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Steven Dentali, Ph.D.
Chief Science Officer
American Herbal Products Association
8630 Fenton Street, Suite 918
Silver Spring, MD 20910

Re: Technical Comments in Proposed Proposition 65 Safe Harbor Levels for PCBs

Dear Dr. Dentali:

As requested, Exponent has reviewed the basis for the two recently proposed "Safe Harbor Levels" (i.e., exposure levels below which warnings are not required under Proposition 65) for PCBs, and for reasons discussed below, we believe the bases for the new values are scientifically sound and consistent with regulations and policies developed by the State for deriving "Safe Harbor Levels" under Proposition 65.

As you are aware, the Office of Environmental Health Hazard Evaluation ("OEHHA") within Cal/EPA released a Notice of Proposed Rule Making on April 13, 2012 in which they proposed to adopt a new No Significant Risk Level ("NSRL") for PCBs of 0.35 micrograms per day and a new Maximum Allowable Dose Level ("MADL") of 2.3 micrograms per day of PCBs. Both of these "Safe Harbor Levels" are specifically developed for PCBs in food chain exposures.

Summary of Our Assessment

The "Safe Harbor Levels" proposed by OEHHA are predicated on reviews and findings presented in previous OEHHA evaluations of PCB toxicity, and on reviews and study evaluations prepared by the ATSDR and the U.S. EPA. As such, the Safe Harbor Levels are well grounded in scientific precedent and represent a logical application, rather than an extension, of previous determinations. OEHHA relies on studies involving Aroclor mixtures to represent the mixtures of PCBs in the food chain in general. This is a common (and often

necessary) approach in PCB assessments. While using the commercial Aroclor 1254 mixture as a surrogate for the range of PCBs mixtures that tend to be found in the food chain can entail some uncertainty, OEHHA's approach is consistent with approaches used in other regulatory programs and is technically defensible in light of our current understanding of PCB mixtures. Finally, OEHHA's calculations of the NSRL and MADL can be duplicated and are accurate given OEHHA's evaluative approach.

In the remainder of this letter we comment on some of the technical details supporting the proposed NSRL and MADL.

Discussion of OEHHA's Proposed NSRL and MADL

Both of these new Safe Harbor Levels are based on the use of toxicity factors (one for carcinogenicity and one for reproductive toxicity) selected to represent a mixture of PCBs. Among the few different approaches for evaluating the toxicity of chemical mixtures, using a single toxicity factor for a particular mixture is one of the approaches recommended by the U.S. EPA and other regulatory agencies for addressing mixtures, and it is the most commonly applied approach for the evaluation of PCBs. Alternative approaches include the use of toxicity factors for all of the individual constituents of a mixture or, using a subset of "indicator" chemicals selected to represent the toxicity of the entire mixture. Because toxicity factors are not available for all of the congeners that comprise mixtures of PCBs and because not all of the synergistic and antagonistic interactions are well understood, it is not feasible to evaluate the toxicity of these mixtures by evaluating all of the individual congeners in mixtures of PCBs. For cancer risk assessment, OEHHA allows the use of two approaches. In addition to the use of single cancer slope factors for specific mixtures of PCBs, OEHHA uses an "indicator" chemical approach in which Toxicity Equivalent Factors ("TEFs") are assigned to twelve dioxin-like PCB congeners. Cancer risks for PCB mixtures can be estimated using these TEFs when levels of the twelve congeners are known for specific PCB mixtures, although the synergistic and antagonistic interactions are not explicitly addressed or well understood for this approach. Because the mechanism of action assumed to underlie the derivation of the TEFs for carcinogenicity (i.e., Ah receptor affinity) does not appear to be the same toxicological mechanism of action that underlies the noncancer toxicity of PCBs (see Yang et al. 2010)[1], these TEFs cannot be used for the evaluation of health effects other than cancer. Even though the NRC (2009)[2] has recommended that TEFs be developed to support the evaluation of the reproductive toxicity of PCBs, such factors are not yet available.

While there are two approaches that can be used to evaluate the carcinogenicity of PCB mixtures (i.e., the TEF approach and the use of recommended cancer slope factors for PCB mixtures), there is only one approach applied to the evaluation of noncarcinogenic effects of PCBs. The approach used for the evaluation of noncarcinogenic effects of PCBs is the application of a

[1] Yang, J-M, A.G. Salmon, and M.A. Marty. 2010. Development of TEFs for PCB congeners by using an alternative biomarker–thyroid hormone levels. Regul. Toxicol. Pharm. 56(2): 225–236.

[2] NRC. 2009. Health risks from dioxin and related compounds: Evaluation of the EPA reassessment. National Research Council, National Academics Press, Washington, DC. 268 pp.

single noncancer toxicity factor to specific mixtures of PCBs. For example, the U.S. EPA has also developed Reference Doses for evaluating noncarcinogenic effects of specific, commercial PCB mixtures (see U.S. EPA IRIS data base for various Aroclors). OEHHA's proposed adoption of a single MADL for PCBs in the food chain is a similar approach.

A critical consideration in the adoption of a single toxicity factor for the evaluation of a mixture is the determination of whether the mixture on which the toxicity factor is based is "sufficiently similar" to the mixture in question. When the mixtures are "sufficiently similar," the use of toxicity factors based on toxicity testing of a mixture is generally preferable to toxicity evaluations based on evaluation of individual constituents of mixtures. The use of this approach requires critical evaluation when dealing with mixtures like PCBs in which there can be varying compositions. U.S. EPA (2000)[3] mixtures guidance, for example, notes that risk assessment should be performed on the components of a mixture only if adequate data are not available on the mixture or a sufficiently similar mixture: "If adequate data are not available on the mixture of concern, but health effects data are available on a similar mixture, a decision should be made whether the mixture on which health effects data are available is or is not 'sufficiently similar' to the mixture of concern to permit a risk assessment. The determination of 'sufficient similarity' should be made on a case-by-case basis, considering not only the uncertainties associated with using data on a surrogate mixture, but also contrasting the inherent uncertainties if one were to use other approaches, such as component-based methods."

In developing their cancer slope factors for PCBs, U.S. EPA considered the varying mixtures of PCBs found in different environmental media, including the food chain, and made a determination that the mixture of PCBs found in the food chain is "sufficiently similar" to the more highly chlorinated Aroclor mixtures for which toxicity data were available. Building on the U.S. EPA evaluation of PCB toxicity in the development of Fish Advisories[4] for the State, OEHHA noted that a mixture of more chlorinated congeners that tends to resemble the Aroclor 1254 and Aroclor 1260 are found in fish.

Exponent compared congener patterns in published results of PCBs in several commercial fish oil dietary supplements to congener patterns for Aroclor 1254 and Aroclor 1260. We found that while there were some variations in the congener patterns of PCBs found in various fish oils, the patterns found in the tested fish oils looked very similar to the patterns of Aroclor 1254 and Aroclor 1260. Thus, while the PCBs in fish oil are somewhat variable and do not present an exact match to the congener pattern of Aroclor 1254 or Aroclor 1260, there is a reasonably good match. We believe that the mixture of PCB congeners in the fish oil products we considered meet the U.S. EPA's test noted above of being "sufficiently similar" to Aroclor 1254 and Aroclor 1260 that toxicity results from testing of these commercial mixtures can reasonably be applied to the PCB mixtures in fish oil dietary supplements. Accordingly, OEHHA's proposed MADL and NSRL readily apply to this category of foods (i.e., fish oils).

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[3] U.S. EPA. 2000. Supplementary guidance for conducting health risk assessment of chemical mixtures. EPA/630/R-00/002. Risk Assessment Forum. U.S. Environmental Protection Agency, Washington, DC. 209 pp.

[4] OEHHA. 2008. Development of fish contaminant goals and advisory tissue levels for common contaminants in California sport fish: Chlordane, DDTs, dieldrin, methylmercury, PCBs, selenium and toxaphene. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (OEHHA), Sacramento, CA. 122 pp.

No Significant Risk Level

The newly proposed NSRL for PCBs in the food chain is based on a cancer slope factor of 2 $(mg/kg\text{-}day)^{-1}$ that was developed by the U.S. EPA and was also adopted by OEHHA for PCBs in the food chain, including fish, fish oil, eggs, meat, shellfish, poultry, and dairy products.[5] OEHHA adopted the cancer slope factor of 2 $(mg/kg\text{-}day)^{-1}$ as the recommended cancer slope factor for PCBs in food chain exposures several years ago. This slope factor replaced the previously recommended cancer slope factor of 7.7 $(mg/kg\text{-}day)^{-1}$ that had been was used for other regulatory programs and that served as the basis for the previously recommended NSRL for PCBs of 90 nanograms per day. The newly proposed NSRL for PCBs in the food chain brings the recommended NSRL for food chain PCBs into line with the treatment of PCBs in other State and Federal regulatory programs. In short, this is merely an update, importing current criteria already widely used in other programs into the Proposition 65 program. In that respect, OEHHA is doing nothing new—it is just harmonizing Proposition 65 with other programs so the Proposition 65 NSRL is not based on obsolete science.

Maximum Allowable Dose Level

The newly proposed MADL for PCBs in the food chain is based on a study in monkeys in which the researchers observed adverse effects on reproduction (increased fetal mortality) at the highest tested dose of 80 micrograms per kilogram of bodyweight administered to pregnant females. No effects on reproduction were seen in the control group or in groups administered lower doses of 5, 20, and 40 micrograms per kilogram. OEHHA identified the dose of 40 micrograms per kilogram as the No Observed Effect Level and as the basis of the MADL.

Although it does not directly affect the derivation of the MADL under Proposition 65 guidelines, it is worth noting that monkeys are recognized to be particularly sensitive to PCBs (OEHHA 2008). These findings from the Arnold et al. (1995)[6] study were consistent with the statements from the ATSDR (2000, at pages 245 and 389)[7] that there is no evidence that PCBs are teratogenic in humans and that adverse effects are seen in animals only when administered at very high doses. Accordingly, one would not expect to see birth defects in humans at the low dose levels administered in the Arnold et al. (1995) study.

ATSDR (2000) and OEHHA (2008) noted that other health effects were observed in observed in the low-dose (i.e., 5 µg/kg) exposure group reported by Arnold et al.(1995), but these effects were the result of postnatal rather than prenatal exposure of the test animals. Because the effects

[5] Cal/EPA. 2012. Initial statement of reasons (ISOR). Title 27, California Code of Regulations. Proposed amendment to: Section 25705(c), Specific Regulatory Levels Posing No Significant Risk. Section 25805(b) Specific Regulatory Levels: Chemical causing reproductive toxicity. Safe Drinking Water and Toxic Enforcement Act of 1986, Proposition 65. Polychlorinated biphenyls (food chain exposure). California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Sacramento, CA.

[6] Arnold, DL, F Bryce, PF McGuire, R Stapley, and JR Tanner. 1995. Toxicological consequences of aroclor 1254 ingestion by female rhesus (Macaca mulatta) monkeys. Part 2. Reproduction and infant Findings. Fd. Chem. Toxic. 33(6):457–474.

[7] ATSDR. 2000. Toxicological profile for polychlorinated biphenyls (PCBS). U. S. Department of Health and Human Service, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. 948 pp.

were the result of postnatal exposure, they did not meet the definition of "developmental toxicity" as that term is defined under Proposition 65. Accordingly, those effects do not bear on the calculation of a Proposition 65 MADL.

Please let me know if you have any further questions about our evaluation.

Sincerely,

Robert Scofield, D.Env.
Director of the Center for Exposure
Assessment and Dose Reconstruction