational Safety (NIOSH) recommends an occupational exposure limit of 0.001 mg/m^3 for PCBs for a 10-hour workday, 40-hour workweek.

The U.S. EPA has also determined PCBs to be a probable human carcinogens (B2) and has assessed cancer risk from environmental PCBs by considering both toxicity and environmental processes (Cogliano, 1998; U.S. EPA, 1996a; IRIS, 2006). With this approach, U.S. EPA calculated a range of slope factors to represent the potency of representative classes of environmental PCB mixtures. The slope factors were based on rat liver tumor incidence for Aroclors 1260, 1254, 1242, and 1016 from the Mayes *et al*. (1998; ATSDR, 2000) study and for Aroclor 1260 from the Norback and Weltman (1985) study. The highest slope factor (2.0 per [mg/kg-day]$^{-1}$) is for the high risk and persistent category. An intermediate slope factor (0.4 per [mg/kg-day]$^{-1}$) is for a low risk and persistent category. The lowest slope actor (0.07 per [mg/kg-day]$^{-1}$) is for the lowest risk and persistence category.

The U.S. EPA has established an oral reference dose of 0.02 μg/kg-day for Aroclor 1254 based on dermal/ocular and immunological effects in monkeys, and an oral reference dose of 0.07 μg/kg-day for Aroclor 1016 based on reduced birth weight in monkeys (IRIS, 2006). Drinking Water Equivalent Levels (DWEL) of 10 μg/L (10 ppb), 1 μg/L (1 ppb), and 0.1 μg/L (0.1 ppb) for excess cancer risk levels of 10^{-4}, 10^{-5} and 10^{-6}, assuming 100 percent exposure from water, were proposed based on the upper-bound cancer potency slope for a high risk and persistent category discussed above (IRIS, 2006).

The International Agency for Research on Cancer (IARC) has determined that PCBs are probably carcinogenic to humans (Group 2A) (IARC, 1987). In addition, the U.S. Department of Health and Human Services (DHHS) concluded that there was sufficient evidence that PCBs are carcinogenic to animals and that PCBs are reasonably anticipated to be carcinogenic in humans (NTP, 2000). The American Conference of Governmental and Industrial Hygienists has listed PCBs as a confirmed animal carcinogen (ACGIH, 1998). They have established threshold limit values of 1 mg/m^3 for Aroclor 1242 and 0.5 mg/m^3 for Aroclor 1242 as 8-hr time-weighted-averages for inhalation exposure. PCBs are also listed as known to cause cancer and reproductive toxicity by the California Environmental Protection Agency under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) (OEHHA, 2002).

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