Office of Environmental Health Hazard Assessment

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January 22, 2013

Steven G. Hentges, Ph.D.
Executive Director
Poylcarbonate/BPA Global Group
American Chemistry Council
1300 Wilson Boulevard
Arlington, Virginia 22209

Dear Dr. Hentges:

Thank you for your letter of May 13, 2010, responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65[1]. BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies provision[2] of Proposition 65 and based on findings by the National Toxicology Program (NTP). NTP made its findings in a report[3] by the NTP Center for the Evaluation of Risks to Human Reproduction that BPA causes developmental toxicity at "high" doses.

OEHHA has carefully reviewed the comments prepared by Drs. Murray and Lawyer and Messrs. Landfair and Volz and submitted by you. A document providing our responses to your comments is enclosed.

After review of all the submissions received in response to the Request for Relevant Information, OEHHA has determined that BPA meets the criteria for listing under the authoritative bodies provision of Proposition 65. Accordingly, a Notice of Intent to List BPA will be published in the near future. Following its publication, there will be a 30-day period for submission of public comments regarding the possible listing. Comments should focus on whether or not the criteria for listing have been met.[4] In the

[1] The California Safe Drinking Water and Toxic Enforcement Act of 1986, California Health and Safety Code section 25249.5 et seq.
[2] Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regulations, section 25306.
[3] National Toxicology Program – Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR, 2008). *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A.* NIH Publication No. 08 – 5994.
[4] Title 27, Cal. Code of Regulations, section 25306.

event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation.[5]

Thank you for your interest in Proposition 65. If you have any questions or concerns, please contact me at (916) 322-6325 or by email at Lauren.Zeise@oehha.ca.gov.

Sincerely,

Laure Zeise, Ph.D.
Deputy Director for Scientific Affairs

Enclosure:

Response to Comments from the American Chemistry Council on the Request for Relevant Information on Bisphenol A as a Chemical under Consideration for Listing under Proposition 65.

[5] Title 27, Cal. Code of Regulations, section 25306(i).

Response to Comments from the American Chemistry Council on the Request for Relevant Information on Bisphenol A as a Chemical under Consideration for Listing under Proposition 65

Office of Environmental Health Hazard Assessment

January 2013

On February 12, 2010, the Office of Environmental Health Hazard Assessment (OEHHA) published in the California Regulatory Notice Register (CRNR) a Request for Relevant Information for Bisphenol A (BPA) for possible listing as a chemical known to cause reproductive toxicity under Proposition 65.[1] The listing would be based on the authoritative bodies provision[2] relying on findings by the National Toxicology Program (NTP) in a final report from the NTP Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) that BPA causes developmental toxicity at "high" doses (NTP-CERHR, 2008).

On May 13, 2010, OEHHA received comments concerning the possible listing of BPA under Proposition 65 from the American Chemistry Council (ACC). This document provides a response to these comments. Supplemental responses to the Request for Relevant Information dated August 10 and September 1, 2011, were also submitted to OEHHA substantially after the close of the comment period. Although OEHHA has no obligation to respond to these late submissions, responses to these comments are included. The comments received in August 2011 were expansions of the comments made in the May 2010 submission, and those of September 2011 brought new studies to our attention.

Under the Authoritative Bodies listing process, a chemical must be listed under Proposition 65 when the following criteria are met:

1) **Formal Identification**: An authoritative body formally identifies the chemical as causing reproductive toxicity (Section 25306(d)[3])
2) **Sufficiency of Evidence**: The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulations (Section 25306(g)). However, the chemical is not listed if scientifically valid data which were not considered by the authoritative body clearly establish that the sufficiency of evidence criteria were not met (Section 25306(h)).

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[1] The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq*.).
[2] Title 27, Cal. Code of Regulations, section 25306.
[3] All referenced sections are from Title 27 of the Cal. Code of Regulations.

Formal Identification

Sections IV.A, IV.B, IV.C and parts of section G of the comments are relevant to formal identification.

Section IV.A

1. Comment: ACC states that "…the statements to which OEHHA refers do not represent a conclusion by NTP-CERHR that BPA is a developmental toxicant in humans."

Response: Chemicals are added to the Proposition 65 list when OEHHA determines, based on an authoritative bodies report or other document that meets the regulatory criteria in Section 25306(d)(1), that the chemical causes reproductive toxicity in humans or animals.[4] There is no requirement that developmental or reproductive effects have actually been demonstrated in humans. Although the biological plausibility that effects could occur in humans is considered under the criteria in Section 26306(g), it is a fundamental assumption of toxicology that the results of toxicity testing of chemicals in animal models are indicative of potential effects in humans.

The U.S. Environmental Protection Agency's "Guidelines for Developmental Toxicity Risk Assessment" (U.S. EPA, 1991), for example, state that "…it is assumed that an agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans following sufficient exposure during development." Thus, in the absence of convincing data that effects are not plausible in humans because of metabolic, physiologic or other biological considerations, it is assumed that a chemical that causes developmental toxicity in an animal model may do so in humans.

Further, there is no requirement in the law or regulations that the authoritative body must determine that effects have occurred in humans, or that effects that have been demonstrated in animals are biologically plausible in humans. Section 25306(c) states that "*the lead agency* [OEHHA] shall determine which chemicals have been formally identified by an authoritative body as causing cancer or reproductive toxicity" (emphasis added). Section 25306(g) specifies the criteria that the lead agency must apply in determining whether the chemical is identified "as causing reproductive toxicity". This interpretation of the regulation has been upheld by the courts.[5] Section 25306(g)(2) requires OEHHA to consider whether the chemical's effects in animals are indicative of

[4] AFL-CIO v Deukmejian (1989) 212 Cal.App. 3d. 425

a biologically plausible adverse effect in humans. As discussed below, OEHHA has made this determination for BPA. In addition, in this case the authoritative body also concluded, based explicitly on data in animals, that it is possible that bisphenol A can affect human development or reproduction. That conclusion is equivalent to concluding that such effects are biologically plausible in humans.

ACC has apparently misidentified the relevant conclusions in the NTP-CERHR document that OEHHA is using as the basis for Formal Identification. As stated in the Request for Relevant Information:

> "OEHHA is relying on the NTP-CERHR's conclusions in the report that BPA causes reproductive toxicity. The NTP-CERHR report concludes that there is clear evidence of adverse developmental effects in laboratory animals at 'high' levels of exposure. Developmental effects include fetal death and reduced litter size in rats and mice exposed prenatally."

The NTP-CERHR monograph states:

- "These 'high' dose effects of bisphenol A are not considered scientifically controversial and provide clear evidence of adverse effect on development in laboratory animals" NTP-CERHR, p.7
- "The NTP finds that there is clear evidence of adverse developmental effects at 'high' doses of bisphenol A"... NTP-CERHR, p.7
- "High dose developmental toxicity → Clear evidence of adverse effects" NTP-CERHR, p.8, Figure 2b
- "The 'high' dose effects of bisphenol A that represent clear evidence for adverse effects on development…" NTP-CERHR, p.36

These conclusions about effects at high doses, and the data supporting the conclusions, are the basis for OEHHA's determination.

In section IV.A the commenters compare the format of the NTP-CERHR monograph on BPA to some previous NTP-CERHR monographs as a reason for disregarding the conclusions of the BPA monograph. OEHHA agrees that the formats of these documents can differ, and that the conclusions in the BPA document were formatted specifically for that chemical, including different weight-of-evidence conclusions for

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[5] *Exxon Mobil Corp, v. OEHHA* (2009) 169 Cal.App. 4th 1264, *Western Crop Protection v. Davis* (2000) 80 Cal.App.4th 741.

“high” dose effects on some endpoints and “low” dose effects on others. By discounting these weight-of-evidence conclusions because of variations in formatting when compared with previous documents, the commenters identify the level-of-concern conclusions as the only conclusions of the report. Since the level-of-concern conclusions take into account what is known about levels of human exposure, not just the weight-of-evidence for reproductive and developmental toxicity, they are not relevant to formal identification for listing under the Proposition 65 authoritative bodies provision. Levels of human exposure are, of course, important. If BPA is listed, human exposures can be considered under Section 25821to determine whether or not a given exposure requires a warning.

ACC’s contention that the only conclusions of the NTP-CERHR documents relate to levels of concern is not consistent with NTP’s own statements about this process. In a presentation to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) on July 12, 2011, Dr. John Bucher, Associate Director of NTP, described two phases of the NTP-CERHR process, each of which results in conclusions:

> “CERHR evaluated selected chemicals, agents, mixtures, or exposure circumstances based on production volume, the potential for human exposure and the extent of public concern, and the extent of available literature with data that were applicable to an evaluation of reproductive and developmental hazard.
>
> “These have been published as NTP-CERHR monographs that assess the evidence, whether the environmental substance causes adverse effects on reproduction and development, which as you heard earlier, is the Phase 1, the hazard identification phase of the document.
>
> “And secondly, the second phase is to provide an opinion on whether these substances may be of concern, given what is known about current human exposure levels. And these are the levels of concern statements that are developed…
>
> “As you saw in one of the slides previously, the hazard identification portion of this used a seven point hazard identification scale, weighting the evidence from both human and experimental animal data. And these were considered independently. And then the

conclusions are reached on a case-by-case basis"[6] (emphasis added).

OEHHA disagrees with ACC's contention that weight-of-evidence statements concerning "high" doses are descriptions rather than conclusions (p.16 and 17 of the comments) based on Figure 2b in the NTP-CERHR document. An important feature of Figure 2b, where the weight-of-evidence conclusion is outlined, are the alternatives provided in bulleted form:

- "Clear evidence of adverse effects
- Some evidence of adverse effects
- Limited evidence of adverse effects
- **Insufficient evidence for a conclusion**
- Limited evidence of no adverse effects
- Some evidence of no adverse effects
- Clear evidence of no adverse effects" p. 7 (*emphasis added)*

These choices make it clear that if "insufficient evidence for a conclusion" is not selected, the other choices are conclusions based on sufficient evidence. In addition, OEHHA is not relying on "…five words from Table 2b…" for formal identification, but on a conclusion that is discussed and reiterated throughout the NTP brief section of the monograph as illustrated above.

In the supplemental comments of August 10, 2011, a presentation made by Dr. Kris Thayer of NTP to the NTP Board of Scientific Counselors (BSC) on June 11, 2008, is cited in support of the argument that the only conclusions in the NTP-CERHR document are the level-of-concern conclusions voted upon by the BSC. The comment notes that a figure essentially identical to Figure 2b in the final NTP monograph was included in the presentation. That figure indicated the weight of evidence for each relevant endpoint, including clear evidence of adverse effects for "high" dose developmental toxicity. What the comment omits is that the slide in the presentation immediately following the figure poses the question "How were these *conclusions* reached?" (emphasis added). It is clear that the authoritative body itself considers its weight-of-evidence determinations to be conclusions.

<u>Section IV.B</u>

Comment 2. Section IV.B

[6] Transcript of the July 12 meeting of the DARTIC, pp. 142-143, available at http://www.oehha.ca.gov/prop65/public_meetings/pdf/DARTIC071211trans.pdf

> "Because BPA is not "Formally Identified" in the NTP-CERHR monograph as causing reproductive toxicity, it is beyond the authority of OEHHA to re-examine the data to reach a different conclusion."

Response: See response to Section IV.A above.

Section IV.C

Comment: Section IV.C is titled, "The authoritative bodies mechanism does not allow OEHHA to effectively overrule the State's Qualified Experts in evaluating the same data," and comments supporting this contention are made.

Response: OEHHA also disagrees with ACC's contention that the law creates a "hierarchy" where the "state's qualified experts" mechanism trumps the other three listing mechanisms. Proposition 65 provides four mechanisms for listing of chemicals, all of which are independent of each other. The Labor Code mechanism is set forth in Health and Safety Code section 25249.8(a) and the other three are listed in the disjunctive in Health and Safety Code section 25249.8(b). The only connection in the statute between the state's qualified experts mechanism and the authoritative bodies' mechanism is the requirement for the state's qualified experts to identify the authoritative bodies. The statute does not create a hierarchical structure or consensus requirement. It lists each mechanism separately, and each has slightly different criteria that are applied to listing decisions. Therefore, the 2009 determination of the Developmental and Reproductive Toxicant Identification Committee (DARTIC) that BPA does not meet the criteria for listing pursuant to the state's qualified experts listing mechanism does not address the entirely separate question of whether BPA meets the criteria for listing pursuant to another listing mechanism. Thus, the state's qualified experts cannot "overrule" the authoritative body process, and vice-versa. If the criteria for listing by any of the four mechanisms are met, the law requires that the chemical be added to the list.

The fact that the Health and Welfare Agency expressed its opinion that the state's qualified experts would be the "primary" approach to listing at the time the authoritative bodies regulations were being adopted does not change this analysis. That statement of opinion does not create a hierarchy. Further, the Proposition 65 implementing

regulations cannot impose such a hierarchy where none exists in the statute, since such an action would not conform with or further the purposes of the statute.[7]

OEHHA agrees with the statement of reasons for Section 25306, which states that the purpose of the authoritative body provision of Proposition 65 is to conserve the resources (specifically the time and effort) of the state's qualified experts. This is because the committees need not re-evaluate chemicals for which a thorough scientific evaluation has already been conducted. Generally, the chemicals that are brought to the committees are there for a *de novo* review because the chemical has not been considered by an authoritative body.

In the case of BPA, the NTP-CERHR report was published during the pendency of BPA's review by the DARTIC. OEHHA could have removed the chemical from DARTIC consideration and initiated the authoritative bodies listing process, but chose not to do so. However, OEHHA can and indeed must consider whether BPA meets the authoritative bodies listing criteria, whether or not it has been previously reviewed by the DARTIC. Nothing in the statute or regulations allows OEHHA to ignore a chemical that may qualify for listing under one of the four listing mechanisms, simply because it has already been considered under another mechanism.

Sufficiency of Evidence

ACC quotes extensively from the Statements of Reasons for Section 25306 to argue that the Scientific Advisory Panel (the predecessor entity of the DARTIC) wanted to ensure that criteria used to list chemicals under the authoritative bodies mechanism would be consistent with the criteria used by the panel at that time. The resulting regulation, Section 25306, specifies the criteria that OEHHA uses in making authoritative bodies listings. As is discussed in the responses to the following comments, OEHHA applied these criteria when evaluating the NTP-CERHR monograph as well as the comments provided by ACC.

Section IV.D.
Comment: ACC states in Section IV.D.1.a (beginning on pg. 36 of the May 13, 2010 comment letter) that the studies to be examined for sufficiency of evidence include eight studies in the footnote of Figure 2b and that only three of these studies are relevant to Proposition 65 because the others include postnatal exposure (see Table 1, p. 39).

Response: Regarding these eight studies:

[7] Health and Safety Code section 25249.12

- Only one of the studies includes only postnatal exposure.
- The endpoint identified by NTP-CERHR from this study, delayed puberty, is not mentioned in the Request for Relevant Information.
- In studies including prenatal and postnatal exposure, many endpoints are determined prior to postnatal exposure.
- The endpoints named in the Request for Relevant Information, fetal death and reduced litter size, were observed prior to postnatal exposure.

The studies are discussed further below, in response to comments on the application of criteria for identifying chemicals "as causing reproductive toxicity" (Section 25306(g)).

Comment: On pg. 41 the comments state that the "possibility exists that the decrease in litter size at birth was not due to prenatal exposure." A number of statements are made in this paragraph, none of which reference data in the study report or other scientific research, for example:

- "An underweight dam might cannibalize live pups after birth due to hunger and general stress."
- "…pups may be up to 24 h old before the birth of a litter is discovered…"
- "…if the mother is not lactating properly, a decrease in litter size on PND0 may have been the result mother (sic) failing to feed their pups or mothers killing their pups…"

The discussion of NTP reference 37 contains extensive speculation about how litter size could be determined postnatally during the first few hours after birth before pregnancy outcome measures were taken. No scientific references are provided.

OEHHA was unable to locate the scientific basis for these claims. The first statement that "[a]n underweight dam might cannibalize live pups due to hunger" is difficult to accept given that food was freely available to the dams throughout the study. It is possible that the dams would avoid the food due to its BPA content, but the data show that dams in the highest two BPA dose groups did not differ from controls in daily food intake during gestation. In terms of being underweight, the dams in the top BPA dose group increased their weight by 5% less than controls from the beginning of pregnancy to the day after birth, a small weight gain differential, while weight gain was similar to controls in the second highest dose group. The second statement, that "…pups may be up to 24-h old before the birth of a litter is discovered..," is inaccurate. OEHHA's review of the study protocol for reference 37 found that dams "…were observed twice daily (a.m. and p.m.) for evidence of littering". The same was true for the mouse one-generation and two-generation studies (references 39 and 41).

Comment: To begin a discussion of maternal toxicity, ACC includes a paragraph on table salt.

> "For example, in a classical developmental toxicity study, a high (but not maternally lethal) dose of table salt (sodium chloride) was shown to cause an increase in resorptions, a decrease in fetal body weight, and fetal malformations in mice (Nishimura and Miyamoto, 1969). In fact, the spectrum of developmental effects observed in mice that were administered high doses of table salt was far more serious than the developmental effects observed after administration of maternally toxic doses of BPA. In this study, pregnant mice were given 0, 1900 or 2500 mg/kg bw/day of table salt on gestation day 10 or 11. These doses approached the maternally lethal dose of table salt, which has an LD50 (the acute dose required to kill 50% of the animals) of 4000 mg/kg bw/day in mice. When table salt was administered subcutaneously to pregnant mice on a single day of gestation, table salt caused an increase in fetal malformations, (e.g. cleft palate[8], missing digits, extra digits, club foot, shortness of forelimb) and up to 48% fetal death or resorptions at doses of 1900 and 2500 mg/kg bw/day. These dose levels of table salt are only slightly higher than the oral dose levels of BPA that were associated with less severe developmental effects and greater maternal toxicity. While there is "clear evidence of adverse effects" for high dose developmental toxicity in laboratory animals exposed to table salt, table salt is not considered to be a human hazard for developmental toxicity, taking into consideration the nearly lethal doses of table salt required to produce developmental toxicity."

Response: The ACC statement, "Even common substances, such as table salt, can cause developmental toxicity in animals, (including even birth defects) at doses high enough to injure the mother," is not supported by the Nishimura et al. study. Nishimura et al. state that the dams in their experiment "did not show any obvious symptoms and lost no weight after the injections." Thus the study report provides no indication that sodium chloride overwhelmed the maternal system and caused developmental toxicity secondary to maternal toxicity.

[8] OEHHA did not find mention of cleft palate in Nishimura et al. 1969

Comment: The ACC states that "[t]hese [subcutaneous] dose levels of table salt are only slightly higher than the oral dose levels of BPA that were associated with less severe developmental effects and greater maternal toxicity". .

Response: Table salt was administered by injection, while BPA was administered orally in the studies cited by NTP-CERHR in their conclusions. As stated elsewhere in the comments, the toxicity of BPA (and probably also sodium chloride) differs by injection and oral routes. Thus comparing the two chemicals by dosage across routes is not very informative.

Comment: On pg. 43, the commenters discuss the following premise:

> "…the critical objective in a developmental toxicity study is to determine whether the test substance is a *selective* developmental toxicant in humans, i.e. to determine whether exposure to the substance is likely to cause adverse effects to the fetus at doses that are not expected to cause so much harm to the mother that the adverse effects to the mother in turn cause adverse effects to the fetus."

Response: NTP draws conclusions about developmental toxicity rather than "selective" developmental toxicity. Similarly, there is no mention in Proposition 65 of "selective" developmental toxicity. As regards the relationship between maternal and developmental toxicity, two examples of the generally accepted principles in this regard as expressed by regulatory agencies are given below:

> "Agents that produce developmental toxicity at a dose that is not toxic to the maternal animal are especially of concern because the developing organism is affected but toxicity is not apparent in the adult. However, the more common situation is when adverse developmental effects are produced only at doses that cause minimal maternal toxicity; in these cases, the developmental effects are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity. At doses causing excessive maternal toxicity (that is, significantly greater than the minimal toxic dose), information on developmental effects may be difficult to interpret and of limited value. Current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity; rather, when the LOAEL is the same for the adult and developing organisms, it may simply indicate that both are sensitive to that dose level. Moreover, whether developmental effects are secondary to maternal toxicity or not, the maternal effects may be reversible while effects on the offspring may be permanent." U.S. EPA (1991) Guidelines for Developmental Toxicity Risk Assessment.

> "Developmental effects, which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case by case basis that the developmental effects are secondary to maternal toxicity." United Nations Economic Commission for Europe Globally Harmonized System of Classification and Labeling of Chemicals (Section 3.6.2.4.2, 2009)

Also at a recent (July 12, 2011) meeting of the DARTIC, Dr. John Bucher, Associate Director of the NTP, described how NTP-CERHR regularly considers maternal toxicity in reaching its conclusions:

> "I think when the literature are initially valuated by the expert panel and by the NTP, we take into consideration maternal toxicity, in essence weighing the influence that the outcome would have on the overall determination. So I don't think that we have a statement anywhere that specifies exactly how one would utilize information with maternal toxicity but is taken into consideration……I'm sympathetic with the problems that maternal toxicity presents in interpreting these studies. And all I can say is that we recognize this. When we designed the evaluation criteria for our own NTP developmental and reproductive toxicity studies, we have, in fact, taken into consideration how maternal toxicity might figure into an overall evaluation."

Thus, NTP has considered maternal toxicity while evaluating the evidence that BPA causes developmental toxicity and concluded that there is clear evidence of developmental toxicity. The alleged distinction between developmental toxicity and "selective" developmental toxicity in regard to BPA is therefore irrelevant.

Comment: In subsequent review and description of developmental and maternal toxicity information relevant to the NTP-CERHR conclusions on BPA, the commenters repeatedly state their interpretation of the relationship between maternal and fetal toxicity as reported in the studies relied upon by NTP.

- "Both of these studies demonstrated that the degree of maternal toxicity observed is more than sufficient to account for developmental effects" ACC, p.44
- "The degree of maternal toxicity observed in this study is more than enough to explain the decrease in litter size observed at the high dose in this study." ACC, p.46
- "The developmental effects are easily explained by the degree of maternal toxicity…" ACC, p. 47

- “The degree of maternal toxicity observed was more than enough to account for the developmental effects reported in these studies. In all cases the developmental effects were secondary to maternal toxicity.” ACC, p.47-48
- “The degree of maternal toxicity reported at the high dose in NTP Reference 37 was more than sufficient to account for the observations of developmental effects.” ACC, p. 48
- “The results of this study show that the developmental effects are secondary to maternal toxicity.” ACC, p. 48
- “The degree of maternal toxicity observed at the high dose is sufficient to have caused the developmental effects reported in this study.” ACC, p. 48
- “In every case, the degree of maternal toxicity observed was more than sufficient to explain the developmental effects.” ACC, p.50

As discussed above, NTP has stated that maternal toxicity was taken into account in determining the level of evidence that BPA caused developmental toxicity in laboratory animals. The comments provide the commenter’s interpretation of the relationship between maternal and developmental toxicity, but do not provide any references to the scientific literature to support these interpretations. Similarly, the comments.contain no factual information that contradicts NTP’s conclusion that there is clear evidence of developmental toxicity for BPA. Although the commenters’ interpretation of these studies differs from the interpretation of the studies by the authoritative body, OEHHA must rely on the NTP interpretation of these studies. NTP stated that there is clear evidence that BPA causes developmental toxicity at “high” doses in laboratory animals. This conclusion is sufficient for the report to provide a basis for listing the chemical via the authoritative bodies provision of the Proposition 65 regulations. OEHHA concurs with the conclusion by the NTP. Even if that were not the case, OEHHA cannot substitute its judgment for that of the authoritative body.[9]

Comment: Section D2 states that OEHHA did not adequately identify successful application of the sufficiency of data criteria in the Request for Relevant Information. ACC states:

> “The only information offered in the Request to indicate that the ’sufficiency criteria‘ are satisfied, however, is the following statement at page two: ‘The NTP-CERHR report concludes that there is clear evidence of adverse developmental effects in laboratory animals at high” levels of exposure. Developmental

[9] Amendment to 25301 – 25306 (formerly 12301- - 12301) Final Statement of Reasons (available at http://www.oehha.ca.gov/prop65/law/pdf_zip/12301_12306FSORJan1995.pdf).

> effects include fetal death and reduced litter size in rats and mice exposed prenatally.' "

Response: The sufficiency of evidence criteria are as follows:

> "Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible."[10]

OEHHA's statement concerning sufficiency of evidence is found on page two of the Request for Relevant Information:

> "Based on the NTP-CERHR report and the references cited in the report, the evidence appears sufficient for listing by the authoritative bodies mechanism."

In making that finding, OEHHA noted that NTP concluded there is clear evidence that BPA causes developmental toxicity in animals at high doses. NTP found that BPA caused decreases in litter size or number of live pups/litter in rats (Kim et al. 2001, Tyl et al. 2002b) and in mice (Morrissey et al. 1987, Tyl et al. 2002a, NTP, 1985), effects on prenatal or early growth in rats (Kim et al. 2001, Tyl et al. 2002b) and in mice (Morrissey et al. 1987, Tyl et al. 2002a, Tyl et al. 2008) and delayed puberty in male mice (Tyl et al. 2008), male rats (Tyl et al. 2002b, Tan et al. 2003) and female rats (Tyl et al. 2002b, Tinwell et al. 2002). The studies NTP cited in making these findings are provided in parentheses above. These studies are briefly summarized in Table 1. These studies were reviewed by OEHHA with regard to the criteria in regulations (Section 25306(g)(2)) cited above. Information reviewed in these studies included experimental design, route of administration, numbers of test animals, choice of species, choice of dosage levels and maternal toxicity. The table emphasizes data relevant to the criteria in regulations and does not provide a comprehensive description of all findings in the studies tabulated.

[10] Section 25306(g)(2)

Table 1. Information from studies cited by NTP in concluding that BPA had clear evidence for high dose developmental toxicity.

Study	Design	Observations at the LOAEL	
		Maternal Toxicity	Developmental Toxicity
Morrissey et al., 1987	CD-1 mice N=21–26 Exposures - Period: GD 6–15 Route: gavage Doses: 0, 500, 750, 1000, or 1250 mg/kg-day	LOAEL: 1250 mg/kg-day ↑ mortality ↓ body weight gain ↑ liver weight ↑ clinical observations Not reported: Food intake Kidney weight Histopathology	LOAEL: 1250 mg/kg-day ↑ % resorptions/litter ↓ fetal body weight
Kim et al., 2001	SD rats N=14–20 Exposures - Period: GD 1–20 Route: gavage Doses: 0, 100, 300, 1000 mg/kg-day,	LOAEL: 300 mg/kg-day No mortality ↑ clinical observations ↓ body weight gain ↓ food intake GD4 Not reported: Organ weights Histopathology	LOAEL: 300 mg/kg-day ↓ fetal body weight/litter ↓live fetuses/litter
NTP, 1985	CD-1 mice N=19 Female exposure only, beginning one week prior to mating, for 14 weeks Route: Diet Dose: 1920 mg/kg-day	LOAEL: 1920 mg/kg-day No ↑mortality ↑ liver and kidney weights ↑ liver/kidney histopathology Not reported: Clinical observations Food intake (reported for mating pairs)	LOAEL: 1920 mg/kg-day ↓ live pups/litter ↓ live male pups/litter ↓ live female pups/litter

Table 1. (continued)

Study	Design	Observations at the LOAEL	
		Maternal Toxicity	**Developmental Toxicity**
Tyl et al., 2002b	SD rats 3-Generation Study F_0 N=30 Male and female exposures Period: premating through lactation Route: Diet Doses: 0, 0.001, 0.02, 0.3, 5, 50, 500 mg/kg-day	LOAEL: 500 mg/kg-day No mortality Clinical observations not statistically analyzed ↑ food intake during gestation ↓ postpartum body weight ↑ kidney, liver, brain weight ↓ ovary weight ↑ liver/kidney histopathology	LOAEL: 500 mg/kg-day ↓ live pups/litter ↓ pups/litter ↓ implantation sites ↓ pup body weight pnd 4, 7, 14, 21 LOAEL: (Fi generation) 50 mg/kg-day ↑ age at vaginal opening ↑ age at preputial separation
Tyl, 2008	CD-1 mice 2-Generation Study N=55 (control) 19–25 (BPA) Exposures: Period: premating through lactation Route: Diet Doses: 0, 0.003, 0.03, 0.3,5, 50, 600 mg/kg-day	LOAEL: 600 mg/kg-day No mortality Clinical observations not analyzed statistically No reduced food intake No body weight effects ↑ liver and kidney weight; ↑ liver/kidney histopathology	LOAEL: 600 mg/kg-day ↓ pup body weight pnd 7,14,21 ↑ age at preputial separation
Tyl et al., 2002a	CD-1 mice, 1-Generation Study N=20 Exposure: Period: premating through birth Route: Diet Doses: 0, 875, 1750 mg/kg-day during gestation	LOAEL: 1750 mg/kg-day No mortality Clinical observations not analyzed statistically No reduced food intake (g/kg) ↓ postpartum body weight ↑ postpartum liver kidney weights ↑ gestation length ↑ liver, kidney histopathology	LOAEL: 1750 mg/kg-day ↓ live pups/litter ↓ total pups/litter Significant trend test; no pairwise effects ↓female pup weight
Tinwell et al., 2002	SD and Wistar rats, male and female N=7 Exposure: Period: GD 6–21 Route: gavage Doses: 20, 100 µg/kg, 50 mg/kg,	LOAEL: 50 mg/kg-day No mortality Not reported: Body weight Liver /kidney weight Food intake Clinical observations Histopathology	LOAEL: 50 mg/kg-day No effects litter size, sex ratio, birth weight ↑ age at vaginal opening (Wistar)

Table 1. (continued)

Tan et al., 2003	SD rats, Male N=12 Exposure: Period days 23-53 postnatal Route: gavage Dose: 100 mg/kg	Not applicable	LOAEL: 100 mg/kg ↓ number with preputial separation by day 53

↑ = increase; ↓ = decrease; GD= gestation day; pnd= postnatal day; N=number of animals per exposure group; LOAEL = Lowest Observed Adverse Effect Level for maternal or developmental toxicity

Statistically significant results are presented with the exception of clinical observations and histopathology incidence, which were not statistically analyzed. Organ weights are relative to body weight. Maternal weight effects are reported as corrected gestational weight/weight gain or postpartum weight (weights that do not include fetuses). For multigeneration studies, data are from the F_0 generation parents and offspring.

The above-described scientific evidence meets the criteria for listing specified in Section 25306(g)(2). In identifying clear evidence for "high" dose developmental toxicity of BPA, NTP identified the specific studies of individual endpoints of developmental toxicity that led to its overall conclusion. For all of the studies cited by NTP for decreases in litter size or number of live pups/litter in rats and mice, the exposures resulting in this manifestation of developmental toxicity were entirely prenatal (Kim et al. 2001, Tyl et al. 2002b, Morrissey et al. 1987, Tyl et al. 2002a, NTP, 1985). This endpoint provides a clear basis for listing of BPA under Proposition 65. Effects on growth were also identified at birth in some studies (Kim et al. 2001, Morrissey et al. 1987), and early during the postnatal period in others (Tyl et al. 2002b, Tyl et al. 2008). In addition, effects on age at onset of puberty were reported after prenatal exposure only in one study (Tinwell et al. 2002), as well as after perinatal (Tyl et al. 2002b, Tyl et al. 2008) or postnatal exposure (Tan et al. 2003) in others. The formal identification of BPA as causing developmental toxicity is therefore supported by sufficient evidence of adverse developmental effects resulting from exposure during the prenatal period, and is consistent with findings from studies involving exposure during the postnatal period.

Comment: Section D.2., is titled "The Animal Data Do Not Show That an Association Between the Effects Observed in Animals and Adverse Developmental Effects in Humans Is Biologically Plausible".

The comments state that "NTP took [lack of biological plausibility in humans] into account when it declined to conclude that BPA is a reproductive toxicant", and note that "it is important that NTP took this into account because OEHHA is prohibited from

‘substituting its judgment’ for that of the authoritative body”. The comments also offer four reasons in support of the commenter’s conclusion stated in the title of the section:

- Animal studies demonstrate that maternal toxicity in animals is consistently observed at dose levels lower than those required to produce developmental toxicity
- Maternal toxicity is sufficient to cause the developmental effects observed at high doses in developmental toxicity studies of BPA in mice and rats
- Humans are not exposed at levels even remotely close to maternally toxic levels of BPA
- Pharmacokinetic differences between rodents and humans are substantial, and even if humans were exposed to the same high doses of BPA used in the laboratory animal studies, developmental effects would not be expected in humans due to differences in pharmacokinetic handling.

Response: As discussed extensively above, NTP concluded that BPA causes developmental toxicity in laboratory animals. Thus, the basic premise for this comment is incorrect. OEHHA is required by regulations[11] to determine whether, based on the data in animals identified by NTP, an association between adverse developmental effects in humans and BPA is biologically plausible. As noted above, OEHHA has determined that such an association is biologically plausible. It is a fundamental assumption of toxicity testing in laboratory animals that “an agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans following sufficient exposure during development”.[12] OEHHA reviewed the discussion of metabolism in the NTP-CERHR document and did not find any information that conflicted with NTP’s conclusion that BPA “possibly” could affect human reproduction or development. In addition, NTP stated that “[r]ecognizing the lack of data on the effects of bisphenol A in humans and despite the limitations in the evidence for ‘low’ dose effects in laboratory animals … , the possibility that bisphenol A may alter human development cannot be dismissed.” This represents NTP’s conclusion that developmental toxicity of BPA is biologically plausible in humans. Thus, there is no issue of OEHHA substituting its judgment for that of the authoritative body.

The arguments regarding maternal toxicity have been discussed above. The levels of exposure that humans may currently be experiencing have no bearing on the *biological*

[11] Section 25306(c).
[12] U.S. Environmental Protection Agency Guidelines for Developmental Toxicity Risk Assessment (1991).

plausibility that some levels of exposure may cause developmental toxicity in humans.[13] The final argument regarding pharmacokinetic differences does not address biological plausibility of effects in humans but instead addresses levels of exposure at which such effects might occur.

New Evidence

Comment: In Section G. "Scientifically Valid Data Not Considered by NTP," the commenters discuss in some detail a study that was not considered by the authoritative body. The supplemental comments submitted on September 1, 2011 also discuss several other studies not considered by the authoritative body.

Response: The studies identified by the commenters that investigated developmental endpoints used doses less than or equal to 0.2 milligrams per kilogram per day (mg/kg-day). However, the NTP-CERHR conclusions concerning "high" doses that constitute "formal identification" for purposes of Proposition 65 are explicitly based on studies that used doses greater than or equal to 50 mg/kg-day.

References

Kim JC, Shin HC, Cha SW, Koh WS, Chung MK, Han SS (2001) Evaluation of developmental toxicity in rats exposed to the environmental estrogen bisphenol A during pregnancy. *Life Sci.* 69: 2611 – 2625.

Morrissey RE, George JD, Price CJ, Tyl RW, Marr MC, Kimmel CA (1987) The Developmental Toxicity of bisphenol A in Rats and Mice. *Fundam Appl Toxicol.* 8: 571 – 582.

National Toxicology Program – Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR, 2008). *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A.* NIH Publication No. 08 – 5994, Research Triangle Park, NC.

National Toxicology Program (NTP, 1985) Bisphenol A: reproduction and fertility assessment in CD-1 mice when administered in the feed. NTP-85-192. Research Triangle Park, NC.

[13] *Exxon Mobil Corporation v Office of Environmental Health Hazard Assessment*, (2009) 169 Cal.App.4th 1264 at page 1291-1292

Nishimura H, Miyamoto S. (1969). Teratogenic effects of sodium chloride in mice. Acta Anat.74:121-124.

Stropp GD, Waechter JM (2002b) Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. *Toxicol Sci.* 68:121 – 146.

Tan BL, Kassim NM, Mohd MA (2003) Assessment of pubertal development in juvenile male rats after sub-acute exposure to bisphenol A and nonylphenol. *Toxicol Lett.* 143:261 – 270.

Tinwell H, Haseman J, Lefevre PA, Wallis N, Ashby J (2002) Normal sexual development of two strains of rat exposed *in utero* to low doses of bisphenol A. *Toxicol Sci.* 68:339 – 348.

Tyl R, Myers CB, Marr MC (2002a). Abbreviated one-generation study of dietary bisphenol A (Bisphenol A) in CD-1® (Swiss) mice (sponsored by the Society of the Plastics Industry, Inc.), Research Triangle Institute RTI, Research Triangle Park, NC.

Tyl RW, Myers CB, Marr MC, Thomas BF, Keimowitz AR, Brine DR, Veselica MM, Fail PA, Chang TY, Seely JC, Joiner RL, Butala JH, Dimond SS, Cagen SZ, Shiotsuka RN, Stropp GD, Waechter JM (2002b) Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. *Toxicol Sci.* 68:121 – 146.

Tyl RW, Myers CB, Marr MC, Sloan CS, Castillo NP, Veselica MM, Seely JC, Dimond SS, Van Miller JP, Shiotsuka RN, Beyer D, Hentges SG, Waechter JM, Jr. (2008) Two-generation reproductive toxicity study of dietary bisphenol A (Bisphenol A) in CD-1(R) (Swiss) mice. *Toxicol Sci.* 104:362 – 384.

U.S. Environmental Protection Agency (U.S. EPA, 1991). Guidelines for Developmental Toxicity Risk Assessment, U.S. EPA Risk Assessment Forum, Washington DC.