# Office of Environmental Health Hazard Assessment

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January 22, 2013

James C. Lamb IV, Ph.D., DABT, Fellow ATS
Principal Scientist and Center Director
Center for Toxicology and Mechanistic Biology
Exponent
1800 Diagonal Road, Suite 500
Arlington, Virginia 22314

Dear Dr. Lamb:

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 submitted by you and Dr. Kimmel. 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 event that OEHHA finds the criteria have not been met after review of the comments,

[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.

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,

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

Enclosure:

Response to Comments from Exponent 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 Exponent 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 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).

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)).

On May 13, 2010, OEHHA received comments concerning the possible listing of BPA from Exponent, on behalf of the American Chemistry Council. This document provides a summary and response to those comments.

[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

Comment: Some comments concerning formal identification are included in the introductory section of the comment letter.

> "Under Prop 65, chemicals are labeled for different types of toxicity based on their potential hazard rather than risk. The NTP CERHR also does not label chemicals as such but rather provides 'scientifically sound evaluations of the potential for adverse effects on reproduction or development resulting from human exposures to substances in the environment.' It is not the purpose to generate lists of substances that might or might not be classified as reproductive or developmental toxicants, as required under California's Prop 65 (Prop 65). The Prop 65 determination cannot be made by simply extracting a sentence from the CERHR report."

Response: Proposition 65 requires that chemicals that are "known to the state to cause reproductive toxicity" be added to a list maintained by the Governor of California (Health and Safety Code section 25249.8(a). One mechanism by which a chemical can become known to the state to cause reproductive toxicity is "if a body considered to be authoritative by [the state's qualified] experts has formally identified it as causing…reproductive toxicity". The NTP (solely as to final reports of the Center for Evaluation of Risks to Human Reproduction) is such an authoritative body. The Developmental and Reproductive Toxicant (DART) Identification Committee (the state's qualified experts for reproductive toxicity) made this designation in 2002 and reaffirmed it in 2011.

OEHHA agrees that the NTP-CERHR provides high-quality scientific evaluations regarding the potential of a chemical to cause adverse developmental and reproductive effects. The NTP-CERHR document contains NTP's conclusions about the weight of evidence for the developmental toxicity of BPA. OEHHA is relying on those conclusions in considering BPA for authoritative body listing. The NTP's conclusions meet the criteria for Formal Identification as provided in Section 25306(d). The Proposition 65 regulations allow OEHHA to rely on a number of different types of documents published by authoritative bodies, including lists, reports or other final documents issued by an authoritative body. (Section 25306(d)(1)). In this case, the NTP issued a report that OEHHA is relying on for the proposed listing of BPA.

## Sufficiency of Evidence

Comment: The comments mention that the NTP-CERHR weight of evidence conclusion does not take into account the unlikely potential for human exposure at "high" dose levels.

Response: As noted above, the authoritative bodies listing process requires only that the authoritative body in question formally identify a chemical as a reproductive or developmental hazard. Anticipated human exposures are considered at a later time.

Comment: The majority of Exponent's comments concern sufficiency of evidence, and, in particular, consideration of maternal toxicity as described in regulation. The comments state that the statute requires OEHHA to determine the sufficiency of evidence by taking into account several factors, including maternal toxicity.

Response: Maternal toxicity is taken into account by OEHHA in determining whether a chemical has been formally identified as causing reproductive toxicity. However, as a point of clarification, it is the implementing regulations and not the statute that lay out the criteria for sufficiency of evidence for listing under the authoritative bodies provision:

> "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." (Section 25306(g)(2),emphasis added).

Comment: The comments state that the NTP-CERHR weight of evidence conclusion for the effects of BPA "…does not include the consideration that there was severe maternal/adult toxicity at these same doses, indicating a lack of selective or specific developmental toxicity for BPA..."

Response: At the July 12, 2011 meeting of the DART Identification Committee, 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 evaluated 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 it 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."[4]

Dr. Bucher's description of the process is consistent with the content of the NTP-CERHR report on BPA. Maternal toxicity is specifically discussed in the review of studies identified as the basis for the conclusion that there is clear evidence of developmental toxicity at "high" doses in laboratory animals. For example, the study by Kim et al. (2001) is described as having "fetal effects only at the high-dose that showed marked maternal toxicity", and the study by Morrissey et al. (1987) is described as there being "[c]linical signs reported in mice treated with bisphenol A included arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss, and wheezing. One or 2 of 29–34 dams died in each of the 3 lowest dose groups and 6 of 33 dams died in the 1250 mg/kg bw/day group". Both of these studies are further described as "adequate and of high utility in the evaluation". In contrast, other studies such as that by Berger et al. (2007) are considered "inadequate for the CERHR evaluation process", in part because of the "inability to discriminate between potential maternal toxicity and the findings in the offspring". It is therefore clear that NTP considered maternal toxicity in reaching its conclusion that the studies it relied upon provided clear evidence of developmental toxicity.

Comment: The comments conclude that developmental effects were seen only at high dose levels that also caused severe maternal toxicity, are part of the pattern of general toxicity attributable to BPA at those doses, and are not specific or selective in terms of reproductive or developmental toxicity.

Response: Although the comments do not specifically define "selective or specific" developmental toxicity, the context of the comments implies that it can occur only in the absence of "severe" maternal toxicity. The more specific comments on the relationship between maternal and developmental toxicity are addressed below. However, as noted

[4] Meeting transcript available at http://www.oehha.ca.gov/prop65/public_meetings/pdf/DARTIC071211trans.pdf

above, the NTP-CERHR drew its conclusions about the developmental toxicity of BPA after consideration of the occurrence of maternal toxicity in the relevant studies.

Comment: The subsequent review in the comments concerning maternal toxicity contains three points:

1. Developmental toxicity occurs at the same dose level as maternal toxicity or paternal toxicity.
2. The maternal/paternal toxicity is “severe”.
3. Studies may be difficult to interpret in these circumstances, according to the U.S. Environmental Protection Agency (U.S. EPA) Guidelines for Developmental Toxicity Risk Assessment.

Response: The evidence relied upon by NTP to conclude that there is clear evidence that BPA causes developmental toxicity includes decreases in litter size or number of pups in rats (Kim et al. 2001, Tyl et al. 2002b), and in mice (Morrissey et al. 1987, Tyl et al. 2002b, NTP, 1985); and effects on growth in rats (Kim et al. 2001 and Tyl et al. 2002b) and in mice (Morrissey et al. 1987, Tyl et al. 2002a, Tyl et al. 2008). OEHHA agrees that developmental toxicity occurred at the same dose levels as maternal toxicity in some of these studies. Co-occurrence of maternal toxicity and developmental toxicity is not a basis for dismissing developmental toxicity, according to U.S. EPA guidelines (U.S. EPA, 1991) and other regulatory agencies. Two examples of the generally accepted principles in this regard 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, at page 18)

> "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, Part 3, Section 3.7.2.4.2, 2009, at page 176)

The degree of maternal toxicity and the potential difficulty of interpretation were assessed by OEHHA in considering sufficiency of evidence as described below by individual study.

<u>Morrissey et al. 1987</u>

Comment: After describing the Morrissey et al. rat study, Drs. Lamb and Kimmel noted that significant maternal toxicity occurred at all dose levels.

Response: The Morrissey et al. rat study was not used as supporting evidence for the NTP conclusion that there is clear evidence that BPA causes developmental toxicity in animals at high doses. Thus, the comments relating to that study are not relevant.

Comment:

> "In mice, maternal toxicity occurred at all dose levels except controls, rising to death of 18% of animals at the highest dose. Liver weight relative to body weight was also increased at all doses, indicating maternal metabolic effects of BPA. The only fetal effects were an increase in resorptions and reduced body weight in survivors, both of which occurred only at the highest dose level, clearly a dose producing severe maternal toxicity."

Response: OEHHA agrees that severe maternal toxicity occurred in the mouse study in that 18% mortality occurred in the high dose group. In regard to this issue, OEHHA referred to the research literature on the relationship between occurrence of maternal mortality in a dose group and fetal outcomes in the litters of surviving dams. In a paper by Kavlock et al. (Kavlock et al., 1985), lethal doses of 10 agents were given to pregnant mice. Maternal deaths ranged from 5 to 53% in 30 dose groups in the study. Neither the percent of maternal deaths nor the pregnancy weight gain of the surviving dams in the dose groups was clearly associated with developmental toxicity as

measured by fetal mortality and fetal weight. The authors did find a correlation between maternal weight gain and incidence of supernumerary ribs in the fetuses. The authors concluded that "there was no relationship between the incidence of maternal mortality in treated groups and any endpoints in the fetuses of surviving females." No research with a contrary conclusion was located. Thus, limited relevant scientific information does not suggest that fetal endpoints in mice need to be interpreted differently on the basis that maternal mortality is increased in the same dose group.

The authors of Morrissey et al. (1987) present group differences in weight gain during gestation of 32% in the high dose as compared to the control group. The gravid uterine weight (the uterus containing fetuses and placentas) of the high dose group was also 32% lower than control. This suggests that the difference in gestational weight gain can be referred to the reduced weight of the products of conception. Indeed, the corrected maternal weight gain, not mentioned in the comments, was not statistically different from control in the high dose group. Also, the authors of the article state that maternal weight gain was decreased "principally as a result of the 40% resorption rate in this group". The comments do not discuss the weight gain changes as "severe" maternal toxicity.

Dam liver weight at term was increased in three of the dose groups of this study but was not different from control in the high dose group in which fetal outcomes were affected by BPA. Relative dam liver weights were increased in the high dose group, but the authors mention that this may have been due to reduced dam weight gain in this group. Thus an association between dam liver weight and fetal outcome was not seen in the study.

The study also describes clinical observation of gross toxicity although the prevalence in each dose group is not given and no statistics were provided. Thus it is not possible to assess an association of these observations in the dam with fetal outcomes.

<u>Kim et al., 2001</u>

Comment: After describing the fetal effects observed in the study, Drs. Lamb and Kimmel concluded:

> "Thus, fetal effects were seen only at doses in this study that produced severe maternal toxicity."

Response: There was no maternal mortality in this study. The authors describe clinical signs of overt toxicity in the two highest dose groups, and describe these observations as treatment related and dose dependent, but no information on incidence and no statistical analysis were presented so a possible relationship to fetal outcome cannot be evaluated. The comments mention reduced food intake, which was reported as lower in the high dose group than controls on only the first of the eight days during gestation when it was measured. OEHHA does not consider this early, transient decrease in food intake to represent “severe” toxicity.

Maternal body weight and body weight gain were lower during gestation, as was the weight of the gravid uterus (fetuses, placentas and uterine tissue). The corrected maternal body weight gain (weight effect attributable to maternal toxicity) was 15% less in the high dose than the control group. Dam organ weights and organ histopathology were not evaluated in the study. Thus the main index of maternal toxicity that might be considered “severe” and interfere with interpretation was the 15% lower corrected maternal body weight gain.

In regard to this issue, OEHHA referred to the research literature on the relationship between corrected maternal weight gain and developmental toxicity (litter size and fetal weight at term) in rat developmental toxicity studies.

A rat study (Kavlock et al., 1985) was conducted in which corrected maternal weight gain and pup weight on the day after birth were determined for 9 agents given at 2 doses. Decreased pup weights were seen in 4 of the 15 dose groups. Corrected maternal weight gain was reduced by at least 60% in these dose groups (as compared to 15% in Kim et al. study).

Another rat study, Chahoud et al. (1999) examined the relationship between maternal weight change and fetal parameters, including viable fetuses and fetal weight, in 263 control groups and 331 treated groups from developmental toxicity studies in Wistar rats. The authors concluded that “no correlation was observed between the maternal body weight change and the fetal parameters”. (The data in the report suggest the “maternal weight change” was corrected for gravid uterus). Restrictions on this conclusion include a lack of statistical analysis and use of only litters with 9-12 pups for the fetal weight correlation.

The relationship between maternal and fetal toxicity in 56 rat studies was analyzed (Chernoff et al., 2008). From these studies, the authors selected dose groups in which

a significantly lower maternal weight occurred at some point during gestation and found a significant positive correlation between corrected maternal weight gain and fetal weight. However, a positive correlation between these two variables was also seen in control groups from these studies and thus cannot be attributed to toxic actions of the agents. The authors further state that maternal weight reductions were associated with significant fetal weight reduction in only 40% of the studies. They further conclude that "the complexities involved in both maternal toxicity and fetal development preclude the identification of a single relationship of these factors for all test agents."

Knudsen et al. (2009) looked at the relationship between maternal and fetal toxicity in 383 rat developmental toxicity studies with 2469 dose groups. They found "no correlation between doses that caused maternal and fetal weight changes (correlation coefficient <0.01)". Their analysis was based primarily on cluster analysis.

Taken together, the analysis of empirical data does not indicate a strong association between corrected maternal weight gain and fetal weight that would indicate a predictive or potentially causal relationship.

Reel et al. 1985

Comment: The comments describe results of a study by Reel et al. (1985) that was conducted using the NTP Reproductive and Fertility Assessment by Continuous Breeding Protocol. This appears to be the study cited as NTP (1985a) in the NTP-CERHR report. The comments conclude that "[e]ffects on litter size, number of live pups and survival were seen at 0.5% and 1.0% in the F0 mating pairs (Task 2) and are likely part of the general pattern of BPA toxicity at these exposure levels."

Response: As the comment suggests, adult toxicity data was limited in this study. The comment refers to "severe" adult toxicity in the high dose group at the end of Task 3 and in the F1 animals.

In reviewing the study OEHHA notes that there was no effect of BPA on mortality in the male or female breeders. The dose that produced increased mortality in the dose-finding study (Task 1), described in the comment, was not used in the reproductive assessment (Task 2). As regards body weights, there were no effects of BPA on body weights in the dose-finding study at the doses selected for the reproductive assessment. The high dose for the reproductive assessment (1.0%) was selected "such that it would not depress weight gain in either sex by more than 10%". As stated

in the comment, postpartum weights (day of birth) were 8-9% lower in the high dose group than in controls in Task 2. However, developmental toxicity was also seen at the 0.5% dose which did not influence postpartum weights. Further, there were no BPA effects on postpartum body weights in Task 3 or Task 4 at any dose, and no effects on female body weights measured weekly during the 18 weeks of Task 2. At the conclusion of the study, after 21 weeks of dosing, female body weights were 4% lower in the high dose group and not affected at any other dose. Based on the mortality and body weight data, OEHHA concludes that the maternal toxicity produced by BPA was not "severe" at any dose.

Organ weights and histology were examined at the end of Task 3, at least four additional weeks after the completion of Task 2. Thus, it is not clear whether or to what extent these measures can be referred to the developmental toxicity recorded in Task 2. At this time, liver and kidney weights (adjusted for body weight) were higher in the high dose group than in controls. No other dose groups were examined. The incidence of two histological findings, tubular cell nuclear variability and multifocal cortical tubular dilatation in the kidney, were also significantly elevated in the high dose group relative to controls. The potential influence of these findings on fetal development, had they occurred during pregnancy, is not known. It is not known whether these histological differences were present at the LOAEL for developmental toxicity, 0.5%, during the pregnancies that resulted in developmental toxicity in Task 2 and 3. Histological evaluations were conducted in the 0.5% dose group at the end of Task 4. These F1 females had been exposed to BPA throughout their in utero and postnatal development, as well as during pregnancy. No incidence of tubular cell nuclear variability was recorded. Three of 20 dams showed multifocal cortical tubular dilatation, which was not statistically different from controls. Thus, at the LOAEL for developmental toxicity in this study, 0.5%, no maternal toxicity was reported at any time in the study. The statement in the comment that "Effects of litter size, number of live pups and survival were seen at 0.5% and 1.0% in the F0 mating pairs (Task 2) and are likely part of the general pattern of BPA toxicity at these exposure levels" was not supported by OEHHA's review of the study.

<u>Tyl et al. 2002a</u>

Comment:

> "Toxicity to the F0 males and females was evident at both BPA exposure levels with increases in liver and kidney weights …. In addition, F0 maternal animals

had reduced body weight, weight gain, food consumption and food efficiency, as well as a slight prolongation of gestation length (10 hours in both exposure groups). At necropsy, F0 females were found to have significant liver and kidney histopathology, and changes in clinical chemistries at both doses. Reductions in pup numbers and live litter size were evident only at the higher dose level. Data from this study support the conclusion that litter effects occurred only in the presence of severe maternal toxicity. In the Reel et al. (1985) study, there were also litter effects at 0.5%, but the exposure period in that study was much longer (>98 days versus only 5-6 weeks in this study)."

Response: No maternal or paternal mortality was reported in this study, and there was no report of clinical observations of overt toxicity. The comments state that "litter effects occurred only in the presence of severe maternal toxicity" but do not state what endpoints they think represent "severe" maternal toxicity.

Increased liver and kidney weights and increased incidence of centrilobular hepatocyte hypertrophy were reported in F0 dams after the completion of pregnancy. The hepatocyte hypertrophy was described as "minimal" or "mild" by the pathologist. The renal pathology was also categorized as "minimal" or "mild" with the exception of a total of 3 notations of "moderate" in two of the four lesion categories assessed in 20 mice/group. These changes were not described as "severe" toxicity by the authors or by the CERHR review panel, and are not so considered by OEHHA.

As regards decreased weight and weight gain in the high dose group, the commenter did not provide the percentage of weight difference for this study. OEHHA's review found:

1. No difference in prebreed body weights
2. No difference in body weights on gd 0, 7, 10
3. Lower body weights 7.8% gd 14, 10.6% gd 17, 6.6% pnd 0 (after delivery)
4. Lower body weight gain gd7-10, 26%, gd10-14, 20%, gd14-17, 22%, gd0-17 18%

Corrected body weight gains were not provided. OEHHA notes that body weight gain during pregnancy includes both the body weight gain of the mother and the weight of fetuses and placentas. Because litter size was lower in the high dose group it would be anticipated that the weight of the fetuses and placentas contributing to pregnancy weight gain would be lower. In fact the difference in pregnancy weight gain was 18% between the control and high dose group, while the difference in weight of the offspring

(number of offspring x average weight) at term was also 18%. The difference from control in corrected maternal body weight of 6.6% (after the delivery), representing toxicity to the dam, is not considered by OEHHA to represent "severe" toxicity and was not so described by the study authors or CERHR reviewers.

The text and table provided by the commenter in describing this study mention decreased food consumption and food efficiency in BPA-treated groups during pregnancy in this study. The report itself (Tyl et al., 2002a) states:

> "F0 maternal feed consumption during gestation was equivalent across groups for gd 0-7, 7-10, 10-14 and 0-17 when expressed as either g/day or g/day or g/kg/day. Feed consumption in g/day was significantly reduced at 10,000 ppm for gd 14-17 (but unaffected when the data were expressed as g/kg/day). No other groups or intervals were affected. Percent food efficiency was equivalent across groups for gd 0-7, 7-10, and 14-17. There was a significant dose-dependent downward trend (P<.0.01) for this parameter, but no significant pairwise comparisons to the control group value for gd 7-10, and it was significantly reduced at 5000 and 10,000 ppm for gd 10-14 and 0-17 (gestational period)."

Tables in the study report show the size of the lower food efficiency was 16% in both dose groups. This effect on food efficiency was not identified as "severe" maternal toxicity by the study authors or CERHR reviewers and is not so considered by OEHHA.

Necropsy of the F0 females occurred after weaning of their litters. It is not known whether liver and kidney histopathological changes were present during pregnancy. The potential influence of these findings on fetal development, had they occurred during pregnancy, is also not known.

<u>Tyl et al. 2008b</u>

Comment:

> "Adult systemic toxicity in the F0 animals included centrilobular hepatocyte hypertrophy at 300 and 3500 ppm, renal nephropathy in males only at 3500 ppm, and reduced body weight, increased kidney and liver weight at 3500 ppm. Gestation length was slightly but significantly delayed (0.3 days) in both the F0 and F1 maternal animals. Effects on reproduction and offspring were seen only

at 3500 ppm and included reduced weanling body weight, spleen and testis weight, delayed preputial separation and undescended testes in weanlings. The effects on reproductive organs did not result in adverse effects on adult reproductive structures or functions, so were considered a developmental delay."

"…Developmental toxicity in mice occurred only at doses that also produced severe maternal and adult toxicity (1250 mg/kg/day in the prenatal exposure study, and 600 mg/kg/day in the two-generation study)."

Response: The comments describe "severe maternal and adult toxicity" at the 600 mg/kg dose. No maternal or paternal mortality was reported in this study, and there was no increased incidence of clinical observations of overt toxicity. Increased liver and kidney weights and increased incidence of centrilobular hepatocyte hypertrophy were reported in F0 dams after the completion of lactation and cannot necessarily be referred to pregnancy. These changes were not described as "severe toxicity" by the study authors, or by the CERHR review panel.

Table 5 in the comments also has a downward pointing arrow for "weight" for the 600 mg/kg/day dose. In examining the supplementary materials provided with the publication, OEHHA notes the following concerning the 600 mg/kg-d "high" dose in the F0 generation.

1. No effect on male prebreeding weights or weight gain
2. No effect on female prebreeding weights or weight gain
3. No effect on pregnancy weights or weight gain
4. No effect on dam weights during lactation. Weight gain during lactation was significantly higher in the high dose group than in controls.
5. No effect on male or female weights at necropsy

Thus OEHHA was not able to find support for the commenters' description of decreased maternal/paternal weight in the study report. As mentioned previously, lower body weights of F1 and F2 breeders cannot be clearly attributed to adult toxicity because these animals were exposed throughout development.

Increased liver and kidney weights and increased incidence of centrilobular hepatocyte hypertrophy were reported in F0 dams at necropsy. Specifically, at the high dose, 6 of the 10 dams examined demonstrated "mild" hypertrophy, and at the second highest dose 1 of the10 dams examined were reported with "mild" hypertrophy. No attempt was made by the authors of the paper, CERHR or the commenters to ascribe the

developmental toxicity in this study as secondary to mild hepatocyte hypertrophy in the high dose group.

Given the lack of effect on weight or weight gain and the minimal effects on organ weight and histopathology, OEHHA does not agree with the commenter's description of "severe" toxicity in this study at the 600 mg/kg-d dose.

Tyl et al. 2002b

Comment: After describing the study design, comments were made about adult toxicity and also a synopsis was given of study findings:

> "Adult systemic toxicity included reduced body weight and weight gain, reduced absolute and increased relative weanling and adult organ weights (liver, kidneys, adrenals, spleen, pituitary, and brain) at 750 and 7500 ppm. Females showed slight/mild renal and hepatic pathology at 7500 ppm. Relative ovarian weights were reduced in F0, F1, and F2 females, as were the number of implants, number of pups, and number of live pups/litter on PND 0 and PND 4. On PND 7, 14 and 21, the weight of F1, F2, and F3 pups/litter was reduced. In male offspring, epididymal sperm concentration was reduced in F1s and daily sperm production was reduced in F3s at 7500 ppm."

Results of the study were also tabulated.

Response: The comments do not describe the "adult systemic" toxicity in this study as "severe". OEHHA did not identify "severe" maternal toxicity in this study, although developmental toxicity was reported as a decrease in live pups/litter at birth. There was no maternal mortality or incidence of clinical observations in this study, and pregnancy weight gain was not affected. Since F1, F2, and F3 offspring were exposed in utero, as well as postnatally and as adults, it is not possible to distinguish the time of origin of any toxicity assessed postnatally in these animals or accurately characterize it as "adult" toxicity. The "slight/mild" renal and hepatic pathology was detected in the F0 dams after the conclusion of lactation and it is not known whether it was present during pregnancy.

Details of the effects on weight and weight gain and organ weight are not provided in the comments. OEHHA notes the following concerning the two highest doses in the F0 generation. (As noted previously, weight differences in F1 and F2 adult parental animals cannot be ascribed to adult toxicity because these animals were exposed to

BPA throughout development and were growth retarded beginning in the early postnatal period.)

1. Male pre-breeding weights lower in high dose group, 21% at end of the pre-breeding period
2. Male pre-breeding weight gain 37% lower in the high dose group
3. Female pre-breeding weights lower in the two highest doses, 8 and 18% lower at the end of the pre-breeding period
4. Female pre-breeding weight gain lower in the two highest dose groups, 17% and 43% lower at the end of the pre-breeding period
5. Pregnancy weights lower in the two highest dose groups, 7% and 20% at term
6. Pregnancy weight gain lower in the highest dose group, 28% at term, corrected weight gain not reported
7. Dam weights during lactation lower in the two high dose groups, 4 and 15%
8. Dam weight gain during lactation higher in the highest dose group, 211% at the end of lactation
9. Male body weights at necropsy 22% lower than controls in the high dose group
10. Female body weights at necropsy 13% lower than controls in the high dose group

Because an estimate of corrected dam body weight at term was not provided, OEHHA calculated the percent difference in pup mass (number of pups × average weight of pups) for comparison to F0 dam body weight gain at term. In the high dose group, maternal weight gain was 28% lower than control at birth, while pup body weight mass was 21% lower than control, suggesting that the corrected maternal weight gain would average 7% lower in the high dose group relative to controls. The corrected weight gain can be determined from the weight of the dam on the day of birth after delivering her litter relative to her body weight on the first day of gestation. OEHHA found that controls gained 9.9% of their initial weight, while the 750 ppm group gained 10.6% and the 7500 ppm (high dose) group gained 4.6%. Thus the high dose group gained 5.3% less weight than controls. OEHHA does not consider this differential to represent severe toxicity.

Comment:

> "We have reviewed the critical studies cited by the NTP CERHR report and have summarized the key findings above. In every case, effects on offspring seen were at dose levels that also produced maternal/adult systemic toxicity greater than what would be considered minimal toxicity. In addition, the levels of

exposure at which the maternal/adult toxicity and reproductive and developmental toxicity occurred are far above those exposure levels that might plausibly occur in humans. We believe that the developmental effects reported as a result of BPA exposure are part of the pattern of general toxicity caused by BPA and are not specific or selective for developmental toxicity."

"We do not believe the data provide sufficient evidence of developmental toxicity, even at high doses of BPA, due to the degree of maternal/adult toxicity at the same dose levels. Therefore, it is inappropriate to list BPA under Prop 65 as a developmental toxicant in any case, and particularly on the basis of "high dose" effects because the effects seen are part of a general pattern of overall toxicity."

Response:

Although the commenter's opinion of these studies differs from the interpretation of the studies by the authoritative body, OEHHA is relying on the NTP interpretation of these studies. Proposition 65 does not allow OEHHA to substitute its judgment for NTP's judgment in the 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 Proposition 65.

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