COMMENTS

by David Roe (as individual), Mateel Environmental Justice Foundation, Sierra Club, Center For Environmental Health, Californians For Alternatives To Toxics, and Ecological Rights Foundation

RE: proposed updated NSRL and proposed MADL for PCBs (notice dated 4/13/12)

These comments are informed in part by testing for each of the 209 individual congeners of polychlorinated biphenyl compounds (PCBs) in fish-derived products intended for human consumption, and by a recent Proposition 65 settlement with 30 refiners, distributors and retailers of fish oil supplements and related fish- and shark-derived products that sets negotiated safe harbor limits for PCBs in those products.

Our comments in summary, with detailed discussion following:

1) OEHHA has not accounted for the enormous variation in toxicity among the 209 individual PCB congeners, even though others (including some businesses themselves) have already done so by applying much more stringent standards to the very food chain items that OEHHA bases its analysis on.

2) OEHHA’s entire analysis collapses without its assumption that one or a few specific mixtures of PCB congeners “closely approximate the . . . . PCBs found in fish” – but congener-by-congener laboratory testing of fish oils shows no consistent mixture of individual congeners from one commercial fish oil sample to another.

3) Under a worst-case congener mix, the proposed new NSRL for PCBs would allow 70,000 times as much carcinogenicity risk as the long-established NSRL for 2,3,7,8 TCDD – i.e., a statistical cancer risk of 7-in-10 -- from the same carcinogenicity mechanism.

4) The proposed MADL would allow worst-case exposure to nearly 16,000 times the statutory limit that would be derived from existing reproductive toxicity studies of individual PCB congeners – none of which OEHHA has taken into account.

5) The proposed MADL would remove defendants’ burden-of-proof responsibility on reproductive toxicity of PCBs, despite no cited scientific evidence on the reproductive toxicity of any individual congener and despite no reliable information on the actual mixtures of individual congeners, or the range of variability in mixtures, as they actually occur in any part of the food chain.

6) Industry’s own voluntary PCB standards recognize that the 12 dioxin-like PCB congeners require separate limits that are orders of magnitude more stringent in effect than the current proposal.

7) OEHHA should seek input from the state’s Prop. 65 reproductive toxicity experts, duly appointed by the Governor to the DART panel, before issuing any new MADL including any proposed MADL for PCBs.
INTRODUCTION

It is an understatement to say that these two proposed safe harbor levels for PCBs lack adequate scientific foundation and that they would not protect the public as the law intends NSRLs and MADLs to do. But among the many flaws in OEHHA’s supporting analysis, two basic ones stand out.

First, OEHHA relies only on toxicity data about the 209 PCB congeners in a group, ignoring much more developed and more accurate toxicity data about the few individual PCB congeners of highest known toxicity and therefore of greatest concern. This is like calculating the risk from a box of bullets using studies of the box being thrown by hand, and ignoring the fact that at least one bullet in the box is going to be shot from a gun.

Second, OEHHA relies on information about only one fixed mixture of the 209 congeners, and then struggles for reasons to assume that the one mixture is the only one actually found across the food chain. This is the classic error of looking for the lost keys only under the lamppost. It is exactly backwards: to be protective, analysis must start with what the public’s actual exposures are likely to be, and then assess the risks of those actual exposures. In this particular case, there is strong proof that mixtures in the food chain are in fact widely varying instead of being consistent (much less, consistent with the one mixture OEHHA exclusively relies on for MADL purposes) – in other words, that there are many lampposts to take into account.

DISCUSSION

1) OEHHA has not accounted for the enormous variation in toxicity among the 209 individual PCB congeners, even though others (including some businesses themselves) have already done so by applying much more stringent standards to the very food chain items that OEHHA bases its analysis on.

OEHHA acknowledges that there are 209 individual PCB congeners, and it is true that congener-specific toxicological data is lacking for many of them. But OEHHA has ignored the thorough, detailed, and well-vetted toxicological data, over 15 years old, that is available for the handful of individual PCB congeners that have been individually tested for carcinogenicity and other toxicity. Standards for those individual PCB congeners – which are orders of magnitude more stringent than what the proposed NSRL and MADL would allow -- have been adopted as
standards in Europe, by industries voluntarily, and as legally binding under Proposition 65 by 30 companies for fish-oil-related products. See comment (6) below.

In 1996, after review by an international panel of distinguished experts, the World Health Organization published Toxic Equivalency Factors (TEFs) for 29 dioxin and dioxin-like compounds, giving each a toxicological weighting factor in reference to the most toxic single dioxin congener, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS number 1746-01-6; listed under Prop. 65 as a known carcinogen in 1988 and as a known reproductive toxin in 1991). Of those 29 dioxin-like compounds, 12 are PCB congeners, the so-called dioxin-like PCBs. The 12 were selected for study because of their close similarity to dioxins in chemical structure and toxicological mechanism (aryl hydrocarbon receptor binding, abbreviated “AhR”). WHO reviewed the 29 compounds and revised their TEFs in 2005 based on more current data. Of the 12 dioxin-like PCBs, the most potent is PCB #126, with a TEF of 0.1, meaning that its toxicological potency is one-tenth the potency of 2,3,7,8 TCDD via the same AhR mechanism.

The WHO TEFs for the 12 PCB congeners vary from 0.1 (#126) to 0.03 (#169) to 0.00003 (all mono-ortho substituted congeners). This is more than a 3,000-fold difference, among only 12 congeners. Given the lack of congener-specific information on any of the other 197 PCB congeners, it is appropriate to assume that their toxicities also vary widely; and it would be highly inappropriate and unscientific to simply assume away any significant toxicity in any or all of the 197.

The obvious implication of these two facts – the huge variation in toxicity among 12 known congeners, and the unknown toxicity of the other 197 congeners – is that the toxicity of any given mixture of PCBs is critically dependent on the exact mix; i.e., which of the 209 congeners are present in the relevant mixture, and in what relative quantities. Even a variance in the proportion of just one or two of the 209 congeners (such as #126) can have a highly significant impact on the toxicity of the mix as a whole.

If no reliable toxicological data at all were available for individual congeners, then toxicological evidence based on testing of mixtures might be an appropriate starting place, if and only if the congener mixes in the food chain items targeted by the proposed safe harbors were reasonably consistent and predictable. (See comment (2) for clear evidence to the contrary). But given the robust existing data on 12 individual congeners, it is irresponsible to ignore that congener-specific data, and/or to assume it away by assuming that tests on a mixture could adequately reflect the cumulative toxicity of all congeners included in the mixture without reference to the quantities or proportions in the mixtures of the specific congeners that have been well studied (especially #126 and #169).

There is no mystery in how to account for the 12 dioxin-like PCB congeners, or the toxicity variations among them. WHO set forth its Toxic Equivalence (TEQ) methodology in 1996 and reaffirmed it in 2005. That methodology measures the quantities of the relevant congeners, weights them by their individual TEFs, and by simple addition produces a total TEQ score. A maximum TEQ score, expressed in picograms per gram, is then set as a standard.
The TEQ methodology and the concept of TEQ-based standards for the dioxin-like PCBs are so well recognized that the European Commission relies on them for the official control of dioxin-like PCBs in foodstuffs. In perhaps even stronger indication of how well accepted TEQ-based standards are for PCBs, the industry-sponsored Council for Responsible Nutrition (CRN) and its more advanced cousin, the Global Organization for EPA and DHA Omega-3s (GOED), both prescribe TEQ-based limits on dl-PCBs as voluntary industry standards for nutritional supplements derived from fish sources (as well as other sources); and 30 member companies of GOED involved in the refining, formulating, and selling of such products in California recently accepted stringent TEQ-based standards for dl-PCBs as binding for purposes of Proposition 65 compliance. See comment (6) below.

It is worth emphasizing that the standards and controls for PCBs in fish and fish oil already adopted by others should be particularly relevant to OEHHA here, since OEHHA’s own analysis relies almost exclusively on evidence derived from fish, and its own calculations are intended to apply to fish and fish oil explicitly.

2) **OEHHA’s entire analysis collapses without its assumption that one or a few specific mixtures of PCB congeners “closely approximate the . . . PCBs found in fish” – but congener-by-congener laboratory testing of fish oils shows no consistent mixture of individual congeners from one commercial fish oil sample to another.**

OEHHA’s analysis in its Initial Statement of Reasons depends entirely on its assumption that there are predictable “types of PCB mixtures” for PCBs in “fish, fish oil, eggs meat, shellfish, poultry, and dairy products” (referencing US EPA 1996), for purposes of deriving a new NSRL, and on its assumption that there is one single PCB mixture that “most closely approximate[s] the . . . PCBs found in fish” (referencing itself in 2008) for purposes of deriving a MADL. This pair of assumptions is clearly and dangerously false, based on current laboratory evidence. And without the assumption that PCBs occur in the food chain in only one or only a few consistent mixtures, OEHHA has no adequate evidence to support the lack of health risk for PCBs in the food chain that its proposed safe harbor levels purport to achieve.

One of these commenting parties, Mateel, recently secured laboratory testing for PCBs in samples of fish oil, fish-liver oil, and shark-liver oil nutritional supplements, testing for each of the 209 PCB congeners individually. In just the ten samples on which information has been made public, a wide variation in the congener mix can be deduced, specifically in the mix of the dioxin-like PCB congeners of greatest concern. See reported test results at http://www.fishoilsafety.com/?page_id=10. In those samples, it is readily apparent that the

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1 The Initial Statement of Reasons in fact describes two mixtures as being “closely approximate” but relies on evidence from only one, admitting that it “was unable to find” any MADL-relevant studies of Aroclor 1260. **NOTE:** this in itself is a deep flaw, since OEHHA is claiming that *either of two* mixtures is “approximate[ly]” representative, but has evidence about only one. In effect, OEHHA is saying it knows about at least two lampposts, but is looking under only one.

2 The significance of the dioxin-like PCB congeners, and the TEQ methodology used to calculate the toxicity of mixtures containing them, are explained in detail in comment (1) above.
overall PCB total by weight in each sample does not correlate even approximately with the TEQ value for the same sample. But if the mixture of congeners in each sample were the same, the PCB totals by weight would have to correlate exactly with the TEQ values—in other words, high overall totals would correlate with high TEQ values, and low with low. The very pronounced lack of correlation can be explained only by differences in the mix of congeners. (One might argue that TEQ variations are highly sensitive to variations of just a few congeners—but that is exactly the point, from a toxicological point of view, since those few are the few of greatest concern and greatest known impact on the toxicity of any particular mixture.)

Recent published studies of PCB (and other) contaminants in fish samples show the same lack of correlation. For example, a 2010 study of 17 oil samples from various marine species commented: "It is interesting to note that the ranking according to PCB concentration [i.e., total PCBs] did not necessarily correspond to the ranking based on TEQ concentration (Fig. 1)." Inspection of that study's results show similarly wide variation in the ratio between total PCBs and TEQ values, from sample to sample. Even wider variation is evident in a 2010 Spanish study of 15 samples of fish- and other-oil supplements when the comparison is made between TEQ values and the total of 7 “marker” PCBs (instead of the total of all 209 PCBs). In a recent British study of 33 samples of fish oil supplements, the ratio of “marker” PCBs to TEQ values varied from less than 5 to greater than 30, once again illustrating the lack of a consistent mixture of PCBs in highly relevant food chain products. That the variation should be so substantial, even when the comparison is between the 12 dioxin-like PCBs weighted for toxicity (i.e., TEQ values) and a mere handful of “marker” PCBs, makes the point with additional strength.

If such significant inconsistency (from a toxicological point of view) exists within even a mere 10 or 17 or 15 or 33 samples of nutritional supplement oils, primarily fish-derived, then it certainly cannot be assumed that any particular congener mix is representative of the PCB congener mixes found in the food chain generally, much less of the congener mixes in fish and fish oils specifically, and specifically the mixes of congeners of greatest toxicological concern.

The lack of mixture consistency demonstrated above, including within Mateel’s small set of exclusively fish oil samples, is especially telling in this context, since nearly all of the

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3 Explained in comment (1) above.
4 See comment (1).
5 Bourdon et al., “Polychlorinated biphenyls (PCBs) contamination and aryl hydrocarbon receptor (AhR) agonist activity of Omega-3 polyunsaturated fatty acid supplements: Implications for daily intake of dioxins and PCBs,” *Food and Chemical Toxicology* 48 (2010) 3093-3097, at 3096.
6 *Id.*, Table 1, at 3095.
7 Martí et al., “Persistent organic pollutants (PCDD/Fs, dioxin-like PCBs, marker PCBs, and PBDEs) in health supplements on the Spanish market,” *Chemosphere* 78 (2010) 1256-1262, see Table 2, at 1258.
8 Fernandes et al., “Dioxins and polychlorinated biphenyls (PCBs) in fish oil dietary supplements: Occurrence and human exposure in the UK,” *Food Additives and Contaminants*, September 2006, 23(9): 939-947; see Table 1 at 942.
supporting evidence for safe harbor calculations that OEHHA uses is derived from fish or fish oil
data; and the only evidence for consistency of mixture that OEHHA cites is fish-based.
Therefore, in the absence of any evidence of a consistent mix or mixes of PCB congeners in any
other part of the food chain, and with the clear contradiction of assumed consistency in fish oils,
the consistent-mixture assumption on which OEHHA’s entire analysis depends is, at best, pure
speculation for the rest of the food chain, and for fish oils is simply false.

3) Under a worst-case congener mix, the proposed new NSRL for PCBs would allow
70,000 times as much carcinogenicity risk as the long-established NSRL for
2,3,7,8 TCDD – i.e., a statistical cancer risk of 7-in-10 – via the same
carcinogenicity mechanism.

The current NSRL for 2,3,7,8-Tcdd, equating to the regulatory standard of a 1-in-
100,000 cancer risk, is 0.000005 micrograms per day. According to WHO’s revised TEFs, the
most toxic PCB congener, PCB #126, has one-tenth (0.1 times) the carcinogenic potency of
2,3,7,8-Tcdd. The equivalent NSRL for PCB #126, therefore, would be 0.00005 micrograms
per day.

If a PCB mix subject to Prop. 65 were composed 100% of PCB #126, the proposed new
NSRL would allow 70,000 times the cancer risk to which NSRLs are required by regulation to
be set; i.e., a statistical cancer risk of 7-in-10. The assumption of a 100% PCB #126 mix is of
course a highly conservative assumption. However, there is no reliable basis for any other
assumed mix, as discussed above.

Assuming instead that PCB #126 is present only in equal proportion to every other
congener (i.e., that only 1/209th of a PCB mixture is PCB #126), the proposed new NSRL would
still be 335 times more lenient than the required 1-in-100,000 level.9 However, an assumption
of equal proportion is very clearly not a conservative assumption, or a justifiable one in the
absence of supporting evidence.

4) The proposed MADL would allow worst-case exposure to nearly 16,000 times the
statutory limit that would be derived from existing reproductive toxicity studies of
individual PCB congeners – none of which OEHHA has taken into account.

There are more than 20 reproductive toxicity studies in the scientific literature for the
single PCB congener PCB #126, as well as at least some for other individual PCB congeners, all
of which OEHHA has ignored for MADL purposes in favor of its exclusive reliance on studies
of one commercial mixture.10 Five selected studies, including the two that yield the lowest
LOAEs (i.e., those most relevant to the identification of an NOAEL for MADL purposes) are
identified and described in detail in Appendix A.

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9 This assumes zero carcinogenicity for 208 of the 209 congeners, obviously an unsafe
assumption.
10 Aroclor 1254; see note 1 above.
One of the less sensitive of these five studies (based on level of detected harm) supports a LOAEL of 250 ng/kg/day. (Three other studies listed, as well as others not listed, would indicate a smaller LOAEL, and the fifth study listed found "complete reproductive failure" at a LOAEL only slightly higher). Assuming the NOAEL is 1/100th of the LOAEL, and then applying the same calculations as OEHHA (58 kg. female; 1/1000th of the of the NOAEL), the resultant MADL would be 0.145 nanograms/day. OEHHA's proposed MADL of 2.3 micrograms/day (i.e., 2,300 nanograms/day) is 15,682 times higher. In the case of a mixture of 100% PCB #126, it would represent exposure to nearly 16,000 times the statutory standard for reproductive toxins.

Again, the assumption of a 100% PCB #126 mixture is highly conservative. Again, assuming a mixture with equal proportions of each congener, and assuming zero toxicity for all congeners except #126, the allowable exposure would still be 75 times the statutory standard. We emphasize again that an assumption of equal proportions is not conservative, is not supported by any evidence, and is not appropriate for a MADL determination in the absence of credible supporting evidence.

TEQ analysis is as relevant to reproductive toxicity as to carcinogenicity. It may be tempting to minimize the significance of TEQ analysis in the context of a MADL, by assuming that TEFs and the AhR mechanism apply only to cancer risk and not to reproductive toxicity risk (notwithstanding the numerous reproductive toxicity studies on PCB #126). However, according to U.S. EPA, the WHO TEF values should be applied for non-cancer as well as cancer effects, because non-cancer effects of dioxin-like PCBs are mediated through the same AhR mechanism as their cancer effects. See EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, Volume I, February 2012, EPA/600/R-10/038F; and its Recommended Toxicity Equivalence Factors (TEFs) for Human Health Risk Assessments of 2,3,7,8 - Tetrachlorodibenzo -p- dioxin and Dioxin-Like Compounds, December 2010, EPA/100/R-005. In both of these documents, EPA "recommends use of consensus TEF values for TCDD and DLCs published in 2005 by the World Health Organization (Van den Berg et al., 2006) for all cancer and noncancer effects mediated through aryl hydrocarbon receptor binding" (emphasis added). Following US EPA’s recommendation means that the proposed MADL is even less protective against reproductive toxicity risk than the calculations in this comment would indicate. It also means that the comments above in Comment (3), showing the inadequacy of the proposed NSRL, apply with equal significance to the proposed MADL.

11 It would be proper to use the single study with the most sensitive LOAEL for Prop. 65 purposes. To be conservative for purposes of these comments, we use one that shows a LOAEL two orders of magnitude higher (i.e., less sensitive).
5) The proposed MADL would remove defendants’ burden-of-proof responsibility on reproductive toxicity of PCBs, despite no cited scientific evidence on the reproductive toxicity of any individual congener and despite no reliable information on the actual mixtures of individual congeners, or the range of variability in mixtures, as they actually occur in any part of the food chain.

The essence of Proposition 65’s reform was to shift the responsibility for determining safe exposure limits for certain toxic chemicals onto the commercial entities actually exposing the public to those chemicals, instead of continuing to rest it solely on government, in situations of scientific uncertainty. The result has been a remarkable acceleration in the setting of those limits, described by Cal EPA’s official review panel after only five years as “100 years of progress [by federal standards] in the areas of hazard identification, risk assessment, and exposure assessment” based on “the application of internally consistent scientific criteria.” 12 Among other things, the history of Prop. 65 proves that responsibility shifted to the regulated community produces much more scientific risk analysis -- and puts it into practical use for public protection much faster and more effectively – than leaving that responsibility solely on government’s shoulders. It also shows that the regulated community can and will cooperate with government to identify and produce the necessary science, once it has the incentive to do so.

To date, over Prop. 65’s 25-year history, OEHHA and its predecessor agency have largely maintained scientific integrity in the process of determining NSRLs and MADLs, enough to keep the regulated community oriented in the same direction. However, if OEHHA is willing to adopt NSRLs and MADLs without a sufficient scientific basis, then Prop. 65’s very productive incentive is eroded; and primary attention shifts to lobbying for scientifically unsound standards in the next case and the next, instead of cooperating to reach sound standards. The current proposals, lacking an adequate scientific basis as discussed above, present exactly that risk. For fundamental policy reasons, it is essential that OEHHA continue to maintain scientific integrity in its NSRL and MADL processes. To do so, it must not act on the inadequate scientific basis that has been put forward so far in this matter. If it resists pressure to do so, better science will be quickly forthcoming, given the commercial significance of food chain items with potential PCB issues.

Adopting the proposed new NSRL and proposed new MADL for PCBs on the basis of the current record would have only one purpose: to relieve the regulated community of its Prop. 65 concerns over PCBs. As protection of the public against unwarmed exposures to carcinogenic and reproductively toxic risks from PCBs in the food chain, it would be a sham; and its effect would be to deceive the public into believing that it was being protected against those risks.

The statutory requirement for a defendant to establish a risk-based exemption under Proposition 65 is that its showing be “based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of such chemical . . . .” Although OEHHA has broad regulatory authority, it would clearly violate the

most basic intent of the statute if it were to adopt safe harbor levels on showings much less rigorous than what is required of defendants.

6) Industry’s own voluntary PCB standards recognize that the 12 dioxin-like PCB congeners require limits that are orders of magnitude more stringent in effect than the current proposal.

As indicated above, several years ago the Council for Responsible Nutrition had already issued a voluntary industry standard for the dioxin-like PCBs of 3 picograms per gram TEQ – in other words, 3 trillionths of a gram per gram of equivalence to the most potent dioxin, using TEF weightings as set forth by the World Health Organization. For PCB #126, this equates to 30 trillionths of a gram per gram. The more rigorous GOED has proposed a standard of 3 pg/g TEQ to take effect in 2013 with an interim standard of 4 pg/g – but applied to dioxin-like PCBs and dioxins and furans cumulatively, leaving even less leeway for the 12 dl-PCBs alone. In addition, late last year, 30 companies in the supply chain for fish oil and related nutritional supplements legally committed themselves to the more rigorous GOED standard as one part of compliance with Proposition 65 (see Consent Judgment dated 12/5/11 in Mateel v. Aker Biomarine et al., Humboldt Sup. Ct. case no. DR110874, available on the Attorney General’s website at http://oag.ca.gov/prop65/60-Day-Notice-2011-00323.

By any conceivable measure, these self-imposed industry standards for PCBs are several orders of magnitude more stringent than OEHHA’s proposed safe harbors in their practical effect. It should give OEHHA great pause that important parts of the food chain industry define PCB safety so much more stringently than it does. The practical effect of OEHHA’s proposals, if adopted, would be to weaken existing industry standards by several orders of magnitude, greatly reducing PCB protections already in place for significant parts of the food chain.

7) OEHHA should seek input from the Prop. 65 reproductive toxicity experts duly appointed by the Governor to the DART panel, before issuing any new MADL including this proposed MADL.

As authorized by Proposition 65, a standing panel of scientific experts in the field of chemical reproductive toxicity (the so-called DART panel) has been appointed and has been providing its outside expertise to OEHHA on listing of reproductive toxins for most of Prop. 65’s existence. The Governor is currently in the process of appointing new members to that panel.

The members of new DART panel, who will have been freshly appointed, will very likely be able to provide helpful guidance and additional expertise on any OEHHA matter involving reproductive toxicity risk assessment, and OEHHA should welcome their input when needed. In this particular matter, given the extreme weakness of scientific support for a PCB MADL that OEHHA has been able to identify so far, additional expertise is badly needed, and OEHHA should not proceed further in trying to determine a MADL for PCBs without fully taking advantage of the new expertise that will become available once the DART appointments are complete.

CONCLUSION

As discussed above, the evidence and calculations in the Initial Statement of Reasons are grossly inadequate at this stage to support safe harbor levels for PCBs that would effectively protect the public at the risk levels prescribed in the statute and regulations. Considerably more is required, including consideration of relevant existing evidence on the dioxin-like PCBs as referenced above and in Appendix A. These commenting parties strongly urge OEHHA to:

a) seek out and invite any and all available test data on PCBs in food chain items that shows congener-by-congener results for all 209 congeners;
b) use that data to evaluate whether there is any consistent or predictable mixture of congeners in some or all food chain items; and if so, to document that mixture or mixtures with statistically significant data;
c) if consistent or predictable congener mixtures can be so documented, to reevaluate the carcinogenic and reproductively toxic risks of such mixtures based on the congeners actually present in the mixture and the proportions in which they are present;
d) limit the application of any safe harbor level calculated from such mixtures to those portions of the food chain in which those mixtures have been reliably shown to be consistent, or as documented case by case;
e) include TEQ-based criteria for the dioxin-like set of PCB congeners as part of any proposed safe harbor for PCBs; and
f) invite advance input from members of the DART panel on any safe harbor level or levels OEHHA intends to propose for PCBs, once that panel’s membership is complete.

Respectfully submitted,

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by: [Signature]

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APPENDIX A

Comments of Roe et al. on proposed PCB safe harbor levels (notice dated 4/13/12)

SELECTED REPRODUCTIVE TOXICITY STUDIES ON PCB #126

1) Muto et al. (2002), “Mammary gland differentiation in female rats after prenatal exposure to 3,3',4,4',5-pentachlorobiphenyl” (http://dx.doi.org/10.1016/S0300-483X(02)00224-X). Responses detected: delayed vaginal opening, reduced serum 17β-estradiol concentrations, fewer alveolar buds and lobules in mammary glands, more estrogen receptor mRNA expression in terminal end buds. LOAEL: 2.5 nanograms/kg/day.

2) Muto et al. (2003), “Estrous cyclicity and ovarian follicles in female rats after prenatal exposure to 3,3',4,4',5-pentachlorobiphenyl” (http://dx.doi.org/10.1016/S0378-4274(03)00175-9). Responses detected: delay in development of estrus cyclicity, fewer antral and more atretic follicles, reduced serum 17β-estradiol and progesterone concentrations. LOAEL: 2.5 nanograms/kg/day.

3) Oskam et al. (2005), “Effects of long-term maternal exposure to low doses of PCB126 and PCB153 on the reproductive system and related hormones of young male goats” (http://dx.doi.org/10.1530/rep.1.00690). Responses detected: increased body weight (males), altered serum testosterone concentrations, more haploid and fewer diploid sperm. LOAEL (for #126): 115 nanograms/kg/day.

4) Wakui et al. (2007), “Spermatogenesis in aged rats after prenatal 3,3',4,4',5-pentachlorobiphenyl exposure” (http://dx.doi.org/10.1016/j.tox.2007.06.097). Responses detected: altered spermatogenesis (staging analysis) indicative of inhibited development of spermatogonia and inhibited conversion of round spermatids to elongating spermatids. LOAEL: 250 nanograms/kg/day.

5) Beckett et al. (2008), The Effects of 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) on Mink (Mustela vison) Reproduction and Kit Survivability and Growth (http://dx.doi.org/10.1007/s00244-007-9002-8). Responses detected: complete reproductive failure, accompanied by female reproductive tract pathology. LOAEL: 352 nanograms/kg/day.