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Via EMAIL & U.S. MAIL

Ms. Cynthia Oshita
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
Post Office Box 4010, MS-19B
Sacramento, California 95812-4010

RE: *Notice of Intent to List Bisphenol A*

Dear Ms. Oshita:

These comments are submitted on behalf of the Polycarbonate/BPA Global Group of the American Chemistry Council (“ACC”), in response to the Office of Environment Health Hazard Assessment’s (“OEHHA”) January 25, 2013 Notice of Intent to List Bisphenol A (“BPA”) as causing developmental toxicity pursuant to the “authoritative bodies mechanism” under California’s Proposition 65. ACC objects to OEHHA’s attempts to list BPA as causing reproductive toxicity (developmental endpoint) on numerous legal and scientific grounds, and has recently filed a complaint for declaratory and injunctive relief against such listing in Superior Court.

Nevertheless, OEHHA’s January 25 Notice of Intent to List BPA solicited public comment on only the narrowly defined issue of whether the evidence on which OEHHA proposes to list BPA satisfies the applicable statutory and regulatory criteria for listing. Although ACC has fully addressed this issue in its prior comments, we wish to highlight in these comments some of the striking evidentiary failures to meet the criteria for listing under OEHHA’s own regulations.

First, as demonstrated in these comments, OEHHA has fundamentally misinterpreted the National Toxicology Program report on BPA that OEHHA cites as the authoritative body basis for proposing to list BPA. In contrast to OEHHA’s assertion that the report formally identifies BPA as causing developmental toxicity, the report does just the opposite. It clearly and unambiguously identifies BPA as NOT causing developmental toxicity.

Second, California Code of Regulations Title 27, Section 25306(g)(2) requires that where a chemical is to be listed by the authoritative bodies mechanism “as causing reproductive toxicity” on the basis of studies in experimental animals, such animal studies must constitute “sufficient data, taking into account the adequacy of the experimental design and other parameters such as ... consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.” For the reasons stated below (and previously), the experimental animal data on which OEHHA proposes to base the listing of BPA, which were identified and discussed in the 2008 NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A, do not satisfy the criteria of Section 25306(g)(2). When proper weight is given to “consideration of maternal toxicity,” “route of administration,” and “choice of dosage levels” in the animal studies in question, the animal data do not indicate that adverse developmental effects in humans from exposure to BPA are biologically plausible.

Third, as detailed below, the clear expert judgment of 23 highly qualified scientific experts, collectively representing many centuries of relevant professional experience, is that the scientific data demonstrate that BPA does *not* cause developmental toxicity at high levels of exposure. OEHHA has no justification for reaching the opposition conclusion based on the same scientific data.

1. THE NTP-CERHR EXPERT PANEL CLEARLY CONCLUDED THAT BPA IS NOT A DEVELOPMENTAL HAZARD

The foundation of OEHHA’s Notice of Intent to List Bisphenol A under Proposition 65 is the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A (“NTP-CERHR Monograph”). The NTP-CERHR expert panel comprehensively evaluated all studies relevant to the potential reproductive and developmental effects of BPA, including the select number of studies on which OEHHA proposes to list BPA as causing developmental toxicity. The conclusions of the expert panel were thoroughly documented in a 239-page report that was published in the peer-reviewed scientific literature¹ and was included as part of the NTP-CERHR Monograph. Certainly OEHHA is aware of the expert panel report since OEHHA selectively quoted from the expert panel report in certain responses to comments that were submitted in regard to OEHHA’s February 12, 2010 Request for Relevant Information on Bisphenol A.

The NTP-CERHR expert panel report is highly significant for two reasons. First, the expert panel report provides the substantive basis on which the NTP Brief on Bisphenol A (“NTP Brief”) was built, and the NTP Brief is the source of the purported “conclusion” that

¹ Chapin, R. E., Adams, J., Boekelheide, K., Gray Jr., L. E., Hayward, S. W., Lees, P. S., McIntyre, B. S., Portier, K. M., Schnorr, T. M., Selevan, S. G., Vandenberg, J. G., and Woskie, S. R. 2008. Birth Defects Research (Part B). 83:157-395.

OEHHA cites as the basis for the proposed listing. To understand the statements and conclusions in the NTP Brief, in particular the meaning of Figure 2b of the NTP Brief (on which OEHHA specifically relies), it is critical to know what the expert panel documented in their report. It was the expert panel that evaluated every study, summarized the data, and drew conclusions based on the data, including explicit conclusions on the developmental hazards of BPA. Based on the expert panel report, NTP then prepared a shorter summary document, the NTP Brief, which is specifically designed to and does closely follow the expert panel report.

The second reason why the expert panel report is significant is that it was prepared by a group of twelve highly qualified scientific experts who were hand-selected by NTP for this task. The experts and their affiliations are listed below:

- Jane Adams, Ph.D. (University of Massachusetts)
- Kim Boekelheide, M.D., Ph.D. (Brown University)
- Robert E. Chapin, Ph.D. (Pfizer Inc.)
- L. Earl Gray, Jr., Ph.D. (U.S. Environmental Protection Agency)
- Simon W. Hayward, Ph.D. (Vanderbilt University Medical Center)
- Peter S. J. Lees, Ph.D. (Johns Hopkins University)
- Barry S. McIntyre, Ph.D. (Schering Plough Research Institute)
- Kenneth M. Portier, Ph.D. (American Cancer Society)
- Teresa M. Schnorr, Ph.D. (National Institute for Occupational Safety and Health)
- Sherry G. Selevan, Ph.D. (U.S. Public Health Service (Ret.))
- John G. Vandenbergh, Ph.D. (North Carolina State University)
- Susan R. Woskie, Ph.D. (University of Massachusetts)

The key findings of the NTP-CERHR expert panel and their linkages to the statements and conclusions in the NTP Brief, in particular the statements in Figure 2b, can be summarized as follows:

**a. NTP-CERHR EXPERT PANEL REPORT –
SECTION “3.0 DEVELOPMENTAL TOXICITY DATA”**

Section 3.0 of the expert panel report provides (1) a detailed summary of each developmental toxicity study examined and (2) a characterization of each study’s

“Strengths/Weaknesses” and “Utility (Adequacy) for CERHR Evaluation Process.”² The most significant studies were designated as “high utility.”

Of particular note, the eight studies cited by OEHHA in the Notice of Intent to List BPA³ were reviewed and the detailed summaries in Section 3.0 are the source of the developmental effects that are cited by OEHHA for these studies.

**b. NTP-CERHR EXPERT PANEL REPORT –
SECTION “3.4 SUMMARY OF DEVELOPMENTAL TOXICITY DATA”**

Data from the studies considered by the expert panel to be the most important and relevant for their evaluation are summarized in Section 3.4. The expert panel relied on their pre-determined criteria to identify high utility studies:

“The studies summarized here are those considered by the Panel to be the most important and relevant for the assessment of the effects of Bisphenol A on the human population. Evaluation of the scientific literature was made on the scientific quality of the study and also on its relevance to the assessment of the level the [sic] concern about potential effects of BPA on human health. The judgment was based on the criteria the Panel adopted which focused on the potential for providing information for the evaluation process. Several excellent studies have been placed in the ‘adequate-but-limited-utility’ category with regard to the evaluation process. The Panel did not consider the source of funding of any of the studies in any of their deliberations.”

² The expert panel evaluated studies based on the following rigorous set of pre-determined criteria:

“The Panel attended to multiple design and analysis characteristics in judging the acceptability of individual studies. It was our consensus that for a study to be acceptable for this review process, several conditions had to be met. First, effects related to litter of origin needed to be accounted for in design and statistical procedures. Second, animals needed to be dosed via the dam or directly under individual housing conditions. Concern that multiple exposures within a cage to different animals could cause cross-animal contamination across cage-mates led to the determination that this design was not acceptable. Third, a minimum of 6 animals per treatment condition needed to be used to provide minimal confidence in results. Fourth, if similar tests were conducted at multiple ages, the statistical analyses needed to account for repeated measurement in order not to inflate degrees of freedom. The Panel carefully considered the merits of each study according to these primary criteria, and the related design characteristics represent the most common reasons for judging a study to be unacceptable for our review process. Our intent was to have our review depend most heavily on studies that would have reduced risks for false negative or false positive findings.”

³ The eight citations are Morrissey et al., 1987; Kim et al., 2001 (2001b in the expert panel report); NTP, 1985 (1985a in the expert panel report); Tyl et al., 2002b; Tyl et al., 2008 (2006 in the expert panel report); Tyl et al., 2002a; Tinwell et al., 2002; and Tan et al., 2003.

Based on the criteria, data from seven of the eight studies cited by OEHHA are summarized in Section 3.4 of the expert panel report. Although not explicitly summarized in this section, the eighth study cited by OEHHA (NTP, 1985) was identified in Section 3.0 as a “high utility” study.

At this point in the expert panel report, no *conclusions* have been drawn about developmental toxicity or hazards of BPA; only the *data* from individual studies are summarized for further analysis and conclusions.

c. **NTP-CERHR EXPERT PANEL REPORT –
“SUMMARY AND CONCLUSION OF DEVELOPMENTAL HAZARDS”
(END OF SECTION 3.4)**

Based on the data summarized in Section 3.4, the expert panel next provided their *conclusions* on the developmental hazards of BPA. The entire set of conclusions is reproduced verbatim below (emphasis, where added, is identified by underlining):

“Summary and Conclusion of Developmental Hazards: There are sufficient data to conclude that bisphenol A does not cause malformations or birth defects in fetuses exposed during gestation at levels up to 640 mg/kg/day (rats) and 1000 mg/kg/day (mice) (Morrissey et al., 1987). This is consistent with the lack of malformations seen in offspring in multigenerational studies (Tyl et al., 2002b, 2006).

There are sufficient data to conclude that bisphenol A does not alter male or female fertility in rats or mice after gestational exposure up to doses of 450 mg/kg/day (Cagen et al., 1999b; Tyl et al., 2000a, 2002b; Ema et al., 2001).

There are sufficient data to conclude that bisphenol A does not change the age of puberty in male or female rats [NOAELs of 0.2 mg/kg/day (Ema et al., 2001) and 1823 mg/kg/day (Tyl et al., 2002b)]. While limited data available suggest an effect on the onset of female puberty in mice [LOAEL 0.2 mg/kg/day (Ryan and Vandenberg, 2006), 0.002 mg/kg/day, (Howdeshell et al., 1999)], the data are insufficient to conclude that bisphenol A accelerates puberty in female mice. The limited data available suggest, but are insufficient to conclude, that bisphenol A slightly delays the age of puberty in male mice at a LOAEL of ca. 550–800 mg/kg/day (Tyl et al., 2006).

There are sufficient data to conclude that bisphenol A exposure during development does not permanently affect prostate weight in adult rats or mice [NOAELs of: 1823 mg/kg/day (Tyl et al., 2002b), 600 mg/kg/day (Tyl et al., 2006), 4 mg/kg/day (Cagen et al., 1999b), 0.2 mg/kg/day (Ema et al., 2001), 50 mg/kg/day (Tinwell et al., 2002), and 320 mg/kg/day (Kwon et al., 2000). There are sufficient data to conclude that bisphenol A does not cause prostate cancer in rats or mice after adult exposure [calculated dose ranges of 25–400 mg/kg/day for rats, 600–3000 mg/kg/day, mice (NTP, 1982)]. There are slight suggestions, but insufficient data to conclude, that bisphenol A might predispose toward prostate cancer in rats in later life following developmental exposure

[at 10 µg/kg (Ho et al., 2006a)]. There are slight suggestions, but insufficient evidence to conclude, that fetal exposure to bisphenol A can contribute to urinary tract deformations in mice [10 µg/kg (Timms et al., 2005)].

There are sufficient data to suggest that developmental exposure to bisphenol A causes neural and behavioral alterations related to sexual dimorphism in rats and mice (ca. 2.5 mg/kg/day, gestation and lactation in rats, (Funabashi et al., 2004a); LOEL 0.00002 mg/kg/day, fetal mice, (Nishizawa et al., 2005a); 0.0002 mg/kg/day, fetal mice, (Nishizawa et al., 2003), 0.04 mg/kg/day, weaning to puberty, rats, (Ceccarelli et al., 2007); 0.1 mg/kg/day, GD 3–PND 20, rats, (Negishi et al., 2004a); 0.2 mg/kg/day, GD 3–PND 20, mice, (Ryan and Vandenberg, 2006); 0.01 mg/kg/day, GD 11–18, mice, (Laviola et al., 2005), although other studies report no change in a related measure, the size of the sexually dimorphic nucleus of the pre-optic area (SDN-POA) [300 µg/kg/day, rats (Nagao et al., 1999); NOEL of 320 mg/kg/day, rats, (Kwon et al., 2000)].”

It is readily apparent that none of the *hazard conclusions* “formally identify” BPA as causing developmental toxicity or could otherwise justify listing BPA under Proposition 65. While the expert panel identified relevant *data* in Section 3.4, that data did not support any *hazard conclusions* that BPA causes developmental toxicity.

In several cases suggestive evidence was identified, but suggestive evidence is not sufficient to support a listing under Proposition 65. Under the Proposition 65 authoritative bodies mechanism, chemicals may be listed only if they are *formally identified as causing reproductive toxicity*. That strict requirement is quite different from merely providing suggestive evidence. In addition to not being sufficient to support a clear hazard conclusion, the suggestive evidence is not related to the developmental effects in the high dose studies cited by OEHHA. In the NTP Brief, suggestive evidence was considered to be inconclusive. As noted in our previous comments, additional research has been completed and reduces the concern that BPA causes developmental effects.

**d. NTP-CERHR EXPERT PANEL REPORT –
SECTION “5.0 SUMMARIES, CONCLUSIONS, AND CRITICAL DATA NEEDS”**

The hazard conclusions above were then repeated in Section 5.1 (“Developmental Toxicity”), which is part of the final section of the expert panel report. As above, the entire set of conclusions from this section is reproduced verbatim below (emphasis, where added, is identified by underlining):

“No data on the effects of human developmental exposure to bisphenol A are available. There is a large literature describing studies in rodents and some work in other species. A large experimental animal literature was reviewed, assessed for its utility, and weighed based on the criteria established by this Panel.

From the rodent studies we can conclude that bisphenol A:

- Does not cause malformations or birth defects in rats or mice at levels up to the highest doses evaluated: 640 mg/kg/day (rats) and 1250 mg/kg/day (mice).
- Does not alter male or female fertility after gestational exposure up to doses of 450 mg/kg bw/day in the rat and 600 mg/kg bw/day in the mouse (highest dose levels evaluated).
- Does not permanently affect prostate weight at doses up to 475 mg/kg/day in adult rats or 600 mg/kg/day in mice.
- Does not cause prostate cancer in rats or mice after adult exposure at up to 148 or 600 mg/kg/day, respectively.”
- Does change the age of puberty in male or female rats at high doses (ca. 475 mg/kg/day).

Rodent studies suggest that bisphenol A:

- Causes neural and behavioral alterations related to disruptions in normal sex differences in rats and mice. (0.01–0.2 mg/kg/day).

The data on bisphenol A are insufficient to reach a firm conclusion about:

- A change in the onset of puberty in male rats or mice at doses up to 475–600 mg/kg/day.
- An acceleration in the age of onset of puberty at a low dose in female mice at 0.0024 mg/kg/day, the only dose tested.
- Whether Bisphenol A predisposes rats toward prostate cancer or mice toward urinary tract deformations.”

Not one of the developmental toxicity conclusions in Section 5.1 can be read as “formally identifying” BPA as causing developmental toxicity; a formal identification is necessary to support a Proposition 65 listing of BPA.

The expert panel also provided their overall “level of concern” conclusions in Section 5.4 entitled “Overall Conclusions”. The overall conclusions, which are expressed relative to current estimates of general population exposure levels in the U.S., do not support listing BPA as causing developmental toxicity. The most severe overall conclusion was “some concern,” which is the mid-point on a 5-level scale and was based on suggestive evidence – but not definitive evidence – from low dose studies. In fact the expert panel was quite explicit that the evidence was neither clear nor definitive; it stated “[t]he panel expresses ‘some’ concern for these effects

even though it is not clear that the reported effects constitute an adverse toxicological response.” The other overall conclusions, based on high-dose studies, were of either “minimal” or “negligible” concern. Moreover, as our previous comments demonstrated, the findings of scientific studies published since the issuance of the NTP-CERHR Monograph reduce the level of “some concern” to “negligible concern.”

One of the developmental effects cited by OEHHA as a basis for listing BPA as causing developmental toxicity is delayed puberty. However, as summarized in the subsections above, and described in detail in the corresponding sections of the expert panel report, the data and conclusions on the potential effect of BPA on age of puberty are inconsistent. The inconsistency between studies and the lack of concordance between rats and mice precludes a clear weight-of-evidence conclusion on whether BPA affects age of puberty at high doses.

Perhaps more importantly, the underlying studies that suggest effects on puberty include both prenatal and postnatal exposure. Only prenatal exposures are relevant for developmental effects under Proposition 65 and, as a result, studies that involved both prenatal and postnatal exposure do not meet the Section 25306(g) sufficiency criteria. There is no basis to conclude that the observed effects are the result of prenatal exposures and the burden would be on OEHHA to clearly demonstrate with scientific data that the effects are due to prenatal exposure. In this regard, it is notable that one of the eight studies (Tan et al., 2003) cited by OEHHA as a basis for listing BPA as causing developmental toxicity reported a delay in preputial separation in rats with postnatal exposure to high doses of BPA. Although this study is not suitable to support listing BPA as causing developmental toxicity, due to the exclusive use of postnatal exposure, it does suggest that the effects on puberty seen in some studies with both prenatal and postnatal exposure are the result of the postnatal dosing.

**e. NTP BRIEF – FIGURE 2B
“THE WEIGHT OF EVIDENCE THAT BISPHENOL A CAUSES ADVERSE
DEVELOPMENTAL OR REPRODUCTIVE EFFECTS IN LABORATORY
ANIMALS”**

OEHHA’s Notice of Intent to List BPA asserts that the NTP-CERHR Monograph satisfies the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations. More specifically, OEHHA asserts that a statement in Figure 2b of the NTP Brief regarding clear evidence of adverse developmental effects at high levels of exposure provides the formal identification necessary to list BPA as causing developmental toxicity.

But the NTP-CERHR Monograph must be evaluated in its entirety. Extracting isolated statements from one part of the Monograph without the context and detail provided by the full Monograph is inappropriate.

The meaning of Figure 2b is clear from the extensive documentation in the expert panel report. As described in the subsections above, the expert panel clearly delineated among *data* on

individual studies (Section 3.0 of the expert panel report), *summaries* of the most important data (Section 3.4 of the expert panel report) and *conclusions* of developmental hazards (end of Section 3.4 and Section 5.1 of the expert panel report). From this detailed and well-documented record, it is clear that Figure 2b is derived from the *data* summarized in Section 3.4 and bears no relationship to the *conclusions* of developmental hazards listed at the end of Section 3.4.

Accordingly, statements in Figure 2b of the NTP Brief summarize the *data* on developmental effects but are not the NTP Brief's *conclusions* on hazards and, therefore, do not provide the formal identification necessary to list BPA as causing developmental toxicity. Consistent with the expert panel report, the NTP Brief further evaluated the *data* in Figure 2b in the context of human exposure to derive NTP's level of concern *conclusions* presented in Figure 3, and those conclusions found only minimal or negligible concern arising from the high-dose studies. As noted above, the *conclusions* of developmental hazards at the end of Section 3.4 in the expert panel report are also insufficient to support listing BPA as causing developmental toxicity under Proposition 65.

f. COMPARISON OF THE NTP-CERHR MONOGRAPH ON BPA WITH MONOGRAPHS ON EIGHT OTHER CHEMICALS LISTED UNDER PROPOSITION 65 CONFIRMS THAT NTP-CERHR DID NOT CONCLUDE BPA CAUSES DEVELOPMENTAL TOXICITY

The NTP-CERHR expert panel that evaluated the potential reproductive and developmental toxicity of BPA followed a well-recognized process and format for its evaluation. First, the expert panel evaluated studies one-by-one and documented their evaluations in Section 3.0. Second, the expert panel summarized the most important and relevant data in Section 3.4. Third, the expert panel analyzed the key developmental toxicity data summarized in Section 3.4 and drew conclusions on whether or not BPA is a developmental toxicity hazard. Finally, a synopsis of the key data summary and hazard conclusions on all endpoints is provided in Section 5.⁴

This process and reporting format is not unique to the BPA evaluation process. In fact, it is precisely what was prescribed in the guidelines that were provided to NTP-CERHR expert panels.⁵ Relevant sections from the NTP-CERHR expert panel guidelines for developmental toxicity are reproduced verbatim below (emphasis, where added, is identified by underlining):

⁴ Reproductive toxicity data was evaluated in a parallel process and documented in Sections 4 and 5. That data and process are not discussed here since OEHHA's Notice of Intent to List BPA with respect to reproductive toxicity is based on a "developmental endpoint."

⁵ Shelby, M. D. 2005. National Toxicology Program Center for the Evaluation of Risks to Human Reproduction: Guidelines for CERHR expert panel members. Birth Defects Research (Part B). 74:9-16.

“3.4. Summary of Developmental Toxicity Data.

This section provides a concise summary of those studies reviewed in sections 3.1 and 3.2 and considered to be of adequate quality for use in making an evaluation of developmental toxicity. Descriptions of studies on which critical comments have been noted in square brackets need not be brought forward to the summary if the study was deemed not of adequate (refers to individual studies) quality or completeness to contribute to the evaluation. Results reported only in abstracts should not contribute to the conclusions.

It is recognized that each chemical evaluated will involve a unique array of data. However, a statement as to whether or not the chemical is considered a developmental hazard is to be presented. The following template provides a general format and guidance on the information that should be included in this statement:

There is (sufficient, insufficient) evidence in (animals and/or humans) that (chemical X) (does or does not) cause developmental toxicity when exposure is (route, dose range, timing, duration). The data are (relevant, assumed relevant, irrelevant) to consideration of human risk.⁽¹⁾

sufficient/insufficient is a scientific judgment based on the amount, quality, and types of available data.

relevant = human data, or animal data for which pharmacokinetic and mechanism information is adequate to demonstrate a particular similarity to humans.

assumed relevant = no information available to modify the assumption that the data are relevant.

irrelevant = pharmacokinetic or mechanistic features of the animal models are known and demonstrated to be inconsistent with human exposure or response.”

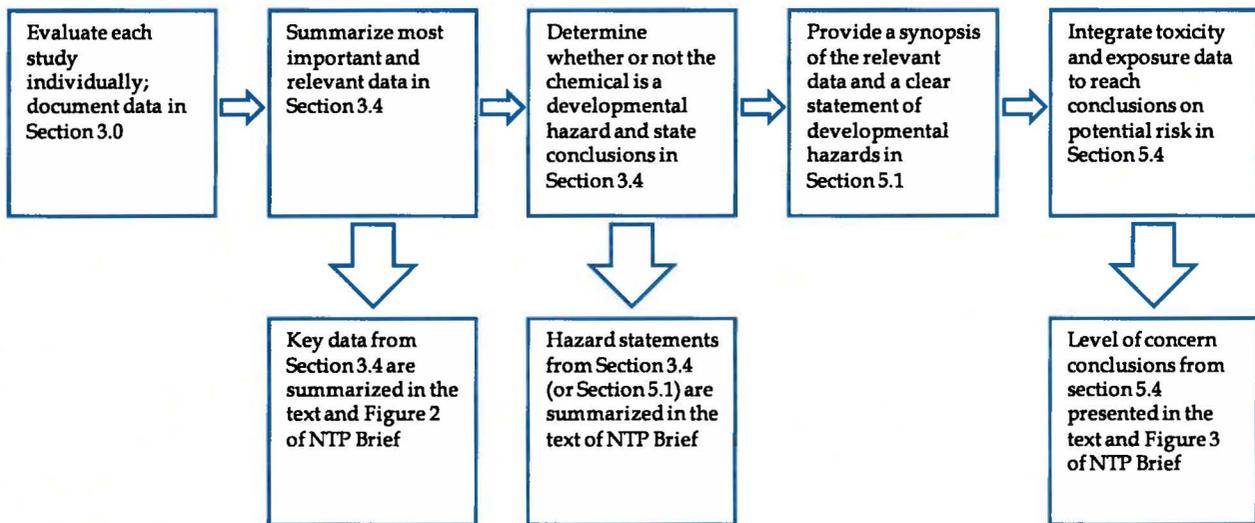
- (1) This template is taken from the National Research Council Report, Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity. Subcommittee on Reproductive and Developmental Toxicology, Committee on Toxicology, Board on Environmental Studies and Toxicology, Commission on Life Sciences. Washington, DC: National Academy Press, 2001.

“5.0. Summaries, Conclusions, and Critical Data Needs

5.1. Developmental Toxicity. This section of the expert panel report provides a brief synopsis of the summaries presented in section 3. It should state whether or not the scientific data reviewed has led the panel to conclude that the chemical assessed is likely or is not likely to be a potential developmental hazard to humans. When data are not sufficient to reach such a conclusion, this should be clearly stated. This evaluation should be made without consideration of human exposure levels or the numbers or subpopulations of people who may be exposed.”

Of particular significance is the explicit requirement for the expert panels to determine in Section 5.1 whether *or not* the chemical being evaluated is a developmental hazard and to clearly state this conclusion. The key elements of the NTP-CERHR expert panel evaluation and reporting process, plus the links between that report and the NTP Brief, are illustrated in the Figure 1 flow chart below. Of particular significance, Figure 2 in the NTP Brief is a *data summary* and does not represent *hazard conclusions*.

FIGURE 1
NTP-CERHR EXPERT PANEL EVALUATION PROCESS AND REPORTING FORMAT, AND
LINKAGE OF KEY ELEMENTS WITH NTP BRIEF



A consistent relationship between the expert panel evaluation and the NTP Brief is also clear from an examination of the eight chemicals that have been listed as causing reproductive or developmental toxicity under Proposition 65 based on NTP-CERHR Monographs. The conclusions from these Monographs amply illustrate the consistent evaluation process and format of expert panel reports, and how the conclusions from the expert panel reports were translated into the NTP Brief format. These points are summarized in Table 1 below. With some minor deviations in wording, in each case the expert panel reported clear conclusions on reproductive and developmental hazards. Also in each case, these hazard conclusions were translated to the NTP Brief. In every case, both the expert panel report and the NTP Brief clearly stated that the subject chemical is a developmental or reproductive hazard.

These eight Monographs and the NTP-CERHR Monograph on BPA followed the same process prescribed in the NTP-CERHR expert panel guidelines.

- Section 3.0 - Evaluations of individual studies are provided in Section 3.0 of the expert panel report.
- Section 3.4 - A summary of the most important and relevant data is provided in Section 3.4.
- The data summary is followed by a clear statement of developmental hazards at the end of Section 3.4.
- Section 5.4 - Finally, the key data is integrated with human exposure data to derive “level of concern” potential risk conclusions in Section 5.4.

Although the process and pattern are the same, there is an extremely important, and unavoidable, distinction between BPA and the other eight chemicals. Neither the expert panel report nor the NTP Brief document *any* developmental hazards for BPA (see Table 2 for a summary of the expert panel report and NTP Brief conclusions on developmental hazards). The expert panel report clearly stated that BPA does *not* cause developmental toxicity and the NTP Brief did not deviate from the clear and unambiguous hazard conclusions of the expert panel. In agreement with the expert panel report, the NTP Brief only stated that “the possibility that bisphenol A may alter human development cannot be dismissed.” A possibility that cannot be dismissed is quite different from finding that BPA has been clearly shown to cause developmental toxicity.

In the context of the requirements for listing a chemical under Proposition 65, the NTP-CERHR Monograph for BPA did *not* formally identify BPA as causing developmental toxicity. In fact, as clearly documented in the expert panel report and the NTP Brief, the NTP-CERHR Monograph did just the opposite. The NTP-CERHR Monograph formally identified BPA as NOT causing developmental toxicity.

As OEHHA has repeatedly stated, Proposition 65 does not allow OEHHA to substitute its judgment for the authoritative body’s judgment. Accordingly, OEHHA may not list BPA as causing developmental toxicity on the basis of the NTP-CERHR Monograph. In light of the clear record of the NPT-CERHR Monograph, to list BPA as causing developmental toxicity would represent an egregious abuse of discretion.

TABLE 1
NTP-CERHR MONOGRAPH HAZARD CONCLUSIONS FOR EIGHT CHEMICALS
LISTED UNDER PROPOSITION 65

| CHEMICAL | EXPERT PANEL HAZARD CONCLUSIONS | NTP BRIEF HAZARD CONCLUSIONS |
|------------------------|---|--|
| Acrylamide | <p>Section 5.1 Developmental Toxicity: <u>These data are sufficient to conclude that acrylamide is a developmental toxicant in rats...</u></p> <p>Section 5.2 Reproductive Toxicity: <u>Collectively, these data clearly show the reproductive toxicity of acrylamide in rats and mice, mediated largely by dominant lethality.</u></p> | <p>In this case, recognizing the absence of human data and clear evidence of adverse effects in laboratory animals (Figure 2), the NTP judges <u>the scientific evidence sufficient to conclude that acrylamide may adversely affect human development and/or reproduction if exposures are sufficiently high.</u></p> |
| 1-Bromopropane | <p>5.1 Summary and Conclusions of Reproductive and Developmental Hazards: <u>The data are sufficient to conclude that 1-BP caused developmental toxicity...</u> <u>There is sufficient evidence to conclude that inhaled 1-BP causes reproductive toxicity in male and female rats.</u></p> | <p>Recognizing the lack of data on 1-BP toxicity in humans, the NTP judges <u>the scientific evidence of effects in laboratory animals sufficient to conclude that 1-BP may adversely affect human development and reproduction if exposures are sufficiently high.</u></p> |
| 2-Bromopropane | <p>5.1 Summary and Conclusions of Reproductive and Developmental Hazards: <u>Therefore the toxicology data from male rats, as from female rats, provide support for the contention, based on limited epidemiological data, that 2-BP is a reproductive hazard in humans.</u></p> | <p>Recognizing the limited evidence of reproductive effects in occupationally exposed humans and clear evidence of effects in laboratory animals, the NTP judges <u>the scientific evidence sufficient to conclude that 2-BP may adversely affect human reproduction if exposures are sufficiently high.</u></p> |
| Butyl Benzyl Phthalate | <p>Section 5.3 Expert Panel Conclusions: <u>With regard to developmental and reproductive toxicity, the database is sufficient to judge that oral exposure to BBP can cause developmental toxicity in rats and mice, and reproductive toxicity in rats..</u></p> | <p>Recognizing the lack of human data and the evidence of BBP effects in laboratory animals, the NTP judges <u>the scientific evidence sufficient to support the levels of concern for effects on development and reproduction expressed below (Fig. 3).</u></p> |

TABLE 1
NTP-CERHR MONOGRAPH HAZARD CONCLUSIONS FOR EIGHT CHEMICALS
LISTED UNDER PROPOSITION 65

| CHEMICAL | EXPERT PANEL HAZARD CONCLUSIONS | NTP BRIEF HAZARD CONCLUSIONS |
|-----------------------|--|---|
| Dibutyl Phthalate | Section 5.1.4 Reproductive Toxicity: <u>Collectively, the data are sufficient to show that oral exposure to DBP can cause reproductive toxicity in male rats, mice, and guinea pigs.</u> | In this case, recognizing the lack of human data and the clear evidence of effects in laboratory animals (Fig. 2), the NTP judges <u>the scientific evidence sufficient to conclude that DBP may adversely affect human reproduction or development if exposures are sufficiently high.</u> |
| Di-n-Hexyl Phthalate | Section 5.3 Expert Panel Conclusions: <u>The data are sufficient to indicate that DnHP is a reproductive toxicant in both sexes of two rodent species following oral exposure.</u> | Second, although <u>there is good evidence of reproductive toxicity in mice and rats, the data are not sufficient to determine the exposure levels at which no adverse reproductive effects would occur in rodents.</u> |
| Di-Isodecyl Phthalate | Section 5.3 Expert Panel Conclusions: <u>The toxicology database is sufficient to determine that oral maternal exposure to DIDP can result in developmental toxicity to the conceptus.</u> | In this case, recognizing the lack of human data and the evidence of effects in laboratory animals, the NTP judges <u>the scientific evidence sufficient to conclude that DIDP is a developmental toxicant and could adversely affect human development if the levels of exposure were sufficiently high.</u> |
| Methanol | 5.1 Summary and Conclusions of Reproductive and Developmental Hazards: <u>The data in mice and rats were consistent and deemed to be sufficient to determine that inhalation or oral exposure to methanol is a developmental hazard.</u> | In this case, recognizing the lack of human data and the clear evidence of laboratory animal effects (Figure 2), the NTP judges <u>the scientific evidence sufficient to conclude that methanol may adversely affect human development if exposures are sufficiently high.</u> |

TABLE 2
NTP-CERHR MONOGRAPH HAZARD CONCLUSIONS FOR BPA

| CHEMICAL | EXPERT PANEL HAZARD CONCLUSIONS | NTP BRIEF HAZARD CONCLUSIONS |
|-------------|---|--|
| Bisphenol A | <p>5.0 Summaries, Conclusions, and Critical Data Needs</p> <p>“No data on the effects of human developmental exposure to bisphenol A are available. There is a large literature describing studies in rodents and some work in other species. A large experimental animal literature was reviewed, assessed for its utility, and weighed based on the criteria established by this Panel.</p> <p><u>From the rodent studies we can conclude that bisphenol A:</u></p> <ul style="list-style-type: none"> • <u>Does not cause malformations or birth defects</u> in rats or mice at levels up to the highest doses evaluated: 640 mg/kg/day (rats) and 1250 mg/kg/day (mice). • <u>Does not alter</u> male or female fertility after gestational exposure up to doses of 450 mg/kg bw/day in the rat and 600 mg/kg bw/day in the mouse (highest dose levels evaluated). • <u>Does not permanently affect</u> prostate weight at doses up to 475 mg/kg/day in adult rats or 600 mg/kg/day in mice. • <u>Does not cause</u> prostate cancer in rats or mice after adult exposure at up to 148 or 600 mg/kg/day, respectively.” • <u>Does change</u> the age of puberty in male or female rats at high doses (ca. 475 mg/kg/day). <p>Rodent studies <u>suggest</u> that bisphenol A:</p> <ul style="list-style-type: none"> • Causes neural and behavioral alterations related to disruptions in normal sex differences in rats and mice. (0.01–0.2 mg/kg/day). <p><u>The data on bisphenol A are insufficient to reach a firm conclusion about:</u></p> <ul style="list-style-type: none"> • A change in the onset of puberty in male rats or mice at doses up to 475–600 mg/kg/day. • An acceleration in the age of onset of puberty at a low dose in female mice at 0.0024 mg/kg/day, the only dose tested. • Whether Bisphenol A predisposes rats toward prostate cancer or mice toward urinary tract deformations.” | <p>Recognizing 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 discussed in more detail below, <u>the possibility that bisphenol A may alter human development cannot be dismissed</u> (see Figure 3).</p> |

2. EXPERT PROFESSIONAL JUDGMENTS DEMONSTRATE THAT THE SCIENTIFIC DATA DO NOT SUPPORT A CONCLUSION THAT BPA CAUSES DEVELOPMENTAL TOXICITY

The judgments of the experts on the NTP-CERHR panel are not the only expert judgments OEHHA apparently intends to reject, however. A number of highly qualified toxicologists have submitted written comments to OEHHA stating their professional, expert judgments that the degree of maternal toxicity in the “high dose” studies was excessive, and accounted for the developmental effects observed in the offspring. Based on their expertise and decades of experience in conducting studies and assessing scientific data, BPA cannot, therefore, be considered to cause developmental toxicity.

a. THE MAY 12, 2010 COMMENTS OF ANTHONY R. SCIALLI, M.D.

Dr. Anthony Scialli submitted written comments on the proposed listing of BPA on May 12, 2010. Dr. Scialli is both a medical doctor and a toxicologist with specific expertise in the evaluation of animal data on developmental toxicology. He is a past President of the Teratology Society, the largest and most respected professional society in the field of birth defects and developmental toxicity. He has served as a consultant on issues of developmental toxicology to the U.S. Food and Drug Administration and Environmental Protection Agency, among other organizations, and from 2004 to 2007 was the principal investigator for his employer, Tetra Tech Sciences, in its contract with NTP-CERHR; as a result, he is very familiar with NTP-CERHR’s goals and methodologies. Dr. Scialli’s written comments addressed both the subject of systemic or maternal toxicity in general, and also the nature and degree of maternal toxicity observed in each of the “high dose” studies on BPA cited by OEHHA in particular. Dr. Scialli concluded:

“In the case of the six studies identified as showing reproductive or developmental effects, the effects occurred with exposure levels that produced clear parental/adult toxicity of a degree sufficient to explain the reproductive or developmental effects; moreover, the developmental effects were those expected to occur from adult toxicity. In my opinion, the data do not support the listing of bisphenol A as a reproductive or developmental toxicant under Proposition 65.”

In its response to comments dated January 22, 2013, OEHHA was dismissive of Dr. Scialli’s professional judgment: “While the comments describe associations between maternal and developmental toxicity, no evidence is presented that maternal toxicity causes the developmental toxicity observed or precludes interpretation of the study [*sic*]” (emphasis added). OEHHA concluded with some references to its position that “existing authoritative guidelines do not preclude the identification of developmental toxicity when associated with maternal toxicity or even when it is caused by maternal toxicity.” While that may be a valid generalization, it entirely misses the point that whether developmental effects in offspring are secondary to maternal toxicity in a *particular* study is inherently a matter of interpretation and expert

judgment. Dr. Scialli had stated that in his expert judgment, the effects observed in these studies were secondary to maternal toxicity. Without putting it so bluntly, OEHHA's response was that its expertise was greater and that Dr. Scialli was wrong.

b. THE MAY 12, 2010 COMMENTS OF ROCHELLE TYL, PH.D., DABT

Dr. Rochelle Tyl, Ph.D., DABT, also submitted detailed written comments on the proposed listing of BPA. Like Dr. Scialli, Dr. Tyl is a very eminent toxicologist with impeccable credentials in reproductive and developmental toxicology – and also a past President of the Teratology Society. In addition to her extensive list of professional degrees and associations, Dr. Tyl has served as Study Director for more than 50 multi-generation studies and more than 150 developmental toxicity studies in experimental animals, and has authored or co-authored more than 100 peer-reviewed articles, 18 book chapters, more than 100 abstracts, and hundreds of study reports. As OEHHA is aware, Dr. Tyl was the Study Director for three of the studies listed in the 2008 NTP-CERHR Monograph on which OEHHA proposes to base the listing of BPA, and presented expert testimony at the July 15, 2009 DARTIC meeting at which the committee voted 7-0 *not* to list BPA.

In nineteen pages of written comments dated May 12, 2010, Dr. Tyl addressed the role and interpretation of maternal toxicity in animal studies generally, and one-by-one analyzed the types and degrees of maternal toxicity and developmental toxicity observed in the “high dose” studies cited by OEHHA in support of the proposed listing. Her discussion of the subject and the particular studies was lengthy and provided references to study data to support her judgment. Her conclusions were clearly stated:

“1. The scientific evidence clearly indicates that BPA is not a selective developmental toxicant. Developmental toxicity occurs only at very high oral BPA doses in the presence of profound maternal toxicity. At lower doses with less, but still significant, maternal toxicity, there is no developmental toxicity.

* * * * *

5. Therefore, BPA does not satisfy the criteria for listing under Proposition 65.

Conclusions

This reviewer strongly believes, based on scientific data, that embryo-fetal offspring toxicity from exposure to high doses of BPA is caused by maternal toxicity.”

In its response dated January 22, 2013, OEHHA was as dismissive of Dr. Tyl's professional judgment as it was of Dr. Scialli's professional judgment. In response to Dr. Tyl's lengthy discussion of the issues related to the interpretation of the role of maternal toxicity in animal studies generally, OEHHA complained that Dr. Tyl's interpretations deviated from the

1991 EPA Guidelines for Developmental Toxicity Risk Assessment “as the exact wording of the comments does not appear in the guidelines document” and concluded that “OEHHA considers the definition of maternal toxicity in the comments to be Dr. Tyl’s opinion and interpretation of the [EPA] Guidelines...” In response to Dr. Tyl’s detailed discussion of the degree and role of maternal toxicity in the particular studies on BPA on which OEHHA relies to support the proposed listing, OEHHA continued its approach of rejecting the comments as mere “opinion”:

“Response: As described above, OEHHA relies on the generally accepted scientific principle that developmental toxicity occurring at the same doses as maternal toxicity is not to be dismissed as secondary to maternal toxicity. The comments provide the opinion of the commenter about the relationship between maternal and developmental effects, however, no evidence is provided in the comments that the developmental toxicity of BPA was secondary to maternal toxicity.” (Emphasis added.)

In its response to Dr. Tyl’s clear statement of her expert judgment in her conclusions, OEHHA repeats the “opinion” theme, ignoring the scientific data cited by Dr. Tyl in support of her expert judgment, and adds an unsupported reference to NTP-CERHR’s review of the studies in question:

“Although the commenter has offered her opinion of the relationship between maternal and developmental effects in the studies relied upon by NTP, she has provided no factual information to demonstrate either that NTP failed to consider maternal toxicity in concluding that there is clear evidence that BPA causes developmental toxicity, or that NTP made factual errors in doing so.” (Emphasis added.)

Similar to OEHHA’s response to Dr. Scialli’s expert judgment, this response falsely implies that OEHHA’s interpretation of the relationship between maternal and developmental toxicity in the studies in question is any less based on “opinion” than Dr. Tyl’s interpretation. To the contrary, Dr. Tyl and Dr. Scialli have greater expertise in this area than OEHHA. Moreover, OEHHA’s response introduces a groundless argument that NTP made a specific conclusion that the developmental effects that it observed were *not* secondary to the maternal toxicity observed in the same studies. There is no basis for that claim, and thus no reason for Dr. Tyl to have addressed it.

c. THE MAY 13, 2010 COMMENTS OF CAROLE A. KIMMEL, PH.D. AND JAMES C. LAMB, PH.D., DABT AND FELLOW ATS

Doctors Carole A. Kimmel and James C. Lamb also submitted joint comments on the proposed listing of BPA on May 13, 2010. Dr. Kimmel has over 40 years of experience in reproductive and developmental toxicology; led the National Toxicology Program’s Reproductive and Developmental Toxicology Program from 1980 to 1984; and from 1984 to 2004, was a Senior Scientist in USEPA’s National Center for Environmental Assessment, with a

particular focus on reproductive and developmental toxicity and neurotoxicity risk assessment. Significantly, Dr. Kimmel played a leadership role in developing USEPA's 1991 Guidelines for Developmental Toxicity Risk Assessment, a document OEHHA repeatedly cites as authoritative. Dr. Kimmel was on the organizing panel that led to the creation of the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction.

Dr. Lamb was also on the organizing panel that led to the creation of NTP-CERHR; has over 30 years of experience in toxicology and risk assessment; and was the Head of the Fertility and Reproduction Group at the NTP. Dr. Lamb has served on several National Academy of Sciences committees on risk assessment, endocrine disruption and toxicology, and has served as President of the American Board of Toxicology.

Drs. Kimmel and Lamb provided lengthy and detailed comments that addressed both the NTP-CERHR process and approach generally and the specific "high dose" animal studies from the NTP-CERHR Monograph on which OEHHA is proposing to list BPA. Drs. Kimmel and Lamb stated, based on their many years of experience with NTP-CERHR's processes and their review of the studies in question, that in their expert judgment NTP-CERHR's statement in the 2008 report that the high dose animal studies showed "clear evidence of developmental effects" did not represent a conclusion by NTP-CERHR that those effects were not secondary to maternal toxicity. Drs. Kimmel and Lamb then examined the specific results of the studies in question, discussed the observed effects in the offspring in relation to the effects observed in the dams at the same and in some cases, lower doses, and stated their expert judgment that the effects observed in the offspring were all secondary to maternal toxicity.

"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 were seen at dose levels that also produced maternal/adult systemic toxicity greater than what would be considered minimal toxicity. 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."

In its response dated January 22, 2013, OEHHA expressed various disagreements with Drs. Kimmel's and Lamb's characterizations of the severity of maternal toxicity observed in some of the studies. For the most part, however, OEHHA took the position that it wasn't a matter of OEHHA's opinion, but rather of NTP-CERHR's opinion, and that NTP-CERHR had

reached a clear conclusion that the effects observed in the offspring in the studies were *not* secondary to maternal toxicity:

“Although the commenter’s [sic] 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 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.”

This assertion by OEHHA is both internally inconsistent and factually incorrect. It is internally inconsistent in that OEHHA’s responses to Drs. Scialli and Tyl, discussed previously, emphasized OEHHA’s *own* disagreement with the “opinions” stated by those commenters, and *not* the alleged fact that NTP-CERHR had made that decision and that “Proposition 65 does not allow OEHHA to substitute its judgment for [NTP-CERHR’s judgment].” It is factually incorrect as well. OEHHA’s claim that NTP-CERHR made a clear judgment that the effects observed at high doses were not secondary to maternal toxicity is based (1) in part on irrelevant, speculative, and *post hoc* statements by an NTP spokesman, and (2) in part on a few selective quotations from the NTP-CERHR Monograph (specifically the expert panel portion of the NTP-CERHR Monograph).

Specifically, OEHHA quotes a statement made by Dr. John Bucher of NTP at a DARTIC meeting on July 12, 2011 – three years *after* the date of the NTP-CERHR Monograph on BPA. Dr. Bucher’s statement that he “thinks” that when it considers animal studies, NTP “takes into consideration maternal toxicity” is presumably an honest generalization on his part, but it is not testimony that he personally knew that NTP-CERHR specifically weighed the significance of maternal toxicity before making its statement of “clear evidence of developmental effects at high doses” in the 2008 report. A fair review of the 2008 Monograph as a whole much more strongly supports the inference that NTP-CERHR reasonably did not think it was necessary to consider the role of maternal toxicity in those studies because the developmental effects observed *were irrelevant to human risk whether they were secondary to maternal toxicity or not*, since the exposure levels causing the effects were tens of thousands of times higher than any remotely plausible human exposure. That inference is supported by the fact that NTP-CERHR expressed either a “*minimal*” or “*negligible level of concern*” with regard to the developmental effects observed in those studies. The few selective references to statements about Kim, Morrissey and Berger in the NTP-CERHR expert panel report similarly do not constitute a “conclusion” by NTP-CERHR with regard to the role of maternal toxicity in the studies.

As a point of fact, the NTP-CERHR expert panels operated with written guidelines for literature evaluation and expert panel report preparation. Those guidelines, which were also published in the scientific literature,⁶ make no mention whatsoever of maternal toxicity as a factor to consider in the evaluation of studies in experimental studies. Although maternal toxicity was occasionally mentioned in regard to specific studies described in Section 3.0 of the expert panel report, there is no indication that maternal toxicity was systematically considered as a factor in the data summarized in Section 3.4 of the expert panel report, which corresponds to the data summarized in Figure 2b of the NTP Brief.

d. THE DECEMBER 5, 2011 AND JANUARY 13, 2012 COMMENTS OF JAMES C. LAMB, PH.D., DABT, FELLOW ATS; CAROLE A. KIMMEL, PH.D.; ANTHONY SCIALLI, M.D.; AND ROCHELLE TYL, PH.D.

Finally, as OEHHA is aware, a meeting was held in OEHHA's offices on December 5, 2011 to discuss the subject of the interpretation of the role of maternal toxicity in animal studies on developmental toxicity, and more particularly, OEHHA's very restrictive approach to that subject based on an interpretation of USEPA's 1991 Guidelines for Developmental Toxicity Risk Assessment. This meeting was scheduled at ACC's request and was attended by Drs. Lamb, Kimmel, Tyl and Scialli, among others. A letter dated January 13, 2012 (attached again for the record) was sent to Dr. Alexeeff after the meeting summarizing the discussions at the meeting, and forwarding full copies of three of the "high dose" studies cited in the NTP-CERHR Monograph, and now relied upon by OEHHA in support of the proposed listing of BPA. Both at the meeting and in the letter, the four scientists made points similar to those discussed above. In addition, the principal author of the USEPA Guidelines, which had largely been written by Dr. Kimmel and with which all four scientists were familiar from many decades of experience and scores of studies, noted that OEHHA was misinterpreting the Guidelines and urged OEHHA to revisit the agency's interpretation. OEHHA has not responded to the letter, but its responses to the letters discussed above indicate that it has rejected all the information and argument submitted by these four scientists.

3. THE STATE'S EXPERTS ON THE DARTIC REVIEWED THE NTP-CERHR MONOGRAPH AND UNANIMOUSLY DETERMINED NOT TO LIST BPA UNDER PROPOSITION 65; OEHHA CANNOT REACH A DIFFERENT CONCLUSION

The state's own "qualified experts," the Developmental and Reproductive Toxicant Identification Committee ("DARTIC"), considered whether to list BPA as causing developmental or reproductive toxicity on the basis of the available scientific evidence at its

⁶ Shelby, M. D. 2005. National Toxicology Program Center for the Evaluation of Risks to Human Reproduction: Guidelines for CERHR expert panel members. Birth Defects Research (Part B). 74:9-16.

public meeting on July 15, 2009. The committee members present at the meeting and their affiliations are listed below:

- Dorothy T. Burk, Ph.D. (University of the Pacific)
- Ellen B. Gold, Ph.D. (University of California, Davis)
- Calvin Hobel, M.D. (Cedars-Sinai Medical Center)
- Kenneth L. Jones, M.D. (University of California, San Diego)
- Carl Keen, Ph.D. (University of California, Davis)
- Linda G. Roberts, Ph.D. (Chevron Research and Technology Company)
- La Donna White, M.D. (Mercy Family Practice Residency Program)

The evidence considered by the DARTIC at that meeting prominently included the NTP-CERHR Monograph on BPA and the very list of animal studies discussed in the Monograph on which OEHHA now proposes to list BPA. Those specific studies were the subject of expert written submissions prior to the meeting, and expert oral testimony at the meeting.

Consistent with the actual *conclusions* of developmental hazards in the expert panel report, the DARTIC's verdict was unanimous, a vote of 7-0, that the scientific data did *not* clearly show that BPA causes developmental toxicity. The discussion among the DARTIC members of issues of study interpretation prior to the 7-0 vote explicitly focused on maternal toxicity in the "high dose" studies and made it quite clear that the Committee members considered the effects observed in the offspring to be secondary to maternal toxicity. It is also quite clear from the discussion that the Committee members considered the *entire* NTP-CERHR Monograph, not just the NPT Brief in isolation, understood the distinction between *data* presented in the expert panel report and the NTP Brief versus *conclusions* on developmental hazards, and agreed with the conclusions of the NTP-CERHR Monograph. For example, the extract below from the meeting transcript precisely illustrates this point:

"COMMITTEE MEMBER ROBERTS: If I can ask, I'm looking at their publication. And in their publication Birth Defects Research Part B page 329, what they have under summary and conclusion of developmental hazards, "There are sufficient data to conclude that Bisphenol A does not cause malformations or birth defects in fetuses, exposed during gestation at levels up to 640 milligrams per kilogram per day rather than the 1,000 milligrams per kilogram per day mice. This is consistent with the lack of malformation seen in offspring of multi-gen. There are sufficient data to conclude that Bisphenol A does not alter male or female fertility in rats after gestational exposure." The next paragraph goes, "There are sufficient data to conclude that Bisphenol A does not change the age of puberty in male or female rats." Next paragraph, "There are sufficient data to conclude that Bisphenol A exposure during development does not permanently affect prostate weight in adult rats or mice. And then the final paragraph,

there are sufficient data to suggest that developmental exposures to Bisphenol A causes neural and behavioral alterations related to sexual dimorphism in rats and mice.”

In coming to its conclusion, the DARTIC systematically reviewed the NTP-CERHR Monograph and the underlying studies and determined that the studies did not support the conclusion that BPA causes reproductive or developmental toxicity within the meaning of Proposition 65. Specifically, members of the DARTIC stated as follows:

- ***On male reproductive toxicity:*** “[T]he NTP and the CERHR monograph . . . indicate there’s negligible concern about exposure to BPA” [Committee Member Hobel]; “the data on human male reproductive toxicity are largely cross-sectional and derived from very small studies with inadequate control of confounding variables . . . the evidence seems inadequate to determine if BPA . . . has an adverse effect on human male reproduction” [Committee Member Gold]; “BPA has not been shown to be a male reproductive toxicant.” [Committee Member Jones]
- ***On female reproductive toxicity:*** “[T]here was insufficient evidence . . . [to] say that there is an effect with respect to female developmental and reproductive toxicity . . . not so sure that . . . the animal model can extrapolate into the human model, because the doses were so incredibly high. They were very high doses that we would not expect humans to be exposed to.” [Committee Member White]
- ***On developmental toxicity:*** “[T]here are not clear effects on the low-dose levels, because we have seen situations where some studies are positive and some studies are negative” [Committee Member Roberts]; and “As I look at the literature, I see very little evidence that there is an increased risk, absence [sic] of maternal toxicity, of fetal or neonatal mortality. I don’t see any clear trends for malformations or specific birth effects. No clear evidence of reduced birth weight or growth.” [Committee Member Keen]

In the face of this well-informed and unanimous verdict by the State’s, and OEHHA’s *own* “qualified experts,” as well as the unambiguous conclusions of the NTP-CERHR expert panel, OEHHA cannot reach exactly the opposite conclusion with regard to the very same studies without egregiously abusing its discretion.

4. 23 SCIENTIFIC EXPERTS HAVE CONCLUDED THAT BPA DOES NOT CAUSE DEVELOPMENTAL TOXICITY ON THE SAME EVIDENCE ON WHICH OEHHA RELIES

As detailed above, the twelve experts who made up the NTP-CERHR panel (whose assessment of the scientific evidence is the foundation of the NTP-CERHR Report on which

OEHHA relies) expressly concluded that BPA does not cause developmental toxicity. Since that review, an additional 11 scientists reviewing the same data reached the same conclusion – that BPA does not cause developmental toxicity. The expert judgments of the four expert scientists who filed comments in response to OEHHA’s February 10, 2012 Request for Relevant Information on Bisphenol A are discussed above. To that should be added the assessment of the seven experts on the state of California’s DARTIC who not only concluded that BPA does not cause developmental toxicity, but also concluded, after reviewing the same evidence on which OEHHA now relies, that BPA should not be listed under Proposition 65.

Dismissing the professional judgment of these 23 highly qualified experts, collectively with many *centuries* of highly relevant experience, is arbitrary, capricious and an egregious abuse of discretion.

CONCLUSION

The record clearly indicates that OEHHA has fundamentally misinterpreted the NTP-CERHR Monograph on BPA. In contrast to OEHHA’s assertion that the report formally identifies BPA as causing developmental toxicity, the Monograph does just the opposite. The NTP-CERHR Monograph clearly and unambiguously identifies BPA as NOT causing developmental toxicity. Proposition 65 does not allow OEHHA to substitute its judgment for the authoritative body’s judgment. Accordingly, OEHHA may not list BPA as causing developmental toxicity on the basis of the NTP-CERHR Monograph.

Multiple expert analyses of the scientific evidence by NTP-CERHR’s expert panel, the state’s own designated expert body, and eminently qualified toxicologists, demonstrates that the animal data on which OEHHA is proposing to list BPA do not satisfy the criteria of Section 25306(g)(2) because, among other factors, when due weight is given to the “consideration of maternal toxicity” in the studies in question, the animal data do not indicate that adverse developmental effects in humans from exposure to BPA are biologically plausible. That was the unanimous conclusion of the state’s own qualified experts at the July 15, 2009 public meeting of the DARTIC. That is also consistent with the clear conclusions of NTP-CERHR’s expert panel, and the expert judgment and testimony of four toxicologists, all with peerless expertise and credentials in the interpretation of animal studies on developmental toxicity. Taken together, 23 highly qualified experts, including those who served on the DARTIC, have reached a clear and consistent conclusion that BPA does not cause developmental toxicity at high doses.

OEHHA’s responses to the public comments on the proposed listing of BPA are unsupported and cannot be sustained; they range from assertions that OEHHA understands the scientific principles and EPA Guidelines regarding the interpretation of developmental toxicity studies better than the authors of those Guidelines do, to characterizations of those experts’ scientific judgments as merely “the opinions of the commenters” and not “evidence” or “factual information,” to unsupported claims that NTP-CERHR reached a definitive conclusion on the issue of the effects of maternal toxicity in the studies in question and that OEHHA is not

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permitted to disagree with that NTP-CERHR “conclusion.” It is simply not plausible that all 23 expert scientists, including members of two eminent expert bodies that were comprised of scientists specifically selected for their expertise, are wrong, and OEHHA’s contrary opinion is right. OEHHA does not have greater expertise in the interpretation of animal data than the many experts whose interpretations it rejects.

With its Notice of Intent to list BPA as causing developmental toxicity under the authoritative bodies mechanism, OEHHA has demonstrated a fundamental misunderstanding and misinterpretation of the NTP-CERHR Monograph on BPA. In combination with OEHHA’s dismissal of the professional judgment of 23 highly qualified experts, collectively with many centuries of highly relevant experience, as mere “opinion,” OEHHA’s proposal to list BPA is nothing short of arbitrary and capricious, and represents an egregious abuse of discretion.

In light of the extensive and clear record, OEHHA cannot list BPA as causing developmental toxicity under Proposition 65 based on the NTP-CERHR Monograph.

Very truly yours,

MCKENNA-LONG & ALDRIDGE LLP



Christian Volz
Stanley W. Landfair

CV/SWL/gmp

cc: George Alexeeff, Ph.D., DABT, Director
Carol J. Monahan-Cummings, Chief Counsel
SF:27570560.2

ATTACHMENT

January 13, 2012

George V. Alexeeff, Ph.D.
Acting Director
Office of Environmental Health Hazard Assessment
1001 "I" Street
Post Office Box 4010
Sacramento, California 95812-4010

Dear Dr. Alexeeff:

As requested, we are pleased to send you copies of the three full reports prepared by the National Toxicology Program (NTP) on the developmental and reproductive toxicity of bisphenol A (BPA). These reports are distributed through the National Technical Information Service online.ⁱ

The reports provide additional technical detail to the published articles on the same studies (Morrissey et al., 1987; Morrissey et al., 1989)ⁱⁱ that do not change but confirm the major points raised in our meeting by Drs. Kimmel, Lamb, Tyl and Scialli on the lack of BPA developmental toxicity except at highly maternally toxic doses. These studies were all done and reported in 1985 under the direction of Drs. Kimmel and Lamb who were with the NTP. They were performed at RTI and Dr. Tyl was the study director of the developmental toxicology studies. These studies were used by Dr. Scialli as he prepared the draft report of the CERHR review that is currently being held out as a possible basis for listing BPA as a developmental toxicant at high doses.

DATA INTERPRETATION

Developmental Toxicity

*Reproduction and fertility assessment (continuous breeding) study:*ⁱⁱⁱ You will recall that the continuous breeding study was conducted with a complex design that is uniquely suited to assess potential effects on fertility. It was not designed or intended to evaluate maternal and developmental toxicity in sufficient detail to

address the potential for classification as a developmental toxicant under California Proposition 65 (Prop 65). The full NTP continuous breeding study report supports this view on the strengths and limitations of that study design. This study does not support classification of BPA as a reproductive or developmental toxicant under Prop 65.

Developmental toxicity studies:^{iv} The two developmental toxicity studies conducted by RTI are more relevant to the question of the potential for developmental toxicity of BPA.

In the rat study, there were signs of significant maternal toxicity at all dose levels, including reduced maternal weight gain during treatment and gestation, as well as reduced maternal weight gain corrected for gravid uterine weight (GUW). The latter effect, together with the fact that there were no effects on fetal body weight indicates that reduced weight gain during gestation was due to maternal toxicity. No fetal effects of any kind were seen in this study. Review of the full NTP report confirms these findings. These data do not support listing as a developmental toxicant under Prop 65.

In the mouse study, maternal toxicity occurred at all dose levels compared to the controls, rising to a death rate of 18% in the pregnant animals at the highest dose. Maternal 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. The full NTP report corroborates these findings and does not support listing as a developmental toxicant under Prop 65.

Maternal Toxicity

The EPA's Guidelines for Developmental Toxicity (DT) Risk Assessment^v outline an approach to interpreting data in the context of dose, route, duration and timing of exposure and point out how to interpret data in the context of all toxicity data. The result is a holistic description of the potential toxic effects of a chemical dependent on the conditions of exposure. As Dr. Kimmel emphasized in our

meetings in OEHHA's offices on December 5, 2011, it appears that OEHHA is misinterpreting EPA's DT guidelines with their position that less than 10% maternal mortality defines "minimal maternal toxicity." The guidelines detail a number of indicators of maternal toxicity, including maternal death ("an obvious indicator of maternal toxicity"), changes in body weight and weight gain, gestation length, etc. (see Table 1, section, 3.1.1.1). In the context of study design, the highest acceptable dose is described as a range of effects, the least of which might be changes in maternal body weight or weight gain to as much as 10% or fewer maternal deaths. What constitutes minimal maternal toxicity is something that must be determined vis-à-vis what is known about the biological actions and mechanisms of the chemical, whether there is a dose-response relationship, and comparison with the study control data. The minimal maternal toxic dose level is used to set the LOAEL and is often one of the lower doses in a study. As the DT Guidelines indicate (section 3.1.1.4), the relationship between maternal and developmental toxicity is important, especially when there are developmental effects that occur at doses below those causing maternal toxicity.

To be consistent with this approach, the interpretation of the BPA developmental toxicity data must be done in the context of maternal toxicity. OEHHA's selection of the NTP-CERHR statement^{vi} that "there is clear evidence of adverse developmental effects at "high doses" of BPA "in the form of fetal death, decreased litters size," does not account for the maternal toxicity seen at these high dose levels. Not only is OEHHA's reliance on this isolated statement about developmental effects made in the absence of consideration of maternal toxicity, but the effects are at admittedly "high doses" which means that they are far above the LOAEL for maternal toxicity.

CONCLUSIONS

The NTP studies performed by RTI in the 1980s and the studies performed at RTI for the American Chemistry Council BPA Group in 2001-2008 came to the same conclusions: Adult (parental) toxicity was treatment- and dose-related, with the highest doses causing morbidity and mortality. Target systemic organs were liver

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and kidneys, with altered organ weights and some (or no) histopathology. There was some evidence of male reproductive effects (reduced sperm motility, reduced reproductive organ weights) and of female effects (see crossover matings where the female was exposed and the male was not), but all in the presence of systemic toxicity; the reproductive effects were only observed at the highest dose levels with the most profound systemic toxicity in both sets of studies in both rats and mice. In our opinion, and supported by the statements previously submitted by Drs. Tyl and Scialli, the concordance between species, between study designs and between different teams at the different times provides the strongest evidence that maternal (parental) toxicity drives the observed embryofetal, neonatal and postnatal effects and that BPA is *not* a reproductive or developmental toxicant in rodents when maternal toxicity is taken into account.

The relationship between developmental toxicity and maternal or other forms of toxicity is extremely important in drawing conclusions about the potential human hazards of chemicals. The US EPA DT Guidelines are important to consider in reviewing such data. The arbitrary selection of interim and incomplete conclusions by NTP-CERHR that BPA is developmentally toxic at "high" dose levels with no regard for other toxicity occurring at those or lower doses is inappropriate and does not follow the EPA's guidance. In short, NTP-CERHR never formally identified BPA as causing reproductive or developmental toxicity.

Once again, we are pleased to submit these final reports for your consideration. We appreciate your willingness to carefully consider the arguments in the potential listing of BPA and we continue to find that the data do not support listing under Prop 65.

Sincerely,

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ⁱ www.ntis.gov

ⁱⁱ Morrissey, R.E., J.D. George, C.J. Price, R. W. Tyl, M.C. Marr, C.A. Kimmel. 1978. The developmental toxicity of bisphenol A in rats and mice. *Fund. Appl. Toxicol.* 8:571-582; Morrissey, R.E., Lamb, J.C., Morris, R.W., Chapin, R.E., Gulati, D.K., Heindel, J.J.. 1989. Results and evaluations of 48 continuous breeding reproduction studies conducted in mice. *Fundam Appl Toxicol* 13:747-777.

ⁱⁱⁱ NTP (1985) Bisphenol A: reproduction and fertility assessment in CD-1 mice when administered in the feed. NTP-85-192. Research Triangle Park, NC. NTIS Accession No. PB86103207.

^{iv} NTP. 1985c. Teratologic evaluation of bisphenol A (Cas No. 80-05-7) administered to CD(R) rats on gestational days 6 through 15. Final study report. NCTR contract 222-80-2031(C). NTP-85-089. National Toxicology Program/National Institute of Environmental Health Sciences. NTIS Accession No. PB85205110. NTP. 1985b. Teratologic evaluation of bisphenol A (Cas No. 80-05-7) administered to CD-1 mice on gestational days 6 through 15. Final Study Report. NTP-85-088. National Toxicology Program/National Institute of Environmental Health Sciences. NTIS Accession No. PB85205102.

^v U.S. EPA. 1991. Guidelines for Developmental Toxicity Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, EPA/600/FR-91/001.

^{vi} NTP-CERHR. 2008. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NIH Publication No. 08-5994.