May 13, 2010

Via U.S. Mail and Email

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
Post Office Box 4010, MS-19B
Sacramento, CA 95812-4010

Re: Response to Request for Relevant Information on Bisphenol A

Dear Ms. Oshita,

Please find attached written comments from the Polycarbonate/BPA Global Group of the American Chemistry Council in response to the OEHHA Request for Information of February 12, 2010 (Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol-A). The Polycarbonate/BPA Global Group consists of the leading global manufacturers of bisphenol A and polycarbonate plastic, which for many years have supported and conducted scientific research to understand whether bisphenol A has the potential to cause health or environmental effects and to support scientifically sound public policy.

As indicated by the signatures at the end of the attachment, the comments were prepared jointly with Stanley Landfair and Christian Volz (McKenna Long & Aldridge), Dr. F. Jay Murray (Murray & Associates), and Dr. Arthur Lawyer (Technology Sciences Group Inc.).

Please do not hesitate to contact me if I can be of further assistance to clarify any of the information provided or if additional information is needed. I can be reached at (703) 741-5588 or by e-mail at steve_hentges@americanchemistry.com.

Regards,

Steven G. Hentges, Ph.D.
Executive Director
Polycarbonate/BPA Global Group

AMERICAN CHEMISTRY COUNCIL

POLYCARBONATE / BPA GLOBAL GROUP

RESPONSE TO
REQUEST FOR RELEVANT INFORMATION
ON A
CHEMICAL BEING CONSIDERED FOR LISTING
BY THE AUTHORITATIVE BODIES MECHANISM:
BISPHENOL A

F. Jay Murray, Ph.D., D.A.B.T.
MURRAY & ASSOCIATES

Arthur L. Lawyer, Ph.D.
TECHNOLOGY SCIENCES GROUP INC.

Christian Volz
Stanley W. Landfair
MCKENNA LONG & ALDRIDGE LLP

MAY 13, 2010

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I. INTRODUCTION

The American Chemistry Council and its Polycarbonate/BPA Global Group ("ACC") and the undersigned counsel and consultants to ACC hereby submit this Response to OEHHA's February 12, 2010 Request for Relevant Information on a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism: Bisphenol A (hereinafter referred to as the "Request"). The Request follows a petition by the Natural Resources Defense Council ("NRDC"), filed just moments after the Developmental and Reproductive Toxicant Identification Committee ("DART IC") voted unanimously that Bisphenol A ("BPA") should not be listed under Proposition 65,[1] demanding that BPA be listed under the Authoritative Bodies Mechanism on the theory that the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A ("NTP-CERHR Monograph" or "Monograph") "concludes" that BPA causes reproductive toxicity.[2] Our September 15, 2009 response to that petition and our June 30, 2009 submission to the DART IC are incorporated as part of this Response, and appear as Attachments 1 and 2.[3]

II. BACKGROUND

Any consideration of BPA under the Authoritative Bodies Mechanism must take into account the unanimous decision of the DART-IC ***not*** to list BPA. Indeed, even the Request points that out. The Request omits, however, that seven members of the DART IC evaluated the same NTP-CERHR Monograph that OEHHA now identifies as a basis for listing, including all of the scientific testing data and studies discussed therein. After careful consideration of this information, the DART IC deliberated in open forum for nearly an hour, and voted as follows:

QUESTIONS TO DART IC	NO	YES
Has BPA been clearly shown to cause developmental toxicity?	7	0
Has BPA been clearly shown to cause reproductive toxicity (female)?	7	0
Has BPA been clearly shown to cause reproductive toxicity (male)?	7	0

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[1] Proposition 65 is the popular name for California's Safe Drinking Water & Toxic Enforcement Act of 1986, Cal. Health & Safety Code § 25249.5 *et seq.*

[2] NTP-CERHR is the acronym for the Center for the Evaluation of Risks to Human Reproduction, operated by the National Toxicology Program under the auspices of the U. S. Department of Health and Human Services.

[3] On April 9, 2010, we submitted two requests to OEHHA pursuant to the Public Records Act ("PRA") for OEHHA documents that we believe are pertinent to the Request and to this Response. As of May 13, 2010, the date this Response is being filed, we have received no documents or any formal response to our PRA requests, and no explanation except for a statement from OEHHA's PRA coordinator that responsive documents are "confidential." We respectfully reserve the right to supplement this Response on the basis of documents responsive to our PRA requests, when they are provided.

In other words, seven members of the DART IC, who serve as the statutorily appointed "State's Qualified Experts," concluded ***unanimously*** that BPA should ***not*** be listed.

The information considered by the DART IC in reaching this conclusion included a comprehensive Hazard Identification Document ("HID"), prepared by OEHHA in May 2009 to "address the reproductive toxicity of [BPA]," and to "provide information on whether this compound should be identified as known to cause reproductive toxicity under Proposition 65."[4] The HID acknowledged the Monograph and the fact that NTP-CERHR was an "authoritative body" for purposes of Proposition 65. OEHHA pointed out that the Monograph included studies that identified "clear evidence of 'high' dose developmental toxicity of BPA ***in laboratory animals***," acknowledged that the agency staff had reviewed those studies, incorporated the Monograph as part of the HID and then referred the matter to the State's Qualified Experts, explaining that "the most efficient, timely and appropriate mechanism for consideration of BPA for listing under Proposition 65 was to bring it forward for consideration by the DART IC."[5]

At the July 15 public meeting, OEHHA identified and summarized all of the relevant data, including the data in the NTP-CERHR Monograph and all of the data that OEHHA now identifies as the potential basis for listing. At no place in its HID or at any time during this presentation did OEHHA or any member of its staff indicate or offer any opinion that the NTP-CERHR Monograph, the NTP Brief on BPA (2008) ("NTP Brief"), or the NTP Expert Panel Report concluded that BPA is a reproductive toxicant within the meaning of Proposition 65. [6,7] It defies both legislative intent and logic to assert that the exact same evidence that the State's Qualified Experts rejected now be treated as the basis for listing BPA under the Authoritative Bodies Mechanism.

III. SUMMARY

Any proposal to designate BPA as a "chemical known to cause . . . reproductive toxicity"[8] would be unlawful under Section 25249.8(b) of the Act and Section 25306 of the implementing regulations, because:

- the NTP-CERHR Monograph that OEHHA identifies as the basis for an authoritative bodies listing does not "formally identify" BPA as a developmental toxicant, as required under Section 25306(d);
- the determination by the State's Qualified Experts that the information in and the data underlying the Monograph do not support listing BPA cannot

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4 OEHHA (2009) Evidence on the Developmental And Reproductive Toxicity of Bisphenol A, Draft, at 8.

5 OEHHA (2009) Evidence on the Developmental And Reproductive Toxicity of Bisphenol A, Draft, at 8. (emphasis added).

6 OEHHA (2009) Evidence on the Developmental And Reproductive Toxicity of Bisphenol A, Draft, at 8.

7 Transcript, July 15, 2009 Meeting of Developmental and Reproductive Toxicant Identification Committee, pp. 1-259.

8 Cal. Health & Safety Code § 25249.8(a).

be superseded or overruled by a second review of the same information and data by OEHHA under the Authoritative Bodies Mechanism under Section 25306; and

- the scientific data to which OEHHA now points as the basis for listing under the Authoritative Bodies Mechanism, if they were reviewable and reviewed on the merits, are not "sufficient" to indicate an "association between adverse reproductive toxic effects in humans and [BPA]," as Section 25306(g)(2) would require.

For these and other reasons stated below, any decision to designate BPA as a chemical "known to cause . . . reproductive toxicity" within the meaning of Proposition 65 would be arbitrary and capricious and an abuse of discretion.

BPA has not been "formally identified" as "causing reproductive toxicity." It is clear from the text of the Monograph that the document does not "formally identify" BPA as a developmental toxicant. The Monograph is a "report" for purposes of Section 25306(b). As a "report," neither the Monograph nor its summarizing component, the "NTP Brief," expresses a "conclusion" that BPA causes developmental toxicity, as OEHHA indicates in the Request.

According to the Request, "OEHHA is relying on the NTP-CERHR's ***conclusions*** in the report that ***BPA causes reproductive toxicity***." The only explanation is the following: "The NTP-CERHR report ***concluded*** that there is clear evidence of adverse developmental effects ***in laboratory animals*** at 'high' levels of exposure. Developmental effects include fetal death and reduced litter size in rats and mice exposed prenatally."[9]

It is obvious from the face of the NTP Brief, however, that this was not NTP's "conclusion" regarding the potential of BPA to cause reproductive toxicity in humans, which Section 25306(d) would require, but only its evaluation of some of the data ("high" dose tests in laboratory animals) that NTP considered. The NTP Brief plainly expresses a contrary "conclusion" as to whether these animal data are "sufficient" to predict adverse developmental effects in humans.

This is patently clear from the standardized format and terminology that NTP uses to frame the conclusions in its NTP Briefs. A review of every one of the NTP-CERHR Monographs on chemicals that NTP has evaluated for reproductive toxicity reveals below a glaring contrast between the cases where an NTP Brief actually concluded that a chemical agent, in NTP's words, "may adversely affect human development," as opposed to the conclusion that NTP declined to reach with respect to BPA. The NTP Briefs are drafted in a consistent, standardized format. Each NTP Brief expresses the NTP conclusion in a paragraph that (a) uses terms that clearly denominate "conclusions" as "conclusions;" (b) recites that NTP employs a "weight-of-the-evidence" approach in evaluating all of the data to reach a conclusion; (c) summarizes in a sentence or clause the value of the human and animal data; and then (d) pronounces a judgment whether the scientific evidence is "sufficient" to conclude that the

[9] Request at 1 (emphasis added).

chemical under evaluation may (or does not) "adversely effect human development and/or reproduction."

In the NTP Brief on Di-isononyl phthalate ("DINP"), for example, NTP expressed its conclusion as follows:

> Scientific decisions concerning health risks are generally based on what is known as the ***"weight of the-evidence."*** In this case, recognizing the absence of human data, some evidence of developmental effects, and limited evidence of no reproductive effects in animals, the ***NTP judges the scientific evidence sufficient to conclude that DINP might adversely affect development of the human fetus if the levels of exposure are sufficiently high.***

NTP Brief on DINP (2003) at p. 2 (emphasis added).

In the NTP Brief on BPA, by contrast, NTP stated the following:

> 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, ***the possibility that bisphenol A may alter human development cannot be dismissed.***

NTP Brief on BPA (2008) at p. 7 (emphasis added).

We demonstrate herein that the contrasts between the "conclusion" that NTP reached with respect to DINP and the conclusion that NTP failed to reach with respect to BPA, and their outcomes for purposes of Proposition 65: (1) in the case of BPA, NTP did not state that it "concluded" that the evidence was sufficient to show that humans would be affected, and (2) the "conclusion" that NTP did reach – that "the possibility that bisphenol A may alter human development cannot be dismissed – is not a "conclusion" that BPA does cause adverse developmental effects in humans.

Thus, the NTP-CERHR Monograph does not "formally identify" BPA as a developmental toxicant for purposes of Section 25249.8(b), which establishes the Authoritative Bodies Mechanism. Because the Monograph is a "report" within the meaning of Section 25306(d), the question is whether it "concludes" that BPA causes developmental toxicity.

For the reasons above, it obviously does not. OEHHA has confused an ***evaluation of some of the evidence that NTP-CERHR considered***, which applies only to laboratory animals, for a ***conclusion regarding the sufficiency of those data to predict adverse effects in humans***, which OEHHA now would interpret to include a judgment for purposes of Section 25306(g) that those data are "sufficient" to show an association between effects shown in humans and exposure to BPA. As the NTP Brief notes, NTP-CERHR did not reach such a conclusion, but instead acknowledged only that the "possibility" that BPA may alter human development "cannot be dismissed" – and made even that equivocal statement based *not* on the "high" dose data upon which OEHHA now relies, but rather on the "low" dose studies that OEHHA now ignores.

Because BPA is not "formally identified" in the NTP-CERHR Monograph as causing reproductive toxicity, it is beyond OEHHA's authority to examine the data itself to reach a different conclusion. Section 25306(d) of the implementing regulations assigns OEHHA the duty to review documents such as "lists" and "reports" issued by the various "authoritative bodies," in order to "determine which chemicals have been formally identified by an authoritative body as causing cancer or reproductive toxicity." If such a determination is made, OEHHA then is required to review the scientific evidence on which the authoritative body's "formal identification" was made, in order to ensure that the data satisfy the toxicological criteria set forth at Section 25306(g).

This is OEHHA's long-held position, memorialized by the Court of Appeal in *Exxon Mobil v. OEHHA*: "[T]he authoritative body provision is triggered if a body considered authoritative under the statute identifies a chemical in a report, list, or other document as a developmental toxicant. . . . [O]nce the chemical is 'formally identified' by an authoritative body as a developmental toxicant, OEHHA reviews the scientific record before the authoritative body to determine whether there is substantial evidence to support a listing."[10]

The purpose of this review, to be conducted only if, and then after, OEHHA finds that a chemical has been "formally identified," is to prevent "the unrestrained listing of chemicals" by agencies whose criteria might be ***less stringent*** than those imposed by Proposition 65.[11] Thus, the Section 25306 criteria were established with input from the State's Qualified Experts, in order to "ensure that the standards applied by an authoritative body are the same as or substantially similar to those used by the Panel to evaluate chemicals."[12]

Thus, neither Section 25249.8 of the Act nor Section 25306 of the Regulations are a mandate for OEHHA to review data citied in authoritative body documents to make listing decisions on the Agency's own behalf. Where a chemical was not "formally identified" by the authoritative body, the Agency has no further responsibility or authority. Therefore, to proceed further would be contrary to Section 25249.8(b) of the Act, and contrary to Sections 25306(d) and (g) of the implementing regulations.

The Authoritative Bodies Mechanism does not allow OEHHA to effectively overrule the State's Qualified Experts in evaluating the exact same data. Section 25249.8(b) of the Act and Section 25306(g) of the regulations do not allow the Authoritative Bodies Mechanism to be used as vehicle to overrule or supersede a decision by the State's Qualified Experts. Although the Request asserts that these mechanisms are "separate and distinct," the statue and regulations indicate the State's Qualified Experts Mechanism is the

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[10] *Exxon Mobil Corporation v. Office of Environmental Health Hazard Assessment*, 169 Cal.App.4th 1264, 1278 (2009) (hereinafter, "*Exxon Mobil v. OEHHA").*

[11] "Final Statement of Reasons," dated March 29, 1990, accompanying the adoption of Section 12306 of Title 22 of the California Code of Regulations, Division 2, the precursor to Section 25306 at 2.

[12] Final Statement of Reasons at 15.

"primary approach to listing"[13] and that the toxicological criteria that OEHHA is required to apply in executing its purely ministerial duties under the Authoritative Bodies Mechanism are substantially the same criteria that the DART IC applies in evaluating data under the State's Qualified Expert Mechanism. The Final Statement of Reasons for Section 25306 further makes clear that the purpose of the Authoritative Bodies Mechanism, and the delegation of ministerial duties under that mechanism to the OEHHA staff, was merely to conserve the resources of the State's Qualified Experts "to focus [their] attention on chemicals which have not previously been evaluated."[14] For OEHHA to ignore the unanimous views of the State's Qualified Experts and to supersede their conclusions with a contrary interpretation of the very same data would be arbitrary and capricious in itself, and would exceed the agency's statutory authority.[15]

Even if OEHHA were authorized to evaluate the data in the NTP CERHR Monograph anew, the studies cited by NTP-CERHR do not satisfy the "sufficient data" requirement of Section 25306(g)(2). As a preliminary matter, it is unclear from the Request that OEHHA has applied the correct standard under Section 25306(g)(2) in stating its conclusion that the data appear to satisfy the requirements for listing.

The Request recites that the NTP-CERHR Monograph "appears to satisfy the sufficiency criteria in the Proposition 65 regulations," but says nothing more to explain than "[t]he NTP-CERHR report concludes that there is clear evidence of adverse developmental effects in laboratory animals at "high" levels of exposure. Developmental effects include fetal growth and reduced litter size in rats and mice exposed prenatally." It is obvious that such a "conclusion," if it were a conclusion (and even if were correct) would not equate to a finding to satisfy the definitional standard in Section 26305(g)(2). "Evidence of adverse developmental effects in laboratory animals" is only the starting point, not the finish line.

The pertinent question under Section 26305(g)(2) is whether evidence of such adverse effects in laboratory animals is "***sufficient,***" taking into account many specified and unspecified factors, to find that an "***association***" between those effects observed in animals and the same effects due to exposure to BPA "***in humans***" is "***biologically plausible***." The failure to apply the correct standard is cause in itself to bring the listing process to a close.

Examination of the criteria that the DART IC and OEHHA are required to apply reinforces that conclusion. Following the DART IC "Criteria for Recommending Chemicals for Listing as 'Known to the State to Cause Reproductive Toxicity" (hereinafter, "DART IC Criteria") the Experts reviewed the same studies to which OEHHA now points, and employed a ***"weight-of-the-evidence***" approach to determine whether those studies constitute "***sufficient***

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[13] Final Statement of Reasons at 8. *See also Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1282 (referring to State's Qualified Expert Mechanism as "primary approach" to listing).

[14] Final Statement of Reasons at 8.

[15] For reasons explained herein, we believe the Proposition 65 implementing regulations do not extend this authority to OEHHA. To the extent OEHHA would interpret the regulations otherwise, the regulations are contrary to the meaning and intent of the Act, and are invalid. *See Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1279 at n. 11.

evidence in experimental animals, such that ***extrapolation to humans is appropriate,***" taking into account factors such as "study design," "relevan[ce] to expected human exposures," and "***consideration of maternal toxicity.***"[16]

Section 25306(g)(2), the operative provision for OEHHA's analysis, basically restates the DART IC Criteria, in nearly the same words. Section 25306(g)(2) would require the agency to determine whether there are ***"[s]ufficient data***, taking into account the adequacy of the experimental design and other parameters such as . . . route of administration, frequency and duration of exposure . . . 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***." (emphasis added).

As OEHHA is aware, the DART IC considered the issue of maternal toxicity extensively and conclusively. There is no valid reason for OEHHA to disagree with the DART IC on this issue. Moreover, OEHHA has no statutory power to reach a different conclusion under the circumstances presented. Even if OEHHA's staff or management personally disagree, they should defer to the findings of the State's Qualified Experts on this issue. It is simply untenable for the secondary decision maker, whose role was crafted by statute and regulation to carry out the views of the State's Qualified Experts as the primary decisionmaker, to arrogate unto itself the role to make its own decision, which is plainly arbitrary and capricious, and completely outside the statute. That would be the height of arbitrariness, particularly here, where the issue of "of maternal toxicity" was thoroughly "considered."

The agency should recall that the spokesperson for the petitioner NRDC, Dr. Solomon, raised this issue at the DART IC meeting on July 15, 2009. Expert opinion was presented in person by the principal author of three of the eight studies that NTP-CERHR and the DART IC considered. Following these presentations, the State's Qualified Experts addressed, debated and resolved the issue on the public record. The essence of that resolution is summarized in the following colloquy by two of the DART IC members:

> **Committee Member Roberts,** addressing developmental toxicity:
>
> We referred to high dose studies. ***The high dose studies have clear evidence of developmental toxicity. They do occur in the presence of maternal toxicity. And the issue isn't whether or not developmental toxicity occurs. It's whether or not there is sufficient maternal toxicity to potentially be causing the other***.
>
> * * *
>
> **Committee Member Keen**, following Dr. Roberts:
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> My reading of the binders was remarkably similar to what you read . . . As I look at the literature, ***I see very little evidence that there is an increased risk, absence***

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[16] DART IC, Criteria for Recommending Chemicals for Listing as "Known to the State to Cause Reproductive Toxicity" (1993), (referred to herein as "DART IC Criteria"), at 4, attached hereto as Attachment 3.

of maternal toxicity [sic.; Dr. Keen said "absent maternal toxicity" or "in the absence of maternal toxicity"], of fetal or neonatal mortality.[17]

The unanimous vote of the State's Qualified Experts following this exchange reflects the conclusion of the DART IC that the animal studies showing adverse developmental effects at high doses, *i.e*., the same data to which OEHHA now points as the basis for designating BPA "as causing reproductive toxicity" within the meaning of Section 25306(g)(2), did not demonstrate that BPA should be listed. The State's Qualified Experts found, applying the appropriate statutory and DART IC Criteria, that the animal data were not "sufficient" to make "extrapolation to humans . . . appropriate," taking into account factors such as "relevan[ce] to expected human exposures," and "***consideration of maternal toxicity.***"[18]

As to the toxicological data, there are only eight studies to consider, referred to herein as "NTP References 36 – 43," as they are identified in the bibliography to the NTP Brief. They consist of three developmental toxicity studies (NTP References 36, 38 and 43), and five reproductive toxicity studies, all in the mouse and rat (NTP References 37, 39, 40, 41, 42, and 43). Applying the pertinent criteria under Proposition 65 and Section 25306(g)(2) (*i.e.,* "taking into account adequacy of the experimental design and other parameters, such as but not limited to, route of administration, frequency and duration of exposure"), analysis requires that five of the eight studies be excluded or significantly discounted, because they included effects potentially caused in whole or in part by post-natal exposure, which is not pertinent to the designation of a chemical as a developmental toxicant for purposes of Proposition 65. One study had no pre-natal exposure whatsoever; by definition, that study could not possibly demonstrate developmental toxicity, as Proposition 65 treats that effect. Four other studies had both pre-natal and post-natal exposure, and the effects in these studies could be due to exposure that occurs outside of gestation (*i.e*., not pre-natal exposure). Furthermore, both male and female parents were exposed to BPA prior to mating in all four of these studies, raising the possibility that the "developmental" effects, such as a decrease in litter size, may be due to male or female reproductive toxicity, not to developmental toxicity as meant by Proposition 65. In fact, one of these studies specifically looked at male reproductive toxicity through a semen evaluation and a cross-mating study; substantial evidence of male reproductive toxicity (including a decrease in litter size when only the male parent was exposed to BPA and a decrease in sperm quality) was seen at doses that produced systemic toxicity. Just three studies had only pre-natal exposure, and none of these studies showed adverse developmental effects in the absence of severe maternal toxicity (a factor addressed below).

OEHHA would agree that "developmental toxicity" is limited for purposes of Proposition 65 to developmental effects caused by pre-natal exposure alone. NTP's use of that term and the similar term "adverse developmental effects," by contrast, embraces a much broader range of effects, including effects attributable to post-natal exposure. Thus, where the NTP Brief indicates that there is "clear evidence of adverse developmental effects"[19] in animals, the term "adverse

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17 Transcript of July 15, 2009 DART IC Meeting, at pp. 236-238.

18 DART IC Criteria, at 4.

19 NTP Brief at 7.

developmental effects" does not have the same meaning as it does for purposes of Proposition 65. Therefore, the proposal to list BPA on the basis of effects that do not represent developmental toxicity for purposes of Proposition 65 would exceed the mandate under Section 25249.8 of the act, as well as Section 25306(g)(2) of the implementing regulations, and expand the boundaries of Proposition 65 well beyond its well-recognized limits.

Looking to other factors identified under Section 25306(g)(2), "consideration of maternal toxicity" leads to the conclusion that the adverse developmental effects observed at high doses in laboratory animals are likely due to maternal toxicity – not to fetal exposure to BPA. It is a widely accepted principle of developmental toxicology that all virtually all substances are capable of causing developmental toxicity in laboratory animals, if they are administered at doses high enough to cause maternal toxicity. Even common substances, such as table salt, can cause developmental toxicity in animals, (including even birth defects) at doses high enough to injure the mother. Indeed, we present data which show that the spectrum of developmental effects observed in animals given high doses of table salt was far more serious than the developmental effects observed after administration of maternally toxic doses of BPA. The purpose of developmental toxicity testing is not to confirm that every chemical agent is capable of causing developmental effects in animals. Rather, it is to identify substances that pose true developmental hazards to humans — such as ***selective*** developmental toxicants, *i.e.,* substances that cause developmental effects in the absence of maternal toxicity, or developmental toxicants to which humans are likely to be exposed at maternally toxic dose levels (*e.g.,* alcohol or anti-neoplastic drugs). BPA fits neither category.

In two of the eight studies, maternal toxicity was not monitored (or "considered," in the words of Section 25306(g)(2)) at all. (In fact, one of these studies did not use a single pregnant animal (since only young males were exposed to BPA, and then only post-natally). Thus, neither of these studies could possibly constitute "sufficient evidence" of developmental toxicity.

In all six studies where maternal toxicity was evaluated, developmental effects were observed only in the presence of serious maternal toxicity, and the magnitude of the maternal toxicity was sufficient to account for the developmental effects. This universal observation – the presence of significant maternal toxicity in the presence of developmental effects in all of the studies identified in the NTP Brief that "considered" maternal toxicity – is so overwhelming that it dictates the outcome of any analysis under Section 25306(g)(2). And yet, a proper analysis is actually even more restrictive. As noted above, adverse effects attributable to post-natal exposures are not relevant to a determination of developmental toxicity for purposes of Proposition 65, and Section 25306(g)(2) identifies other factors that must be considered as well.

An additional factor identified under Section 25306(g)(2), relating to the "choice of species," is pharmacokinetics. Pharmacokinetic differences between rodents and humans make it "biologically implausible" that BPA would cause developmental effects in humans. While rats and mice are the most commonly used species for developmental and reproductive toxicity studies, it is important to recognize that many scientific organizations and regulatory agencies,

including NTP-CERHR, the European Food Safety Institute,[20] and the United States Food and Drug Administration,[21] have described major species differences in the way the BPA is processed in and eliminated from the bodies of rodents versus humans. Indeed, the NTP-CERHR Expert Report devoted 24 pages to the pharmacokinetics of BPA. To summarize, when BPA is administered orally to humans, the chemical is bio-transformed quickly to BPA-glucuronide, and the kidneys excrete the substance rapidly from the body in the urine. Consequently, blood concentrations of BPA in humans are estimated to be very low under even the heaviest conditions of human exposure. Rodents, by contrast, excrete BPA-glucuronide through the liver into the bile duct where BPA is cleaved from BPA-glucuronide and readily reabsorbed back into the bloodstream, and thus excreted from the body more slowly. Because of these pharmacokinetic differences, even if humans received the same high doses that were given to rodents in the developmental and reproductive toxicity studies, developmental effects would not be expected in humans because relatively little BPA would be found in the blood of humans compared to rodents. In other words, an association between the adverse developmental effects seen in animals and the same effects in humans due to exposure to BPA is not "biologically plausible," based on pharmacokinetic differences alone.

Given these findings, and the additional observation that the level of exposure in the laboratory animals was several ***thousand*** times higher than calculated exposures in the relevant human population, the ***conclusions*** in the NTP Brief (indicating a "***negligible concern*** **that exposure to pregnant women to bisphenol A will result in fetal or neonatal mortality, birth defects or reduced birth weight and growth in their offspring"** (emphasis in original)) demonstrate that NTP did not find that an association between exposure to BPA and developmental toxicity in humans is biologically plausible. To the contrary, NTP found (implicitly if not explicitly) that the animal data do not satisfy the criteria that OEHHA would be required to apply under Section 23506(g)(2).

Further reasons that BPA should not be listed. In addition to the three grounds above, we demonstrate in Section IV of this Response (1) that the studies cited in NTP-CERHR Monograph as "clear evidence of adverse effects" for "'high' dose developmental toxicity" "in laboratory animals" would not satisfy the "weight-of-the-evidence" test if the agency considered only the data that are relevant for purposes of Proposition 65; (2) that, if OEHHA were to reach a conclusion that the studies above satisfy the "sufficient data" above, the agency would be substituting its judgment for that of the authoritative body (and the DART-IC) contrary to Section 25306(g); and that scientifically valid data not considered by NTP, which OEHHA should consider under Section 25306(f), demonstrate convincingly that that the only data that gave NTP-CERHR cause for "some concern" that BPA may cause adverse effects in humans now have been discounted, so there is no basis remaining to consider that BPA is a "known reproductive toxin" for purposes of Proposition 65.

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[20] European Food Safety Institute, 2008. Scientific opinion of the panel on food additives, flavourings, processing aids and materials in contact with food on a request from the commission on toxicokinetics of bisphenol A. The EFSA Journal (2008) 759, 1-10.

[21] FDA (August 14, 2008) Draft Assessment of Bisphenol A for Use in Food Contact Applications.

IV. REASONS WHY BISPHENOL A SHOULD NOT BE LISTED

We present below the reasons that Proposition 65 and its implementing regulations do not allow OEHHA to overrule the unanimous vote of the DART IC and to list BPA instead under the Authoritative Bodies Mechanism. Turning to the scientific merits of the matter, we also present the reasons why the statements in the NTP Brief and underlying data presented in the NTP-CERHR Monograph do not support a conclusion that BPA is a developmental toxicant within the meaning of Proposition 65.

A. *BPA Has Not Been "Formally Identified" as "Causing Reproductive Toxicity"*

In order for BPA to be listed as a reproductive toxicant under the "Authoritative Bodies Mechanism," the chemical must be "formally identified" by a "body considered to be authoritative" as "causing reproductive toxicity."[22] NTP-CERHR is designated as an "authoritative body" for this purpose at the present time,[23] and will remain an "authoritative body" unless that status is revoked or rescinded.[24] Nevertheless, BPA was not "formally identified" in the NTP-CERHR Monograph as "causing reproductive toxicity," as those terms are defined in the Proposition 65 implementing regulations.

1. *The NTP-CERHR Monograph Is a "Report" Within the Meaning of Section 25306(d)*

Section 25306(d)(1), quoted below, establishes three ways in which a chemical may be "formally identified:"

> For purposes of this section, a chemical is ***'formally identified'*** by an authoritative body when [OEHHA] determines that . . . the chemical . . .[1] ***has been included on a list*** of chemicals causing . . . reproductive toxicity; or [2] ***is the subject of a report*** which is published by the authoritative body and ***which concludes that the chemical causes . . . reproductive toxicity;*** or [3] ***has otherwise been identified as causing . . . reproductive toxicity*** by the authoritative body in a document that indicates that such identification is a final action . . . .[25,26]

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22 Cal. Heath & Safety Code § 25249.8(b).

23 Cal. Code Regs., *tit*. 27, § 25306(l)(3).

24 Cal. Code Regs., tit 27, § 25306(i).

25 Cal. Code Regs., *tit*. 27, § 25306(D)(1) (emphasis added).

26 The same regulation goes on, at subsection (2), to establish various alternative criteria by which a "list, report, or document" referred to in subsection (1) may be published or adopted for purposes of the regulation. See Cal. Code Regs., tit. 27, § 25306(D)(2). Publication or adoption is not at issue here.

The Request states that "[i]n 2008, the NTP-CERHR published a ***report*** on BPA [which] ***concludes*** that the chemical causes developmental toxicity at high levels of exposure. . . ." *Id.* at 2 (emphasis added). Thus, it appears that OEHHA has decided that the NTP CERHR Monograph is a "***report*** . . . which ***concludes***" that BPA causes developmental toxicity, and not that BPA has somehow been "otherwise identified as causing . . . reproductive toxicity in a document . . . ."

2. *The NTP-CERHR Monograph Does Not Conclude That BPA Causes Reproductive Toxicity*

As noted above, the Request states that "NTP-CERHR published a report on BPA [that] concludes that the chemical causes developmental toxicity at high levels of exposure. . . ."

> OEHHA is relying on the NTP-CERHR's ***conclusions*** in the ***report*** that BPA causes reproductive toxicity. The NTP-CERHR Monograph concludes that there is clear evidence of adverse developmental effects in laboratory animals at 'high' levels of exposure. Developmental effects include fetal death and reduced litter size in rats and mice exposed prenatally.[27]

We disagree that NTP expressed any such conclusion. The isolated statements in the NTP Brief that OEHHA identifies, which refer only to some of the data that the NTP and the NTP-CERHR Expert Panel reviewed, cannot accurately be called NTP's "conclusions" about the chemical, on which a listing may be based.

It is obvious from reviewing and comparing all NTP-CERHR's monographs regarding chemicals that the statements to which OEHHA refers do not represent a conclusion by NTP-CERHR that BPA is a developmental toxicant in humans. NTP-CERHR's website discloses that to date, NTP-CERHR has issued final monographs on nineteen chemicals, including BPA.[28] Each monograph consists of an expert panel report, public comments on the expert panel report, and the "NTP Brief" in which NTP summarizes its findings and conclusions regarding the chemical in question.

Every NTP Brief follows the same, consistent format. Each NTP Brief consists of four sections, addressing in the same order the following questions: (1) "What is [the chemical in question]?"; (2) "Are people exposed to the chemical?"; (3) "Can the chemical affect human reproduction or development?"; and (4) "Are current exposures to the chemical high enough to cause concern?" In this format, section (1) provides basic information about the chemistry of the product or chemical at issue, its economic uses, and its presence in products and/or the

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[27] Request at 1, paraphrasing the NTP Brief at 7.

[28] The chemicals are: acrylamide, BPA, 1-bromopropane, 2-bromopropane, fluoxetine, ethylene glycol, propylene glycol, hydroxyurea, methanol, butyl benzyl phthalate, di-n-butyl phthalate ("DBP"), di(2-ethylhexyl) phthalate ("DEHP"), diisodecyl phthalate ("DIDP"), diisononyl phthalate ("DINP"), di-n-hexyl phthalate ("DNHP"), di-n-octyl phthalate, amphetamines, methylphenidate, and styrene. In addition, a "soy formula" monograph is in draft form, and genestein (a compound related to soy formula) has an expert report but no monograph. Copies of the NTP Briefs for these chemicals appear in a separate binder submitted with this Response.

environment. Sections (2) and (4) are closely related, and provide NTP-CERHR's conclusions regarding the estimated risks to humans from exposures to the chemical. Section (3) provides NTP-CERHR's conclusions regarding hazard identification, *i.e.*, whether available human and animal data are sufficient to conclude that the chemical in question is a reproductive or developmental toxicant in humans. NTP-CERHR's conclusions in Section (3) alone can potentially be the basis for an "authoritative bodies" listing of a chemical under Proposition 65; and in fact, OEHHA's Request for BPA refers to certain statements and figures in Section (3) of the NTP-CERHR Brief on BPA as OEHHA's proposed basis for finding that NTP has "concluded" that BPA is a developmental toxicant in humans.

While OEHHA is correct in looking to Section (3) of the NTP Brief on BPA for NTP-CERHR's conclusions, OEHHA is mistaken in suggesting that NTP "concluded" that BPA causes developmental toxicity in humans. The nineteen NTP-CERHR monographs demonstrate clearly that when NTP has reviewed the human and animal data on a chemical and reached a conclusion concerning its human reproductive or developmental toxicity, NTP consistently expresses its conclusions in Section (3) by using the key words "conclude" and "conclusion." Indeed, NTP consistently uses almost the exact same wording in expressing its conclusions, with only slight and insignificant variations. For example, in the NTP Brief for DINP, in answering the question "Can DINP affect human development or reproduction?", NTP stated:

> Possibly. . . .
>
> * * * * *
>
> Scientific decisions concerning health risks are generally based on what is known as the ***"weight of the evidence."*** In this case, recognizing the absence of human data, some evidence of developmental effects, and limited evidence of no reproductive effects in animals, ***the NTP judges the scientific evidence sufficient to conclude*** that DINP might adversely affect development of the human fetus if the levels of exposure are sufficiently high.[29]

In the NTP Brief on hydroxyurea, in answering the question "Can hydroxyurea affect human development or reproduction?", NTP stated:

> Probably…
>
> * * * *
>
> Scientific decisions concerning health risks are generally based on what is known as the ***"weight of evidence."*** In this case, the NTP recognizes the lack of sufficient data on the effects of hydroxyurea in humans and the clear evidence of adverse effects in laboratory animals and ***judges the scientific evidence sufficient***

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[29] NTP Brief on DINP (2003), at p. 2 (emphasis added).

> ***to conclude*** that hydroxyurea may adversely affect human development and reproduction if exposures are sufficiently high (see Figure 3).[30]

In the NTP Brief on methanol, in answering the question "Can methanol affect human development or reproduction?", NTP stated:

> Possibly…[T]he NTP believes it is reasonable and prudent to ***conclude*** that the results reported in laboratory animals indicate a potential for adverse effects in humans.
>
> Scientific decisions concerning health risks are generally based on what is known as ***"weight of evidence"*** approach. In this case, recognizing the lack of human data and the clear evidence of laboratory animal effects (Figure 2), the NTP ***judges the scientific evidence sufficient to conclude*** that methanol may adversely affect human development if exposures are sufficiently high.[31]

In the NTP Brief on 1-bromopropane, in answering the question "Can 1-BP affect human development or reproduction?", NTP stated:

> Possibly…
>
> Scientific decisions concerning health risks are generally based on what is known as a ***"weight of evidence"*** approach. Recognizing the lack of data on 1-BP toxicity in humans, the NTP ***judges the scientific evidence of effects in laboratory animals sufficient to conclude*** that 1-BP may adversely affect human development if exposures are sufficiently high.[32]

We could go on. In addition to the NTP Briefs quoted from above, the conclusion paragraphs in the NTP Briefs for the following chemicals read almost identically to the ones above: acrylamide (at p. 3), 2-bromopropane (at p. 1), amphetamine (at p. 2), DEHP (at p. 3), DBP (at p. 2), DIDP (at p. 1), and ethylene glycol (at p. 2). In ***every case*** NTP refers to the ***"weight-of-the-evidence"*** principle and provides a clear statement that "***NTP judges the scientific evidence sufficient to conclude*** that [the chemical] may adversely affect human" development or reproduction. We emphasize for the record that we do not endorse the accuracy of NTP's conclusions regarding these chemicals and, moreover, that an NTP conclusion that a chemical "might" or "may" cause reproductive or developmental toxicity does not appear to satisfy Proposition 65's "known to the state to cause" standard. Nevertheless, the point for present purposes follows: ***this is how NTP states its conclusion that a chemical causes adverse***

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30 NTP Brief on hydroxyurea (2008), at pp. 2-3 (emphasis added).

31 NTP Brief on methanol (2003), at p. 2 (emphasis added).

32 NTP Brief on 1-bromopropane (2003), at p. 2 (emphasis added)

reproductive or developmental effects in humans, if and when NTP judges the data sufficient to reach a conclusion.[33]

Section (3) of the NTP Brief for BPA presents a clear departure from the systematic, indeed formulaic, articulation of conclusions in all other NTP Briefs. Consistent with all the other Briefs, NTP asks the question, "Can Bisphenol A affect human development or reproduction?" Also consistent with its practice in several Briefs, NTP answers that question: "Possibly." Also consistent with other Briefs, NTP then briefly discusses the human and animal data on BPA.

The consistency ends there, however. Rather than pronouncing judgment regarding the sufficiency of the evidence and expressing a conclusion whether BPA can cause developmental or reproductive effects in humans, NTP stops short. Instead, in the critical place in the NTP Brief where NTP always states its "conclusions," based on the "weight of the evidence" and its judgment concerning the "sufficiency of the data," as illustrated by the passages from NTP Briefs above, the NTP Brief for BPA states only the following:

> 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, ***the possibility that bisphenol A may alter human development cannot be dismissed*** (see Figure 3).[34]

Several crucial points can be drawn from this paragraph. First, and most important, NTP makes ***no reference to the "weight-of-the-evidence"*** principle and ***does not state NTP's "judgment"*** that the scientific evidence is ***"sufficient to conclude"*** that BPA causes reproductive or developmental toxicity in humans. Considering that in virtually every other NTP Brief, NTP ***does*** explicitly state its ***judgment***, based on the ***weight of evidence***, whether the available evidence is "sufficient" to reach a ***conclusion***, NTP's avoidance of that language in BPA's case

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[33] NTP-CERHR followed the same pattern and used essentially the same language in five other Briefs in which NTP "concluded" that the available data did ***not*** suggest that the chemical in question was a developmental or reproductive toxin: (1) DNHP, "NTP judges the scientific evidence insufficient to reach a conclusion . . . ."; (2) di-n-octyl phthalate, "NTP judges the scientific evidence to indicate DNOP is not likely to affect human reproductive systems. The data are insufficient to make a judgment on possible developmental effects."; (3) Methylphenidate, "the panel judged the data largely insufficient to support clear conclusions . . . "; (4) Styrene, "NTP judges the total scientific evidence sufficient to conclude that it is unlikely that styrene [causes DART effects in exposed humans]"; and (5) Propylene glycol, "NTP judges the scientific evidence sufficient to conclude that PG probably does not adversely affect human development or reproduction."

Finally, in two Briefs NTP used slightly different language that still unambiguously communicated NTP's conclusions. In the NTP Brief on butyl benzyl phthalate, NTP stated "NTP judges the scientific evidence sufficient to support the levels of concern for effects on development and reproduction expressed below . . . ." In the case of fluoxetine, the NTP Brief stated in Section (3) that fluoxetine "probably" affects human development and reproduction, and cited to human studies showing developmental toxicity and impaired male and female sexual function, as well as animal studies supporting those human studies. It appears that the evidence on fluoxetine was so strong that NTP did not think it necessary to refer, as usual, to "weight-of-the-evidence."

[34] NTP Brief on BPA (2008), at p. 7 (emphasis added).

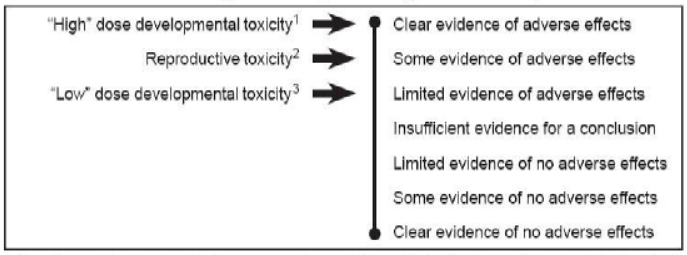
must be understood to mean that NTP ***did not reach a conclusion*** whether BPA does or does not cause developmental toxicity in humans**.**

Second, even if one were to ignore NTP's conspicuous avoidance of the terms that it constantly uses to express a conclusion and focus on the substance of what NTP says "as if" it were a "conclusion," all NTP says is that "the possibility that bisphenol A may alter human development cannot be dismissed." That statement is consistent with the interpretation stated above: NTP was unable to conclude whether BPA does or does not cause developmental toxicity in humans. Conversely, NTP's opinion that "the possibility cannot be dismissed" falls well short of a ***conclusion*** by NTP that BPA ***does*** cause developmental toxicity in humans, and cannot be the basis for a Proposition 65 listing.

Third, it is noteworthy that NTP's highly equivocal statement that the "possibility" of adverse developmental effects "cannot be dismissed" was based ***not*** on the "high-dose" studies to which OEHHA now points as the basis for listing, but rather exclusively on the controversial "low-dose studies" on BPA that OEHHA now disregards. NTP specifically referred to those studies showing adverse effects in laboratory animals on the same page, and just two paragraphs prior to its above-quoted opinion, or "conclusion," about possible adverse effects in humans, so NTP's failure to reference those "high-dose" data in addition to the low dose studies must be considered intentional. Specifically, it must be interpreted to mean that NTP considered those "high-dose" studies to be of so little relevance to potential adverse effects ***in humans*** that those studies were not even supportive of NTP's opinion that adverse effects in humans are a "possibility" that "cannot be dismissed." NTP does not explain why it deemed those high-dose effects in animals not to be evidence of potential adverse effects in humans, but one obvious explanation would be the reason stated by the DART IC—the effects seen in animals were secondary to maternal toxicity.

We understand that OEHHA's tentative determination in the Request that the NTP-CERHR Brief "concluded" that BPA "causes developmental toxicity" in humans is based on Figure 2b, reproduced below, and on certain isolated references in the text of the NTP Brief that are summarized in Figure 2b. We note, however, that Figure 2b does not purport to state or summarize NTP's "conclusions" but instead summarizes the "weight of the evidence that bisphenol A causes adverse developmental or reproductive effects in laboratory animals." As noted above, in the section of the NTP Brief in which NTP always states its "conclusions" about a chemical agent's potential adverse developmental or reproductive effects in humans, NTP conspicuously did not state that the weight-of-the-evidence is sufficient to conclude that BPA causes developmental toxicity in humans, and conspicuously did not even refer to the "high dose developmental effects" studies referenced in Figure 2b in support of its highly equivocal statement that adverse developmental effects in humans are a "possibility."

Figure 2b. The weight of evidence that bisphenol A causes adverse developmental or reproductive effects in laboratory animals



[1]Based on reduced survival in fetuses or newborns (≥500 mg/kg bw/day) *(36–40)*, reduced fetal or birth weight or growth of offspring early in life (≥300 mg/kg bw/day) *(36, 37, 41)*, and delayed puberty in female rats (≥50 mg/kg bw/day) and male rats and mice (≥50 mg/kg bw/day) *(37, 41–43)*.

[2]Based on possible decreased fertility in mice (≥875 mg/kg bw/day) *(40)*; altered estrous cycling in female rats (≥600 mg/kg bw/day) *(110)*, and cellular effects on the testis of male rats (235 mg/kg bw/day) *(111)*.

[3]Based a variety of effects related to neural and behavior alterations (≥10 µg/kg bw/day) *(44–50)*, lesions in the prostate (10 µg/kg bw/day) *(51)* and mammary glands (0.0025–1 mg/kg bw/day) *(52, 53)*; altered prostate gland and urinary tract development (10 µg/kg bw/day) *(54)*, and early onset of puberty (2.4 and 200 µg/kg bw/day) *(48, 55)*.

As the title of Figure 2b reflects, the figure itself and the statements within it and referenced by it do not purport to be NTP's "conclusions" about BPA based on NTP's weighing of all the human and animal data; rather, they are just observations about some of the animal data that NTP-CERHR considered. NTP's actual "conclusion" about BPA has been quoted and discussed above. It is illogical and improper to conflate the observations in Figure 2b about some of the data with an NTP "conclusion" about the ultimate weight of those data on the question to be answered — whether the studies are sufficient evidence to conclude that BPA causes developmental effects in humans.

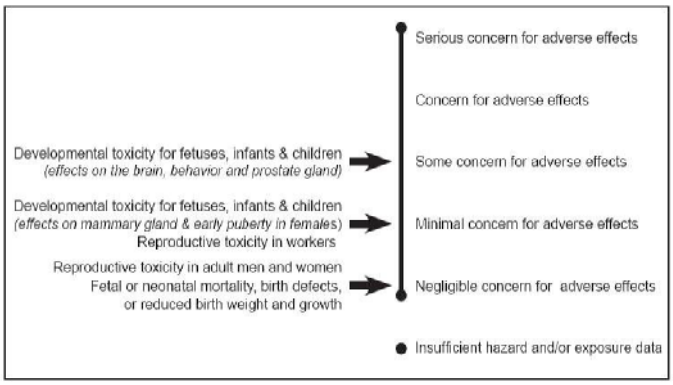
In this regard, it is important to note that every NTP Brief, like the NTP Brief on BPA, contains a "Figure 2b," and that the Figure 2b for BPA is unique among all NTP Briefs for all of the chemicals that NTP has examined. This is the only Figure 2b that has more than one arrow to depict the weight of the evidence for developmental effects in laboratory animals. The first arrow, labeled "high dose developmental toxicity," points to "clear evidence of adverse effects," and the footnote clarifies that those effects are reduced survival in fetuses and newborns, reduced fetal or birth weight or growth early in life, and delayed puberty in female rats and male and female mice. This arrow, and this statement referring to "clear evidence of adverse effects" at "high doses," is what OEHHA mischaracterizes as a "conclusion" by NTP that BPA causes developmental effects in humans. The second arrow, labeled "low dose developmental toxicity," points to "limited evidence of adverse effects," and the footnote clarifies that those effects are neural and behavioral alterations, lesions in the prostate and mammary glands, altered prostate and urinary tract development, and early onset of puberty. OEHHA's Request does not refer to this arrow and it is clear that OEHHA is not proposing to list BPA on the basis of those effects and NTP's assessment of the evidence for them.

The use of two arrows here reinforces the fact that the arrows and the words in the table, consistent with its title, are intended only to summarize the "weight of the evidence that bisphenol A causes adverse developmental or reproductive effects ***in laboratory animals***," and not to convey a "conclusion" about potential adverse developmental in humans, as noted above. This point is underscored by a review of NTP's conclusions about potential risks to humans, summarized in Figure 3, below. Comparison of the "conclusions" in Figure 3 with the statements

in Figure 2b further demonstrates that OEHHA is confusing the two, with a tortured, illogical result.

Figure 3, reproduced below, consistently with Figure 2b, includes more than one arrow to depict the potential for adverse effects in humans.

Figure 3. NTP conclusions regarding the possibilities that human development or reproduction might be effected by exposure to bisphenol A



Each arrow corresponds to different types of reproductive or developmental effects, and the placement of the arrows from top to bottom corresponds to NTP's hierarchical "levels of concern," with "Serious" appearing at the top of the table and lower levels below. The top-most arrow for BPA, which points to "***some*** concern for adverse effects" (the highest level of concern expressed by NTP for BPA), corresponds to "developmental toxicity for fetuses, infants and children (effects on the brain, behavior and prostate gland)." Clearly, those effects are not the effects associated with "high dose developmental toxicity" in Figure 2b. The middle arrow points to "minimal concern for adverse effects," and corresponds to "developmental toxicity for fetuses, infants and children (effects on mammary gland and early puberty in females)." Clearly, those effects also are not the effects associated with "high dose developmental toxicity" in Figure 2b, either. Finally, the third arrow, which corresponds to "Reproductive toxicity in adult men and women, fetal or neonatal mortality, birth defects, or reduced birth weight and growth," points to "Negligible concern for adverse effects." It is these effects – fetal or neonatal mortality, reduced birth weight and growth – that are associated with "high dose developmental toxicity" in Figure 2b.

Given the interrelationship of these tables in the NTP Brief, it makes no sense for OEHHA to equate the five words from Table 2b – "clear evidence of adverse effects" – which obviously characterize only the weight of the evidence that BPA causes developmental effects at high doses in certain animal studies, as a "conclusion" on the part of NTP regarding the potential for an association between those effects in animals and similar effects in humans. Indeed, Figure 3 is proof that this is not the intended meaning: there, the NTP Brief indicates that NTP has only "negligible concern" (the lowest possible level) concerning the possibility of these effects ***in humans,*** and expresses a greater level of concern for other adverse effects in humans for which there was only "limited evidence" in laboratory animals.

The comments (indeed, the ***conclusions***) of the DART IC on this point are instructive: the DART IC members ***agreed*** with NTP's observation that there is "clear evidence of adverse

effects" at high doses in certain laboratory animal studies, but concluded that maternal toxicity accounted for those effects, and thus, that the studies are not evidence of potential adverse effects in humans. DART IC Member Roberts summarized this point perfectly at the hearing in July 2009, in discussing the very same animal studies referenced in Figure 26:

> We referred to high dose studies. ***The high dose studies have clear evidence of developmental toxicity. They do occur in the presence of maternal toxicity. And the issue isn't whether or not developmental toxicity occurs. It's whether or not there is sufficient maternal toxicity to potentially be causing the other***.
>
> And when you have situations where the animals are either losing weight or gaining very little weight or they're described as emaciated, that to me can be a cause of something like an increase in resorptions pre-natally. Surprisingly, ***even when there were some fairly strong forms of maternal toxicity, it did not cause malformations. So it doesn't seem that that particular endpoint out of the four is of concern.***
>
> ***When there is maternal toxicity, it does have a decrease in fetal body weight. It has an increase in pre-natal loss. Those are both endpoints that are more commonly associated with severe maternal toxicity than others.***
>
> And a decrease in ossification does not – as long as it is a decrease in ossification, and not a structural change, it tends to go along with decrease in fetal body weight. Tr. at 236 – 237 (emphasis added).

These conclusions by the State's Qualified Experts, along with NTP's pointed and conspicuous refusal to state a "conclusion" that the weight of the evidence is sufficient to identify BPA as a developmental toxicant in humans (referring instead to only a "possibility that . . . cannot be dismissed . . . .") conclusively refute the proposition that the isolated characterization of the "high dose findings" in Table 2b was intended by NTP-CERHR to "formally identify" BPA as "causing . . . reproductive toxicity" within the meaning of the Act. By the regulatory standard applicable here, set forth in Section 25306(d)(1), it cannot be said that the NTP-CERHR Monograph "concludes that [BPA] causes reproductive toxicity."

B. *Because BPA Is Not "Formally Identified" in the NTP-CERHR Monograph as Causing Reproductive Toxicity, It Is Beyond the Authority of OEHHA to Re-examine the Data to Reach a Different Conclusion*

OEHHA is exceeding its authority in issuing the Request, and in proposing to list BPA under the Authoritative Bodies Mechanism. Under the Act, a chemical is to be listed as a reproductive toxicant under this "mechanism" if "a body considered to be authoritative by [the State's Qualified Experts] has formally identified it as causing . . . reproductive toxicity."[35]

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[35] Cal. Health & Safety Code, § 25249.8(b).

Because the Act does not indicate expressly who should make this determination, OEHHA, as the "lead agency," was assigned by regulation the responsibility to "determine which chemicals have been formally identified by an authoritative body."[36] If an authoritative body does "formally identify" a chemical as a reproductive toxicant, then OEHHA has a further responsibility to determine whether the underlying data constitute "sufficient evidence" for support that identification, by the standards set forth in Section 25306(g)(2).[37]

But the converse is not true. Where an authoritative body declines to "formally identify" a chemical as a reproductive toxicant, nothing in the Act or the implementing regulations gives OEHHA the authority, much less responsibility, to examine the underlying data to see if the agency would reach a different conclusion.

If this is not clear from the face of the regulations themselves, it is abundantly clear from the Statement of Reasons, which indicates that the Authoritative Bodies Mechanism was intended primarily "to establish a streamlined process for the [Scientific Advisory] Panel."[38] The Statement of Reasons explains that the State's Qualified Experts Mechanism, referred to as the "***primary approach to listing***," is a "time-consuming process."[39] Therefore, the Authoritative Bodies Mechanism was designed as a "streamlined" process, and duties were delegated to OEHHA, rather than to the Panel, simply to conserve the Panel's resources.

Nevertheless, as recounted above, the Scientific Advisory Panel expressed significant concerns that the Authoritative Bodies Mechanism would result in "unrestrained listings" if adequate controls and criteria were not put in place. The regulations that were drafted to address that concern created essentially a two step-process. First, OEHHA is required to "determine which chemicals have been formally identified by an authoritative body as causing cancer or reproductive toxicity."[40] Then, if a determination is made that a chemical has been "formally identified," OEHHA must also determine whether there is "sufficient evidence" to support that formal identification.

This is clear from the structure of the regulations, which address the phrases "formally identified" and "as causing reproductive toxicity" separately, in Sections 25306(d) and 25306(g), respectively. With respect to Section 25306(d), the Final Statement of Reasons explains:

> [Section] 25306(d) defines the circumstances under which a chemical is "formally identified" within the meaning of section 25249.8. The lead agency must make a determination that specified requirements of identification and formality have been satisfied.

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36 Cal. Code Regs., *tit.* 27, § 25306(c).

37 *Exxon Mobil v. OEHHA,* 169 Cal.App.4th at 1282.

38 Final Statement of Reasons at 8.

39 Final Statement of Reasons at 8 (emphasis added).

40 Cal. Code Regs., *tit.* 27, § 25306(c).

> [Section] 25306(d)(1) requires some kind of written identification. Specifically, the chemical must (1) be included on a list of chemicals causing cancer or reproductive toxicity, or (2) the subject of a report which is published by the authoritative body concluding that the chemical causes cancer or reproductive toxicity, or (3) be otherwise identified as causing cancer or reproductive toxicity by the authoritative body in a document which indicates that such identification is a final action. List and reports are methods of identification commonly used by governmental and non-governmental entities alike to identify chemical hazards.

The purpose and meaning of Section 25306(g) are explained by portions of the Statement of Reasons that address Section 25306(e) as well as Section 25306(g), because those provisions are virtually identical, and are different only insofar as one addresses cancer and the other addresses reproductive toxicity. Addressing Section 25306(e), the Final Statement of Reasons explains:

> [Section] 25306(e) provides that, for purposes of section [25306, the phrase "as causing cancer" means that either of two scientific criteria have been satisfied. Generally, the authoritative body may rely on either studies in humans or studies in animals . . . .
>
> As originally proposed, subsection (e) (then subsection (d)) provided:
>
> "Except as provided in subdivisions (e), (h), or (i), the lead agency shall determine that a chemical is formally identified by an authoritative body as causing cancer when either of the following criteria has been satisfied: . . . **[**passage regarding proposed-and-rejected changes omitted for brevity] . . . To avoid . . . confusion, subsection (e) was amended . . . to resemble subsection (d), and simply provide, "For purposes of this section, 'as causing cancer' means that either of the following criteria has been satisfied: . . ." ***This made clear that subsections (d) and (e) implement different terms. Subsection (d) implements the terms "formally identified," and subsection (e) implements the terms "as causing cancer."***[41]

By substitution, everything said above about subsection (e) (addressing cancer) also applies to its parallel provision, subsection (g) (addressing reproductive toxicity). Thus, it is clear that in determining whether a chemical has been "formally identified as causing reproductive toxicity," Section 25306(d) addresses the criteria for determining when a chemical has been "formally identified" as a reproductive toxicant, and Subsection 25306(g) addresses separately the criteria for determining whether there are "sufficient evidence" to support that "formal identification." The formal identification comes first; the examination of the supporting evidence comes second.

That is the only reading of these regulations that is consistent with their purpose. Given that the reason for the criteria in Section 25306(g) was to prevent "unrestrained listings," what

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[41] Final Statement of Reasons at pp. 15–16 (emphasis added).

purpose would be served by examining the data underlying an authoritative body's decision ***not*** to formally identify a chemical as a carcinogen or reproductive toxicant? Similarly, and to better illustrate the point, recall that Section 25306 applies to "lists" of chemicals that identify carcinogens and reproductive toxins as well as "reports" that "conclude" that chemicals present those hazards. If a chemical did not appear on an authoritative body's "list" of such hazardous chemicals, would OEHHA proceed to examine the data that were the basis of the decision not to list it? Of course not. Then why, when an "authoritative body" like the NTP-CERHR ***declines*** to conclude in a report that a chemical causes reproductive toxicity, should OEHHA proceed to evaluate the data underlying the authoritative body's "conclusion"? The answer: it should not.

If OEHHA has any doubt concerning these requirements and the relationship between the "formal identification" that must occur under Section 25306(d) as a condition precedent to OEHHA's authority to examine the record for data that would satisfy Section 25306(g), we urge the Agency to reconsider in light of OEHHA's position and the ruling of the Court of Appeal in *Exxon Mobil v. OEHHA*. In that case, Exxon Mobil contended that the listing of DIDP was unlawful, among other reasons, because OEHHA "abused its discretion by concluding, on the scientific record before NTP, that there was substantial evidence that the criteria identified in [Section] 25306(g) had been satisfied."[42] While the case presented many issues not pertinent here, the core analysis is dispositive.

The case turned on two critical issues: (1) whether the NTP Brief "formally identified" DIDP as a developmental toxicant for purposes of Section 25306(d) and if so, (2), whether OEHHA reasonably concluded that the data were "sufficient" evidence to support that formal identification, taking into account the factors prescribed by Section 25306(g). In so framing the case, the court responded to Exxon Mobil's contention that the NTP Brief on DIDP could not serve as the basis for listing under the Authoritative Bodies Mechanism – and hence the matter should have been referred to the DART IC – because the NTP Brief on its face did not include findings to address of the factors identified in Section 25306(g). OEHHA's response is so pertinent here that we quote the Court's recitation of it in full.

> ***[T]he authoritative body provision is triggered if a body considered authoritative under the statute identifies a chemical in a report, list, or other document as a developmental toxicant***. The authoritative body's report must satisfy the "formality" requirements of the statute – that is, it must accurately identify the chemical, have been reviewed by an advisory committee in a public meeting, have been made subject to public review and comment, and have been adopted as a final report by the authoritative body – but it need not include the detailed findings set out in [Section] 25306(g). Instead, ***once the chemical is "formally identified" by an authoritative body as a developmental toxicant, OEHHA reviews the scientific record before the authoritative body to determine whether there is substantial evidence to support a listing.*** If it concludes on the basis of its review that the [Section] 25306 criteria are satisfied – *i.e.,* that the experimental animal

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[42] *Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1287. The ultimate and determinant issue in this case was whether OEHHA was permitted to go beyond the NTP Brief to the underlying scientific record to make these findings. This issue is not presented here.

data considered by the authoritative body are sufficient to support a conclusion that an association between adverse reproductive effects in humans and the toxic agent is biologically plausible – then it lists the chemical.[43]

In this framework, and citing the passage of the NTP Brief quoted above, the court thus ruled:

> "***The NTP Brief unambiguously identified DIDP as a developmental toxicant.*** [Emphasis added here.] It stated: 'Scientific decisions concerning health risks are generally based on what is known as 'weight-of-the-evidence.'
>
> In this case, . . . ***NTP judges 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.' [Emphasis as it appears in court opinion.]
>
> ***Based on this statement***, [emphasis added here] there can be little doubt that ***NTP made the determination pivotal to the authoritative body scheme***: That ***DIDP is a developmental toxicant in humans*** [emphasis added here]."[44]

Thus, Section 25249.8(b) of the Act, Sections 25306(d) and 25306(g) of the implementing regulations, the Final Statement of Reasons, OEHHA's own statement of these requirements before the Court of Appeal and the Court's ruling all demonstrate that "formal identification" of a chemical as a reproductive or developmental toxicant ***in humans*** must be made ***by the authoritative body*** before the Authoritative Bodies Mechanism can be "triggered." It is equally clear that such formal identification for BPA was not made by NTP. The contrast between the "unambiguous" statements that persuaded the Court of Appeal that DIDP was formally identified, versus the patently ambiguous and equivocal observations articulated in the NTP Brief for BPA could hardly be more stark, and demonstrates clearly that BPA was not formally identified as a developmental toxicant in the NTP-CERHR Monograph. In the absence of a "formal identification," there is no basis for an authoritative bodies listing.

C. *The Authoritative Bodies Mechanism Does Not Allow OEHHA to Effectively Overrule the State's Qualified Experts in Evaluating the Same Data*

A proposal to list BPA under the Authoritative Bodies Mechanism on the basis of isolated statements in the 2008 NTP-CERHR Monograph after the DART IC's unanimous July 15, 2009 decision rejecting that very report as a basis to list BPA necessarily presupposes that an authoritative body listing validly can be based on: (1) the very same report and underlying data that the State's Qualified Experts considered and rejected as a basis for listing the chemical, and (2) a scientific/legal standard less stringent than the standard that the Experts applied when they

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[43] *Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1278-79 (emphasis added).

[44] *Exxon Mobil v. OEHHA,* 169 Cal.App.4th at 1285 (reformatted for emphasis and clarity).

determined that BPA should not be listed. That presupposition is contradicted by Sections 25306(e), (g) and (i) of the Proposition 65 implementing regulations,[45] which require an authoritative body listing to be based on scientific evidence that satisfies the standards of the State's Qualified Experts, and which collectively demonstrate a clear intention to prevent the listing of a chemical on the basis of a report that, although issued by an authoritative body, has "formally identified [the chemical] as causing cancer or reproductive harm" based on standards less stringent than the State's experts themselves would require.

1. *Section 25306(g) Was Promulgated to Ensure That Decisions Made by OEHHA in Implementing the Authoritative Bodies Mechanism Would Be Consistent with Those Made by the State's Qualified Experts*

The regulatory history of Section 25306, which implements the Authoritative Bodies Mechanism authorized by Section 25249.8(b) of the Act, makes it very clear that the mechanism is not intended to allow or result in the listing of chemicals that do not satisfy the Proposition 65 listing criteria, as the State's Qualified Experts apply them. The Final Statement of Reasons[46] shows that the State's Qualified Experts,[47] who are the persons authorized by Section 25249.8(b) of the Act to designate – or ***not*** to designate – bodies as "authoritative" and hence empowered to formally identify chemicals as causing cancer or reproductive toxicity, were very concerned to ensure that any listings by such authoritative bodies would satisfy Proposition 65's stringent criteria**.**

The Scientific Advisory Panel was concerned that the Authoritative Bodies Mechanism could result in unjustified or "unrestrained" listing of chemicals that do ***not*** satisfy the Proposition 65 criteria, and was unwilling to designate any body as authoritative unless and until regulatory safeguards were implemented to prevent such unjustified listings. This concern was the genesis of the development of Section 25306 (then Section 12306), as explained in the passage from the Final Statement of Reasons below.

> "PROCEDURAL BACKGROUND
>
> "The concept of this regulation was conceived following the Panel's meeting of October 1987. In that meeting, ***the Panel expressed strong reservations about designating any body as authoritative due to its concern that the designation would result in the unrestrained listing of chemicals. Consequently, the Agency determined that it would be necessary to implement and make specific the provisions of the Act relating [to] authoritative bodies*** to enable the Panel to take advantage of this listing mechanism. Subsequently, the Agency commenced

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45 Cal. Code Regs., *tit*. 27, § 25306(e), (g), (i).

46 Final Statement of Reasons, *supra*.

47 At that time, the "Scientific Advisory Panel" ("Panel"), the precursor to the CIC and DART IC.

drafting this regulatory proposal. Copies of early proposals were circulated to interested persons and the Panel.

"On April 14, 1989, following a command from the Sacramento Superior Court, the Panel considered the question whether the United States Environmental Protection Agency (EPA) is an "authoritative body" within the meaning of the Act and concluded that EPA is authoritative, but ***conditioned the designation upon application of certain controls to the listing of chemicals pursuant to that designation, and asked the Agency to draft rules embodying these controls***. The terms of the condition were similar to the controls in the draft regulatory proposal. Subsequently, on July 17, 1989, the Agency proposed section 12306 [recently renumbered as Section 25306] for adoption."[48]

Section 25306 defines in its subsections the criteria that authoritative body listings must satisfy. For both carcinogens and reproductive toxicants, the Statement of Reasons explains that authoritative body listings are to be based on scientific evidence that satisfies the ***Scientific Panel's own criteria.***

Section 25306(e) sets forth the criteria that must be met for data to support an authoritative body listing for carcinogens. The Statement of Reasons recites:

"SUBSECTION (E)

"Subsection (e) provides that, for purposes of section 12306 [now section 25306], the phrase "as causing cancer" means that either of two scientific criteria have been satisfied. Generally, the authoritative body may rely on either studies in humans or studies in animals. ***These criteria are consistent with the criteria the Panel presently uses in evaluating chemicals for listing.*** The Panel utilizes the EPA's Classification System for Categorizing Weight of Evidence for Carcinogens From Human and Animal Studies [51 Fed. Reg. 33999 (Sept. 24, 1986)]. The same, or substantially similar criteria have been adopted by many regulatory agencies and scientific organizations involved in hazard identification. ***The use of these criteria will ensure that the standards applied by an authoritative body are the same as or substantially similar to those used by the Panel to evaluate chemicals."***[49]

Section 25306(g) defines the scientific criteria that must be met for data to support an authoritative body listing for a reproductive toxicant.[50] As was the case with carcinogens, the Final Statement of Reasons explicitly indicates that any authoritative body listing of a reproductive toxicant must be based on scientific evidence that satisfies ***the Scientific Panel's own criteria*:**

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[48] Final Statement of Reasons at 2 (emphasis added).

[49] Final Statement of Reasons at 15 (emphasis added).

[50] The language of subsection (g) that was adopted in 1990 (as Section 12306(g)) is exactly the same as the current language of § 25306(g).

"SUBSECTION (G)

"Subsection (g) provides that, for purposes of section 12306 [now section 25306], the phrase "as causing reproductive toxicity" means that either of two scientific criteria have been satisfied. Generally, the authoritative body may rely on either studies in humans or studies in animals.

"Paragraph (g)(1) describes the criteria for determining that a chemical causes reproductive toxicity where the authoritative body relied on studies in humans. As with carcinogens discussed above, the proposed regulation requires that sufficient evidence exist from such studies, in that studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity.

"Paragraph (g)(2) describes the criteria for determining that a chemical causes reproductive toxicity where the authoritative body relied on studies in animals for its identification of a chemical as a reproductive toxicant. ***Again, the proposed regulation requires that sufficient evidence exist from such studies. "Sufficient evidence" is defined to mean that there is sufficient data, which take into account the adequacy of the experimental design and other specified parameters,*** indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible. ***This is consistent with the criteria utilized by the Panel when it evaluates reproductive hazards."***[51]).

Finally, Section 25306(i) establishes the procedure that OEHHA must follow in proposing an authoritative body listing. The references in subsection (i) to the scientific criteria of subsections (e) and (g) clearly signify that any authoritative body listing must be based on scientific evidence that satisfies the Proposition 65 listing criteria, as the State's Qualified Experts would apply them. The Statement of Reasons confirms that subsection (i) was intended as a fail-safe mechanism to ensure that in the rare instance in which an authoritative body might "formally identify" a chemical as a carcinogen or reproductive toxicant on the basis of evidence that does ***not*** satisfy the Proposition 65 criteria, the chemical will be referred to the State's experts for review prior to listing ***so that such unjustified listing will be prevented:***

"SUBSECTION (I)

"Subsection (i) sets forth a procedure to be followed by the lead agency prior to the listing of chemicals on the ground that they are formally identified by authoritative bodies as causing cancer or reproductive toxicity. At least 60 days prior to causing the chemical to be added to the list of chemicals known to the state to cause cancer or reproductive toxicity, the lead agency must publish a notice identifying the authoritative body and the chemical, stating its intention to cause the chemical to be added to the list. ***Interested parties will have 30 days within which to object to the proposed listing on the ground that there is no***

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[51] Final Statement of Reasons at 21 – 22 (emphasis added).

substantial evidence that the scientific criteria set forth in subsection (e) and (g) have been satisfied. Such objections must be in writing and be accompanied by supporting documentation.

* * * *

Subsection (i) arises out of concerns that chemicals formally identified by authoritative bodies might be listed even though the criteria utilized by the Panel had not been satisfied.[52]

These provisions of Section 25306, as explained by the foregoing excerpts from the Final Statement of Reasons, conclusively establish that authoritative body listings legally may ***not*** be based on scientific evidence less stringent than the evidence that the State's Qualified Experts – here, the DART IC – apply in their own review of chemicals for potential listing. To the contrary, the Authoritative Bodies Mechanism was implemented with considerable safeguards and requirements to ensure that authoritative body listings would satisfy the ***same*** criteria.[53]

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[52] Final Statement of Reasons at 24 (emphasis added).

[53] There is no authority to support a contrary conclusion. In particular, the July 20, 1998 memorandum authored by a former Chief Counsel to the Agency (hereinafter, "Counsel's Memo") and attached as Attachment 5, is not authority, and does not support a contrary view.

The Counsel's Memo addresses, among other questions, "What effect, if any, does a determination by the CIC or DART Committee to not identify a chemical for listing under Proposition 65 have on the authority of the lead agency to list a chemical as causing cancer or reproductive toxicity on the basis of an authoritative body formal identification?" The author concludes that "each of the three listing mechanisms is independent of the other methods and has its own authority. Accordingly, a determination by the CIC or DART Committee to not identify a chemical for listing under the 'State's qualified expert' mechanism is no bar or limitation on the authority of authoritative body to formally identify a chemical as causing cancer or reproductive toxicity. Again, the Statute (Section 25249.8(b)) is framed in the disjunctive – 'or.' If a chemical meets one of the three listing methods, it may be added to the list."

In response, we note that the Counsel's Memo is not a statute, regulation, rule or other authority, but only an opinion of the former Chief Counsel, by which the Agency is not bound, and which can and should be corrected as a misstatement of the law, if it would be mistaken as authority to allow the Petition to be granted. First, the author cites no authority other than her observation that the three listing mechanisms identified in Section 25249.8(a) of the statute are "independent," because they are connected by the word "or." Second, while it is obviously true that the various "mechanisms" are independent, that is no reason to conclude that the mechanisms are intended to support different results, or that the separate clauses of Section 25249.8(b) that establish separate listing "mechanisms" should be read to establish different listing ***criteria***. Third, the Statement of Reasons, which includes the Agency's official interpretation of the Act and implementing regulations, provides expressly to the contrary. As noted above and in the Statement of Reasons, Section 25249.8(b) of the statute vests in the State's Qualified Experts the exclusive authority to determine what bodies are "considered to be authoritative" and thus, implicitly, to establish criteria for their designation as "authoritative." Given that the clause in Section 25249.8(b) that provides for authoritative bodies – which reads in its entirety as follows: "or if a body considered to be authoritative by such experts has formally identified [a chemical] as causing cancer or reproductive toxicity" – includes ***no*** listing criteria, the Agency at the Scientific Advisory Panel's request promulgated Section 25306, which does include listing criteria, for the express purpose of ensuring that the any bodies that the Panel deemed to be authoritative would be bodies that applied criteria that are ***"consistent with the criteria used by the Panel."***

(footnote continued on next page)

2. *The Section 25306(g) Criteria Thus Are Essentially the Same as the Criteria Employed by the DART IC*

It is important here to examine the criteria by which the DART IC makes its determinations whether a chemical should be listed, because they identify the same factors that OEHHA is supposed to evaluate when it reviews documents published by authoritative bodies to determine whether chemicals that have been "formally identified" as reproductive toxicants. Those criteria, formally known as "Criteria for Recommending Chemicals for Listing As 'Known to the State to Cause Reproductive Toxicity," are referred to herein simply as the DART IC Criteria.[54]

The DART IC Criteria give the Committee "maximum flexibility" to evaluate ***"all pertinent scientific information***," taking a ***"'weight of the evidence' approach."***[55] Like Section 25306(g), the DART IC Criteria require listing where there is ***"sufficient evidence in humans***" to show a "***causal relationship***" between "exposure to the chemical and the developmental or reproductive effect.".[56] Regarding animal studies, and in further similarity to Section 25306(g), they require listing where there is "[***s]ufficient evidence*** in experimental animals (mammals), ***such that extrapolation to humans is appropriate*** , . . . based on the adequacy of the . . . ***experimental design***, [where the] exposure, in terms of route of administration, is relevant to expected human exposures," and taking into account ***"[c]onsideration of maternal … toxicity***."[57]

Regarding maternal toxicity, the DART IC Criteria go on to explain that the ***"high dose level [in animal studies] should elicit maternal toxicity in developmental studies***, and systemic toxicity in female and male reproductive studies, and that ***the low dose should elicit*** no observable adverse effect for adult and offspring."[58] Under the heading "Consideration of maternal toxicity," they indicate that "[d]ifferentiating between (a) the effects of a toxic agent on the conceptus or reproduction and (b) the effects on the conceptus or reproduction that are

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Fourth, putting the above legal premises aside, the ultimate conclusion expressed in the Counsel's Memo – that a ruling by the CIC or DART IC that a chemical does not qualify for listing under Proposition 65 is "no bar or limitation on the authoritative body to formally identify a chemical as causing cancer or reproductive toxicity" – does not address the situation here. We are not faced with the question whether the decision of a Scientific Advisory Panel (here, the DART IC) has any effect on the authoritative body to go about its business, as the Counsel's Memo addresses. Indeed, we would agree with the conclusion that an authoritative body has every right to consider a chemical for whatever purposes its statutory mission may require, and to accept or reject the findings of the DART IC. The different question that we must answer here is whether the Agency may ignore the conclusion of a Scientific Advisory Panel (again, the DART IC) that a report issued by an authoritative body (here, the NTP-CERHR) does not establish that a chemical meets the § 25306(g)(2) criteria for listing under Proposition 65. For the reasons discussed in the text of these comments above, the Agency may not ignore that opinion. The Counsel's Memo does not say otherwise.

54 DART IC Criteria (Nov. 1993), attached hereto as Attachment 3.

55 DART IC Criteria at 1 (emphasis added).

56 DART IC Criteria at 3 (emphasis added).

57 DART IC Criteria at 4 (emphasis added).

58 DART IC Criteria at 4 (emphasis added).

secondary to the maternal or systemic toxicity effects is sometimes difficult and may require special attention, on a case by case basis."[59]

3. *The DART IC Decision Not to List BPA Is Consistent With The DART IC Criteria (and Section 25306(g))*

At the hearing, on the record, the DART IC discussed the animal studies on which OEHHA now relies and stated explicitly that those studies do ***not*** satisfy the DART IC Criteria – and why. The scientific evidence in the HID, reviewed by the DART IC at and prior to the public meeting, included all the scientific evidence reviewed by NTP-CERHR, and in addition, included NTP-CERHR's own discussion of the data. The transcript of the July 15, 2009 public hearing shows that the DART IC reached its decision not to list BPA based on two general conclusions regarding the scientific evidence on BPA:

> (1) the conventional, well-conducted studies described in the NTP-CERHR Monograph as showing "clear evidence of developmental effects at high doses" showed maternal toxicity at the same and lower doses, making the evidence of developmental effects unpersuasive; and
>
> (2) the very large number of "unconventional" studies purporting to show effects at low doses did not qualify as "scientifically valid testing according to generally accepted principles."

The significance of maternal toxicity in the well-conducted conventional studies – the studies cited in the NTP CERHR Monograph as showing "clear evidence of developmental effects at high levels of exposure" – was addressed explicitly, first in oral presentations by Dr. Solomon (for NRDC) and then by Dr. Tyl and Dr. Murray (for ACC) at the July 15 hearing, and then by the DART IC members themselves in their discussion of the scientific evidence prior to their unanimous votes not to list BPA. The issue was introduced by Dr. Solomon, who argued that the principal studies cited in the NTP CERHR Monograph showed "clear evidence of adverse effects with high doses . . . ."[60]

> **Dr. Solomon:**
>
> ***[T]he conclusion was that they're not simply secondary to maternal toxicity*** . . . [M]ost of the ones we're talking about are the Research Triangle Institute studies by Tyl, *et al.*, the study abstracts when you just read those and the conclusions seem to indicate that the developmental effects are only in the setting of maternal toxicity, might not represent true developmental toxicity.
>
> And then when you actually go through and you look at the data in the reports, it's actually quite clear that there are effects in the setting of minimal, if any, maternal

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59 DART IC Criteria at 4-5.

60 Transcript of July 15, 2009 DART IC Meeting ("Transcript"), p. 51 (emphasis added).

toxicity in most of those studies. ***And that's what the CERHR panel based their conclusion of clear evidence of adverse effects on.***[61]

As a matter of context, we must point out that there is no basis in the NTP Brief to support Dr. Solomon's assertion that NTP-CERHR reached the conclusion that Dr. Solomon asserted about the role of maternal toxicity in the studies in question. As to the data themselves, Dr. Tyl, the principal author of three of the crucial studies, described her studies in detail. Tr. at 112 – 129. Dr. Tyl directly addressed and refuted Dr. Solomon's assertion that the developmental effects in certain studies at high dose levels were "not simply secondary to maternal toxicity" and that they occurred "in the setting of minimal, if any, maternal toxicity." Addressing the multi-generation rat study (Tyl, *et al*., 2002b)[62], Dr. Tyl stated:

Dr. Tyl:

[W]e only saw . . . reproductive and developmental effects of BPA at a dose that was clearly systemically toxic and at a dose that was lower than that and still toxic, we still didn't see anything.

We concluded that BPA was not considered a selective reproductive or developmental toxicant in rats. Okay, because ***you didn't see the reproductive or developmental effects, unless you also saw maternal toxicity***.

And even at lower maternal toxicity, you didn't see the effects.[63]

Dr. Tyl went on to explain that there were similar findings in a comparable two-generation study on mice, describing in detail the design, and the results:

Dr. Tyl:

We got adult systemic toxicity at the top two doses, sound vaguely familiar. Hepatic histopathology at 50. And at 600 milligrams per kilogram per day, we got reduced body weights. We got increased liver and kidney weights. And we saw the same kind of histopathological problems in the liver and the kidneys.

"The developmental effects at 600 milligrams per kilogram per day, included delayed testis descent, which you normally see in the last week of lactation. It ultimately happened, but it happened slightly later. Transient hypoplastic testes, because we looked at weanling animals histopathologically, and slightly delayed acquisition of puberty in offspring males okay, considered not driven by estrogenic activity, but ***likely secondary to systemic tox***.

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61 Transcript, p. 52 (emphasis added).

62 The dates for the Tyl studies (e.g., 2002b) are as they appear in the NTP Brief.

63 Transcript, p. 118 (emphasis added).

We saw no effects on adult reproductive functions, including andrology or structures, included testes, epididymides, prostate, ovaries, mammary glands, uterus/cervix. And we looked at those in the weanlings and the adults for the F0 adults, the F1 weanlings, the F1 adults and then the F2 weanlings. There were no low dose effects again at .5 to .003 milligrams per kilogram per day. No evidence for non-monotonic dose response curves for any parameter at any dose in any generation. Responses to the E2 positive control, confirmed the sensitivity of the CD-1 mouse to estrogens and confirmed the findings that we had presented for the one-gen and the two-gen[] study, because ***we only saw effects in the presence of systemic tox, and only at the highest dose. And the second to highest dose also has systemic tox and no reproductive or developmental effects.*** We considered ***BPA was not a selective reproductive or developmental toxicant in mice either***.[64]

* * * * *

[S]o BPA is not a selective developmental reproductive toxicant in rats or mice. ***The reproductive and developmental effects seen at high BPA-dietary doses are only observed in the presence of systemic tox. So they are considered secondary to the systemic toxicity observed.***

[T]here was no evidence of effects at low BPA doses and no non-monotonic dose response curves in any parameter in either species in rats or in mice at any dose level.

[T]he interesting thing is the insensitive rat and the sensitive mouse have exactly the same systemic and reproductive NOELs, which I think is fascinating.

[T]he final comment is the BPA reproductive and developmental effects observed at these high doses are not consistent with estrogenic activity. We know what the normal estrogenic activity should be, because we did the one- and two-generation E2 studies to make sure we could document those. And the effects we saw at high doses are not those associated with an estrogen." Tr. at 126 – 127 (emphasis added).

Dr. Murray followed Dr. Tyl, further contradicted Dr. Solomon's claims about CERHR's "conclusions," and concurred with Dr. Tyl's conclusions. Tr. at 131 – 132. Dr. Murray also addressed the large number of "unconventional" studies listed in the HID. He noted that CERHR had described many of these studies as "inadequate or of limited utility," Tr. at 133, and went on to draw attention to a long list of shortcomings in terms of study design, route of administration, inadequate numbers of test animals, etc. Tr. at 133 – 136. Dr. Murray concluded that the weight of the scientific evidence clearly did not support listing BPA. Tr. at 138 – 139.

Significantly, the transcript leaves no doubt that the DART IC members were focused closely on maternal toxicity, consistently following the DART IC Criteria. The record is quite

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[64] Transcript, pp. 124-125 (emphasis added).

clear that the DART IC concluded that the adverse developmental effects observed in the studies at "high dose levels" (the very studies to which OEHHA points now) occurred only in the presence of significant maternal toxicity, and that the numerous unconventional studies listed in the HID were too inconsistent and of insufficient quality to satisfy the Proposition 65 criteria for listing.

> **Committee Member Roberts,** addressing developmental toxicity:
>
> We referred to high dose studies. ***The high dose studies have clear evidence of developmental toxicity. They do occur in the presence of maternal toxicity. And the issue isn't whether or not developmental toxicity occurs. It's whether or not there is sufficient maternal toxicity to potentially be causing the other***.
>
> And when you have situations where the animals are either losing weight or gaining very little weight or they're described as emaciated, that to me can be a cause of something like an increase in resorptions prenatally. Surprisingly, ***even when there were some fairly strong forms of maternal toxicity, it did not cause malformations. So it doesn't seem that that particular endpoint out of the four is of concern.***
>
> ***When there is maternal toxicity, it does have a decrease in fetal body weight. It has an increase in prenatal loss. Those are both endpoints that are more commonly associated with severe maternal toxicity than others.***
>
> And a decrease in ossification does not – as long as it is a decrease in ossification, and not a structural change, it tends to go along with decrease in fetal body weight.[65]
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> * * *
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> **Committee Member Keen**, following Dr. Roberts:
>
> My reading of the binders was remarkably similar to what you read . . . As I look at the literature, ***I see very little evidence that there is an increased risk, absence of maternal toxicity [sic.; Dr. Keen said "absent maternal toxicity" or "in the absence 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.
>
> In the occasional paper, and there's over 70, which I went back and read each of the individual papers, you'll find a sporadic report of something. But where I get a little concerned or actually quite concerned is the lack of consistency as you go across the reports.[66]

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[65] Transcript, pp. 236-237 (emphasis added).

[66] Transcript, pp. 238-239 (emphasis added).

The DART IC was equally clear that the balance of the data, including the so-called "'low' dose studies," did not support a finding that BPA is a developmental of reproductive toxicant in humans.

> **Committee Member Keen:**
>
> [A]s I read the literature now, it's confusing, and it doesn't, by any criteria, meet my definition of clear. So I'll stop at that point.[67]
>
> **Chairperson Burk, following Dr. Keen:**
>
> But again, most of the studies are not our generally accepted sort of things, due to the numbers, as you mentioned, and the, you know, single dose and all those kind of things***.***[68]
>
> **Committee Member Keen:**
>
> ***But I think it's also worth noting those as when they did signal some out as being, what they thought I guess were, the more robust studies, I see females no effect, males no effect***.[69]
>
> **Committee Member Roberts**, following Dr. Keen:
>
> I'm looking at the NTP brief on page 20. And on the left-hand column, it says, ***Overall the current literature cannot yet be fully interpreted for biological or experimental consistency or for relevance to human health,***" which implies that they think that something may come of this in the future, but they are not there yet."[70]

Thus, the record could not be any more clear. The question of whether the "clear evidence of developmental effects at high doses" in certain studies was, or was not, secondary to maternal toxicity was presented squarely to the DART IC for its decision, and the Committee clearly decided that it was. It is also clear that the DART IC, NTP-CERHR and other expert agencies determined that the numerous "unconventional" were not convincing because they were not conducted according to generally accepted principles.

We recognize that OEHHA has authority, if not a responsibility, to review the NTP-CERHR Monograph to determine whether it "formally identifies" BPA as causing reproductive toxicity, *see* Cal. Code Regs., *tit.* 27, § 25306(d), and if so, whether the data that NTP-CERHR relied on are "sufficient," *see* Cal. Code Regs., *tit*. 27, § 25306(g), to support that identification. Thus, if the DART IC had not reviewed the data already, and if the NTP-CERHR Monograph

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67 Transcript, p. 243.

68 Transcript, p. 243.

69 Transcript, p. 248 (emphasis added).

70 Transcript, p. 248 (emphasis added).

had "formally identified" BPA as a developmental toxicant pursuant to § 25306(d) (which it did not in this case), OEHHA would be justified in reviewing the data summarized in the NTP-CERHR Monograph to determine whether those data were "sufficient" to support listing under Proposition 65. But this is clearly not the case, and OEHHA cannot ignore the fact that the DART IC did review all those data and reached a conclusion exactly the opposite of what OEHHA now proposes. To elaborate, the DART IC reviewed all the available scientific evidence, including not only the studies reviewed by NTP-CERHR but also the conclusions and observations expressed in the NTP Brief, and reached the unanimous conclusion that BPA has ***not*** been "clearly shown through scientifically valid testing according to generally accepted principles to cause . . . reproductive toxicity." Moreover, the DART IC was quite clear in explaining how and why the evidence on BPA fails to satisfy the DART IC Criteria, which are essentially a more detailed statement (or "more fully articulated statement") of the same criteria set forth in Section 25306(g).

Under these circumstances, the DART IC's decision is conclusive. If OEHHA were to determine now that those animal data ***do*** satisfy the requirements of Section 25306(g), it is clear that the agency would be applying a standard different than the DART IC itself applies and substituting its judgment for that of the DART IC, which would be a clear violation of Section 25306 as a whole. For these reasons, OEHHA should acknowledge and respect the conclusions of the DART IC as the State's Qualified Experts, and recognize that as a matter of both fact and law, the Committee has already decided that "there is no substantial evidence that the criteria of [Section 25306(g)] have been satisfied."

D. *Even if OEHHA Were to Evaluate the Data in the NTP CERHR Monograph Anew, the Studies Cited by NTP-CERHR Clearly Do Not Satisfy the "Sufficient Data" Requirement of Section 25306(g)(2)*

For the reasons recited above, it should not be necessary to reach this issue. Because the NTP-CERHR Monograph does not "formally identify" BPA as a reproductive toxicant, it is beyond OEHHA's authority to review the data discussed in the Monograph independently, and substitute its judgment for that of the authoritative body. And because the DART IC explicitly considered the data and determined that BPA has not been shown to cause developmental toxicity (or reproductive toxicity), the only way that OEHHA could determine now that the animal data summarized above *do* satisfy the requirements of Section 25306(g) would be to substitute its judgment for that of the DART IC and to apply a different and less stringent standard than DART IC applies, in clear violation of Section 25306.

Nevertheless, if OEHHA were to re-examine the data, the agency would have to conclude that the studies cited in the NTP-CERHR Monograph as showing "clear evidence of developmental effects at high doses" are not "sufficient" to indicate that "an association between adverse reproductive effects in humans and the toxic agent is biologically plausible" as required under Section 25306(g)(2). Any contrary decision would not be justifiable by scientific

standards, and would be so lacking in evidentiary support as to render the decision arbitrary and capricious and therefore an abuse of discretion by legal standards.[71]

1. *Section 25306(g)(2) Requires Consideration of Many Factors to Determine Whether an Association Between Adverse Effects Observed in Animals and BPA Is Biologically Plausible in Humans*

The starting point for this analysis is Section 25306(g)(2) itself, which provides as follows:

> (g) for purposes of this section, "***as causing reproductive toxicity" means*** that either of the following criteria have been satisfied:
>
> (1) studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or
>
> (2) ***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***.[72]

Turning next to the Request, under the heading "Formal Identification and sufficiency of evidence," OEHHA recites that the NTP-CERHR Monograph expressed "conclusions" that there is "clear evidence of adverse developmental effects in laboratory animals" (including "fetal death and reduced litters size in rats") at 'high' levels of exposure," and that "based on the NTP CERHR report and ***the references cited in the report,*** the evidence appears sufficient for listing by the authoritative bodies mechanism."[73]

Even taking the recitation in the Request at face value – *i.e*., assuming for the sake of argument that the NTP Brief did "conclude" that there is "clear evidence of adverse developmental effects in laboratory animals at 'high' levels of exposure" – that in itself would not be sufficient cause for listing BPA. Under Proposition 65, the critical question remains whether – assuming such effects in animals – an association between those adverse effects observed in animals and the same effects in humans due to exposure to BPA is "biologically

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71 *Exxon Mobil v. OEHHA*, 169 Cal.App.4th at 1277.

72 Cal. Code Regs., *tit.* 27, § 25306(g) (emphasis added; reformatted for clarity).

73 OEHHA, *Request for Relevant Information on a Chemical Being Considered for Listing buy the Authoritative Bodies Mechanism: Bisphenol A [2/12/10]* at 1 (emphasis added).

plausible." In order to reach that conclusion, OEHHA must evaluate the "references cited in the report" against (at a minimum) the factors recited above in the text of Section 25306(g)(2).[74]

The "references cited in the report" are the same eight animal studies identified above and referenced in the footnote of Figure 2b of the NTP Brief on BPA. For purposes of Proposition 65, five of those studies are not relevant in evaluating BPA as a developmental toxicant, because they involved post-natal as well as pre-natal exposure (one involved only post-natal exposure) and it is not possible to distinguish adequately between the effects observed in those studies that are attributable to pre-natal or post-natal exposure. Removing from consideration those studies that are not relevant, the remaining three studies would not support NTP's observation of the "weight of the evidence." Furthermore, to the extent that any of the four "partially post-natal" studies are relevant, the adverse effects observed in the studies continue to be secondary to maternal toxicity.

a. *Pre-Natal v. Post-Natal Exposure*

It is well-recognized that developmental effects attributable to post-natal exposure are not within the purview of Proposition 65. This principle, established from the outset in the implementation of Proposition 65, was explained and confirmed at a public meeting of the DART IC on December 4. 1996. At that meeting, OEHHA's then-Chief Counsel William Soo Hoo confirmed on the record the long-standing principle that "postnatal exposures [are] not encompassed by Proposition 65." This position, Mr. Soo Hoo explained, was first enunciated by Dr. Steven Book, the "former and original Director for OEHHA," who also served as the Science Advisor to the Secretary of the California Health and Welfare Agency (the first "lead agency" responsible for the administration of Proposition 65), as well as Mr. Peter Baldridge, Mr. Soo Hoo's predecessor as Chief Counsel. Mr. Soo Hoo further explained that this principle is "reflected in the DART Committee's . . . guidelines . . . [and] affirm that ***developmental toxicity is to be considered by the DART Committee only with regard to pre-natal exposures.***"[75] Because this standard is imposed as a matter of statutory interpretation, and for all of the other reasons discussed in the Statement of Reasons regarding the designation of authoritative bodies, the same constraint applies to OEHHA in examining the NTP-CERHR Monograph. Judged against this standard, the eight studies cited in the NTP-CERHR Monograph do not constitute "sufficient data," within the meaning of Section 25306(g)(2), to support a finding that BPA causes adverse developmental effects for purposes of Proposition 65.

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[74] We understand from discussions with OEHHA personnel following the issuance of the Request, and from the holding in *Exxon Mobil v. OEHHA*, that the agency applies the US EPA Guidelines for Developmental Toxicity Risk Assessment ("US EPA Guidelines" or "Guidelines") in its application of Section 25306(g). While certain aspects of those Guidelines ***may*** be appropriate in the implementation of Proposition 65, their wholesale adoption in listing decisions clearly is not appropriate. As the full name of the Guidelines indicates, they were developed for purposes of risk assessment, of which hazard identification is just one part. The confusion of these two concepts and their underlying purposes may tend toward confusion in listing decisions. As discussed above, the criteria under Section 25306(g) are intended to be applied consistently with, not different from, the DART IC Criteria.

[75] Statement and testimony of Mr. William Soo Hoo, OEHHA General Counsel, delivered at the December 4, 1996 meeting of the DART IC, pp. 13-14 (emphasis added). Mr. Soo Hoo's statement appears at Attachment 6 to this response. Relevant pages from the transcript of the December 4, 1996 Committee meeting appear at Attachment 7.

In this regard, the references to "adverse developmental effects" in the NTP Brief are themselves unclear for purposes of Proposition 65: the fact that the NTP Brief speaks of "adverse developmental effects" cannot be taken to mean that NTP observed effects that would fall in the category of "developmental toxicity" for purposes of Proposition 65. To explain, there is nothing either in the Expert Report or the NTP Brief to indicate that the term "developmental effects" is restricted to effects from pre-natal exposure. Rather, the studies to which the NTP Brief cites as showing "adverse developmental effects" include many studies where exposure occurred post-natally. In other words, NTP uses terms such as "developmental toxicity" and "adverse developmental effects" to include effects caused by pre-natal ***or*** post-natal exposure, and thus embraces effects that would not cause a chemical to be designated as a developmental toxicant for purposes of Proposition 65. Thus, where the NTP Brief indicates that the eight "cited references" show "clear evidence of adverse developmental effects," NTP is including studies that are not "sufficient," within the meaning of Section 25306(g) to support a conclusion that the chemical is a developmental toxicant for purposes of Proposition 65.[76]

To demonstrate this, the references in the NTP Brief to "adverse developmental effects" are reproduced below. At pages 6 and 7, NTP Brief, raises the question "Can bisphenol A affect human development or reproduction?" The summary response indicates, by its scope, that NTP included effects attributable to post-natal exposure (during the lactation period) in answering that question.

> **CAN BISPHENOL A AFFECT HUMAN DEVELOPMENT OR REPRODUCTION?**
>
> Possibly. Although there is no direct evidence that bisphenol A adversely affects reproduction or development, studies with laboratory rodents show that exposure to high dose levels of bisphenol A during pregnancy ***and/or lactation*** can reduce survival, birth weight, and growth of offspring early in life, and delay onset of puberty in males and females. [Emphasis added.] These effects were seen at the same dose levels that also produced some weight loss in pregnant animals ("dams"). These "high" dose effects of bisphenol A are not considered scientifically controversial and provide ***clear evidence of adverse effects on development in laboratory animals.*** However, the administered dose levels associated with delayed puberty (≥ 50 mg/kg bw/day), growth reductions (≥ 300 mg/kg bw/day), or survival (≥ 500 mg/kg bw/day) are far in excess of the highest estimated daily intake of bisphenol A in children (<0.0147 mg/kg bw/day), adults (<0.0015 mg/kg bw/day), or workers (0.100 mg/kg bw/day).[77] [Emphasis added.]

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[76] Reliance on the US EPA Guidelines similarly may result in the inappropriate consideration of certain adverse effects as "developmental effects." Like NTP-CERHR, US EPA uses the term "developmental toxicity" more broadly than Proposition 65 allows, thus placing the Guidelines in fundamental conflict with Proposition 65. *See, e.g.,* US EPA Guidelines at p. 3 (defining "developmental toxicology" as the "study of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation").

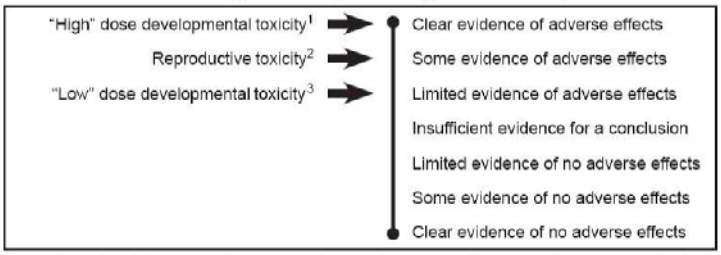
[77] NTP Brief at 6-7.

Elsewhere on page 7, the following appears:

> **SUPPORTING EVIDENCE**
>
> The NTP finds that there is ***clear evidence of adverse developmental effects*** at "high" doses of bisphenol A in the form of fetal death, decreased litter size, or decreased number of live pups per litter in rats (≥ 500 mg/kg bw/day) (36, 37) and mice (≥ 875 mg/kg bw/day) (38,40), reduced growth in rats (≥ 300 mg/kg bw/day) (36,37) and mice (≥ 600 mg/kg bw/day) (38, 39, 41), and delayed puberty in male mice (600 mg/kg bw/day) (41), male rats (≥50 mg/kg bw/day) (37, 42) and female rats (≥ 50 mg/kg bw/day) (37, 43).[78]

Figure 2b (discussed previously and reproduced again below), shows that NTP's response was based in part on NTP References 37, 39, 40, 41 and 42.

Figure 2b. *The weight of evidence that bisphenol A causes adverse developmental or reproductive effects in laboratory animals*



[1]Based on reduced survival in fetuses or newborns (≥500 mg/kg bw/day) *(36–40)*, reduced fetal or birth weight or growth of offspring early in life (≥300 mg/kg bw/day) *(36, 37, 41)*, and delayed puberty in female rats (≥50 mg/kg bw/day) and male rats and mice (≥50 mg/kg bw/day) *(37, 41–43)*.

[2]Based on possible decreased fertility in mice (≥875 mg/kg bw/day) *(40)*; altered estrous cycling in female rats (≥600 mg/kg bw/day) *(110)*, and cellular effects on the testis of male rats (235 mg/kg bw/day) *(111)*.

[3]Based a variety of effects related to neural and behavior alterations (≥10 µg/kg bw/day) *(44–50)*, lesions in the prostate (10 µg/kg bw/day) *(51)* and mammary glands (0.0025–1 mg/kg bw/day) *(52, 53)*; altered prostate gland and urinary tract development (10 µg/kg bw/day) *(54)*, and early onset of puberty (2.4 and 200 µg/kg bw/day) *(48, 55)*.

The table below demonstrates that all five of those studies (NTP References 37, 39, 40, 41, and 42) were reproductive toxicity studies, which by their nature included post-natal exposure. In fact, one of the five reproductive toxicity studies (NTP Reference 42), was conducted on the basis of post-natal exposure only, and thus should not be considered at all. Only three of the eight studies (NTP References 36, 38, and 43) were conducted using pre-natal exposures only.

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78 NTP Brief at 7.

TABLE 1
PERIOD(S) OF EXPOSURE AMONG THE STUDIES CITED IN THE NTP BRIEF

NTP REFERENCE NO. (AUTHOR & DATE)	TYPE OF STUDY	REPORTED EFFECT(S)	PRE- OR POST- NATAL EXPOSURE
36 (Kim *et al.,* 2001)	Developmental toxicity (rat)	Decrease in litter size; decrease in fetal body weight	Pre-natal exposure only
37 (Tyl *et al*., 2002b)	Reproductive toxicity, 3-generation (rat)	Decrease in litter size; decrease in pup body weight; delayed puberty (male and female)	Pre- and post-natal exposure
38 (Morrissey *et al*., 1987)	Developmental toxicity (mouse)	Increase in resorptions and litter size; decrease in fetal body weight	Pre-natal exposure only
39 (Tyl *et al.,* 2002a)	Reproductive toxicity 1-generation (mouse)	Decrease in litter size; decrease in pup body weight	Pre- and post-natal exposure
40 (NTP, 1985)	Reproductive toxicity, continuous breeding (mouse)	Decrease in litter size	Pre- and post-natal exposure
41 (Tyl *et al*., 2008b)	Reproductive toxicity, 2-generation (mouse)	Decrease in pup body weight; delayed puberty (male)	Pre- and post-natal exposure
42 (Tan *et al*., 2003)	Reproductive toxicity (rat)	Delayed puberty (male)	Post-natal exposure only
43 (Tinwell *et al.,* 2002)	Developmental toxicity (rat)	Delayed puberty (female)	Pre-natal exposure only

The distinction between effects caused by pre-natal exposure and effects caused by post-natal exposure is vitally important in designating a chemical as a developmental toxicant, as reflected in the presentation by Mr. Soo Hoo to the DART IC, discussed above. As noted earlier, an adverse developmental effect does not come within the purview of Proposition 65 unless it is attributable to pre-natal exposure.

For purposes of Proposition 65, developmental toxicity studies with "pre-natal exposure only" (*i.e.,* with no post-natal exposure) are of the highest utility in evaluating a chemical for developmental toxicity, because the reviewer can eliminate the possibility that an adverse effect resulted from post-natal exposure. Similarly, a study based on "post-natal exposure only" (*i.e*., with no pre-natal exposure) has no utility at all for purposes of Proposition 65, because such a study cannot demonstrate that an effect is the result of pre-natal exposure. The utility of a study that includes both pre-natal and post-natal exposure depends on whether it is possible to differentiate an effect that resulted from pre-natal or post-natal exposure, or both. Importantly, most of the effects observed in the eight studies may be attributed to exposures other than pre-natal exposure, which means that these effects are not relevant to Proposition 65.

Among the four reproductive toxicity studies, which had both pre-natal and post-natal exposure, the effects in these studies could be due to exposure that occurs outside of gestation (*i.e*., not pre-natal exposure). Further, both male and female parents were exposed to BPA prior to mating in all four of these studies, raising the possibility that the "developmental" effects, such as a decrease in litter size, may be due to male or female reproductive toxicity, not to developmental toxicity as meant by Proposition 65. In fact, one of these studies specifically looked at male reproductive toxicity through a semen evaluation and a cross-mating study; substantial evidence of male reproductive toxicity (including a decrease in litter size when only the male parent was exposed to BPA and a decrease in sperm quality), was seen at doses that produced systemic toxicity.

As noted in the Summary above, "developmental toxicity" is limited for purposes of Proposition 65 to developmental effects caused by pre-natal exposure alone. The use of that term in the NTP-CERHR Monograph, and specifically in the NTP Brief, embraces a much broader range of effects, including effects attributable to post-natal exposure. Thus, where the NTP Brief indicates that there is "clear evidence of adverse developmental effects"[79] in animals, the term "adverse developmental effects" does not have the same meaning as it does for purposes of Proposition 65. Similarly, when the NTP Brief indicates "clear evidence of adverse effects" in laboratory animals for "high dose developmental toxicity,"[80] that determination was made based on the weight-of-the-evidence from eight studies that included effects that would not be considered developmental effects for purposes of Proposition 65. Therefore, the proposal to list BPA on the basis of effects that do not represent developmental toxicity for purposes of Proposition 65 would exceed the mandate under Section 25249.8 of the act, as well as Section 25306(g)(2) of the implementing regulations, and expand the boundaries of Proposition 65 well beyond its recognized limits.

Furthermore, all five of the reproductive toxicity studies cited in the NTP Brief exposed both parents – male and female. There is evidence that at least part of the "developmental" effects observed were due to paternal exposure to BPA, not maternal exposure. In a cross-mating study conducted by NTP (NTP, 1985) employing the same animals used in the continuous-breeding reproduction and fertility study, a 26% decrease in the number of live pups per litter

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79 NTP Brief at 7.

80 NTP Brief at 8, Figure 2b.

was observed when BPA-exposed males (high dose) were cross-mated with control (unexposed) females.

With this background in mind, we examine each of the NTP References summarized above, beginning with the five reproductive toxicity studies.

NTP Reference 37 (Tyl *et al.,* 2002b), a 3-generation reproductive toxicity study, reported a decrease in litter size on post-natal day 0 or "PND" 0, suggesting that pre-natal exposure, rather than post-natal exposure, caused this effect. However, the possibility exists that the decrease in litter size at birth was not due to pre-natal exposure. First, the decrease in litter size may have been due to male or female reproductive toxicity from exposure prior to pregnancy, since both the male and female parents were exposed to BPA throughout the mating period and for a minimum period of 10 weeks prior to mating. Second, the decreased litter size may have been due to post-natal exposure to BPA. Pups may have been exposed post-natally to BPA through mothers' milk prior to any observations on PND 0. Pups begin to nurse shortly after delivery, and pups may be up to 24 hours old before the birth of a litter is discovered (PND 0). Mothers may cannibalize pups during the interval prior to the discovery of the birth of a litter, resulting in an observed decrease in litter size on PND 0. Third, it is possible that a decrease in litter size on PND 0 is due to a direct effect on the mother, and not due to pre-natal exposure of the offspring at all. For example, if the mother is not lactating properly, a decrease in litter size on PND 0 may have been the result mother failing to feed their pups or mothers killing their pups shortly after birth. An underweight dam might cannibalize live pups after birth due to hunger and general stress. In summary, the decrease in litter size on post-natal day 0 in this study may have been due to pre-mating exposure, pre-natal exposure, post-natal exposure or a combination of the three. It is not possible to conclude that the decrease in litter size on PND 0 in Reference 37 is due to pre-natal exposure to BPA.

NTP Reference 39 (Tyl *et al*., 2002a), an abbreviated one-generation reproduction study in mice, also reported a decrease in litter size on PND 0, as well as a decrease in pup body weight on PND 0. For all the reasons articulated in the previous paragraph, it is not possible to conclude definitively that the decrease in litter size on PND 0 in Reference 39 is due to pre-natal exposure to BPA. Similarly, a decrease in pup weight on PND 0 may be due to pre-natal and/or post-natal exposure to BPA.

NTP Reference 40 (NTP, 1985), includes a continuous-breeding reproduction and fertility study in mice. Male and female mice were given 0, 437.5, 875, and 1750 mg/kg bw/day of BPA through dietary administration. At the two higher dose levels, exposure to BPA produced a decrease in the number of litters per mated pair of mice (an apparent effect on fertility) and a decrease in the number of live pups per litter. Males and females were exposed continuously throughout the experiment (including 7 days of pre-mating and 98 days of mating), which incorporated multiple matings and pregnancies. The mice were exposed prior to mating, during mating, during pregnancy, and during the lactation period until the pups were sacrificed. It cannot be concluded with certainty that the decrease in litter size was due to prenatal exposure in this study. For example, the decrease in litter size may have been a male or female reproductive effect that was caused by exposure to BPA prior to pregnancy. In fact, there is direct evidence that the effect may be mediated, at least in part, through the father. As noted previously, a cross-mating study was conducted by the same investigators using the same animals used for the

continuous-breeding study of BPA. When BPA-exposed males (high dose) were cross-mated with control females, there was a decrease of 26% in the number of live pups per litter, even though the males were not exposed to BPA in the diet during the cohabitation period due to the cross-mating study design. In addition, a decrease in semen quality, as manifest by a significant decrease in sperm motility, as also observed in the high dose male mice; semen quality was not evaluated at other dose levels. These results suggest that the decrease in the number of live pups per litter is male-mediated – at least in part. This has implications for all of the other reproductive toxicity studies of BPA because both males and females were exposed to BPA.

When BPA-exposed females (high dose) were cross-mated with control males, a 51% decrease in the number of live pups per litter was observed. This demonstrates that exposure to BPA among the females also plays a significant role. But, it is not clear whether the effect among the offspring of exposed BPA-exposed females is due to exposure prior to pregnancy, during gestation, or post-natally.

As noted regarding the previous studies, it also is possible that the decrease in litter size was due to postnatal exposure of the pups. Finally, the decrease in litter size may have been due to an effect on the mother's ability to maintain her pups shortly after birth.

NTP Reference 41 (Tyl *et al.,* 2008b), a 2-generation reproductive toxicity study in mice, reported a significant decrease in pup weight. Both male and female parents were exposed to BPA prior to mating. This effect was first observed on PND 7. Because this effect was not observed before PND 7 and exposures occurred pre-mating, during gestation, and post-natally, there is no way of knowing whether this effect was caused by pre-natal exposure. The decrease in pup weight may have been due to pre-mating exposure, pre-natal exposure, or post-natal exposure, or to a combination of these exposures to BPA, rather than to pre-natal exposure alone.

NTP Reference 42 (Tan *et al.,* 2003) reported delayed puberty in males as measured by the day of preputial separation. This study was based entirely on post-natal exposure, and thus would not support any conclusions regarding developmental toxicity for purposes of Proposition 65. In fact, exposure did not begin until PND 23. Therefore, the effect that was reported could not possibly have been due to pre-natal exposure to BPA.

Thus, in summary, only three of the eight studies to which OEHHA cites (NTP References 36, 38 and 43) are relevant, because these are the only studies cited upon by NTP in which an effect may be attributed with requisite certainty to pre-natal exposure to BPA. Yet, in two of these studies, maternal toxicity was excessive or severe, indicating that the developmental effects were uninterpretable or secondary to maternal toxicity. In the third study, the investigators did not evaluate maternal toxicity at all. Because maternal toxicity presents a separate reason that the data are not "sufficient," we address that issue separately below.

b. *Consideration of Maternal Toxicity*

Even if one were to ignore the issue of pre-natal vs. post-natal exposure and treat all eight studies as relevant, consideration of maternal toxicity indicates that these studies do not constitute sufficient evidence of developmental toxicity under 25306(g). Like the issue of pre-natal v. post-natal exposure, maternal toxicity is an extremely important factor in evaluating whether a study

that shows adverse developmental effects is of any value in determining whether those effects are biologically plausible in humans. Virtually all chemicals have the potential to cause developmental toxicity when they are given at sufficiently high doses to kill or damage the health of the mother.[81]

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

Thus, the critical objective in a developmental toxicity study is to determine whether the test substance is a ***selective*** developmental toxicant in humans, *i.e*, to determine whether exposure to the substance is likely to cause adverse effects to the fetus at doses that are not expected to cause so much harm to the mother that the adverse effects to the mother in turn cause adverse effects to the fetus. This also is the purpose, if not a re-statement of, the "sufficient evidence" standard, and the reason why it requires "consideration of maternal toxicity."[82]

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[81] If OEHHA is inclined to apply the US EPA Guidelines, it must consider maternal toxicity, as Section 25306(g)(2) requires. Like the regulation, and like the DART IC Criteria, the Guidelines recognize the impact of maternal toxicity on reproductive and developmental health, and caution that "often it is difficult to distinguish between effects mediated through the parents versus direct interaction with developmental processes. For example, developmental toxicity may be influenced by the effect of toxic agents on the maternal system when exposure occurs during pregnancy or lactation." US EPA Guidelines at p. 4. The Guidelines similarly counsel that "individual endpoints of maternal and developmental toxicity are evaluated in developmental toxicity studies. In order to interpret the data fully, an integrated evaluation must be performed considering all maternal and developmental endpoints." *Id*. at 18.

[82] To the extent that OEHHA is considering the US EPA Guidelines, the following is appropriate to the consideration of the factor identified in Section 25306(g) as "experimental design," counseling that a well-designed study should include doses that will produce "some" maternal toxicity in order to stress the test animals, but that the level of toxicity should not be "excessive" if the results are to be considered valid. "The high dose is selected to produce some minimal maternal or adult toxicity (*i.e*., a level that at least produces marginal but significantly reduced body weight, reduced weight gain or specific organ toxicity, and the most produces no more than 10% mortality). At doses that cause excessive maternal toxicity (that is, significantly greater than the minimal toxic level) information on developmental effects may be difficult to interpret and of limited value." US EPA Guidelines at 6. ***(footnote continued on next page)***

The developmental effects reported in the BPA studies cited by the NTP are to be expected, given the degree of maternal toxicity reported by the investigators (with the obvious exception of the study that did not evaluate maternal toxicity). In fact, many of the investigators themselves concluded that the developmental effects observed in these studies were secondary to maternal toxicity. Thus, after consideration of maternal toxicity, these studies do not provide sufficient data to support a conclusion that would, in the words of Section 25306(g) "indicat[e] that an association between adverse [developmental] effects ***in humans*** and [BPA] is biologically plausible" (emphasis added).

(1) *Maternal Toxicity in the Three Developmental Toxicity Studies*

As noted above, only three of the eight studies relied upon by NTP, References 36, 38, and 43, produced effects that can be definitively attributed to pre-natal exposure to BPA. These are the only studies that should be relevant to the issue of whether the data that NTP relied upon present sufficient evidence of developmental toxicity. None of these studies demonstrated developmental effects in the absence of maternal toxicity. In fact, one of these studies (NTP Reference 43) did not even monitor or measure maternal toxicity, precluding any evaluation of the role of maternal toxicity in this study. The other two studies (NTP References 36 and 38) did measure maternal toxicity, and both of these studies demonstrated that the degree of maternal toxicity observed is more than sufficient to account for developmental effects.

Table 2, below, summarizes the evidence of maternal toxicity observed in the three developmental toxicity studies, and compares the Lowest Observed Adverse Effect Level ("LOAEL") for maternal and developmental effects.

TABLE 2
EVIDENCE OF MATERNAL TOXICITY IN THE THREE DEVELOPMENTAL TOXICITY STUDIES WITH PRE-NATAL ONLY EXPOSURE CITED IN THE NTP BRIEF

NTP REFERENCE NO. (AUTHOR & DATE)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
36 (Kim *et al.,* 2001)	Decrease in litter size; decrease in fetal body weight	Abnormal clinical signs (severe diarrhea and urination throughout the study, decreased in locomotor activity, emaciation, sedation, piloerection, dull fur, reddish tear, perineal soiling; expansion and/or congestion of the stomach and	300 mg/kg bw/day 1000 mg/kg/ bw/day

In observing this Guideline, OEHHA should take note that this guidance is directed at study design, and counsels investigators to design their studies using dose levels that produce adult mortality rates no higher than 10%. The Guideline should not be interpreted as a directive to evaluators to treat adult mortality rates of lower than 10% as insignificant, or to decline to acknowledge maternal toxicity as the cause of adverse developmental effects unless adult mortality exceeds 10%.

TABLE 2
EVIDENCE OF MATERNAL TOXICITY IN THE THREE DEVELOPMENTAL TOXICITY STUDIES WITH PRE-NATAL ONLY EXPOSURE CITED IN THE NTP BRIEF

NTP REFERENCE NO. (AUTHOR & DATE)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
		intestines); decrease in body weight (15% decrease in corrected body weight) and body weight gain (52% decrease); decrease in food consumption; inc. pregnancy failure. In a preliminary study, a dose of 1200 mg/kg bw/day caused maternal death.	
38 (Morrissey *et al*., 1987)	Increase in resorptions and litter size; decrease in fetal body weight	Maternal death (18% death rate); decrease in weight gain; increase relative liver weight, clinical signs, including arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss, and wheezing	500 mg/kg bw/day 1250 mg/kg bw/day
43 (Tinwell *et al.,* 2002)	Delayed female puberty (vaginal patency) in one of two strains of rats; no effect on estrous cycle in either strain.	Not measured	Not Available

A more detailed analysis of each study confirms this.

NTP Reference 36, Kim *et al*., (2001), reported serious maternal toxicity at the high dose (1000 mg/kg bw/day), which is the only dose that produced developmental toxicity (*i.e*., decreased litter size). According to the summary in the NTP Expert Panel Report, the "[s]tudy authors concluded that exposure of rats to a maternally toxic dose of bisphenol A during the entire gestation period resulted in pregnancy failure, post-implantation loss, reduced fetal body weight, and retarded fetal ossification but no dysmorphogenesis."[83] The Expert Panel apparently agreed. Commenting on the strengths and weaknesses of the study, the Expert Panel wrote: This report presents a fairly standard embryo-fetal developmental toxicity study. One strength is that

[83] NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A ["NTP-CERHR Expert Panel Report"] (2008) Birth Defects Research (Part B) 83:157-395, at 238.

the doses utilized incorporated both a no-effect dose and a high maternally toxic dose, reveal fetal effects only at the high-dose that showed marked maternal toxicity."[84]

Looking to the data themselves, the clinical observations of toxicity reported among the pregnant rats at this dose were substantial and included: severe diarrhea and urination throughout the study, decreased locomotor activity, emaciation, sedation, piloerection, dull fur, reddish tear, perineal soiling, expansion and/or congestion of the stomach and intestines. Other signs of maternal toxicity included decreased body weight (15% decrease in corrected body weight), decreased body weight gain (52% decrease), decreased food consumption, and an increase in pregnancy failure. Importantly, in a range-finding study by the same investigators, a slightly higher dose (1200 mg/kg bw/day) caused maternal death. The degree of maternal toxicity observed in this study is more than enough to explain the decrease in litter size observed at the high dose in this study. In fact, given the degree of maternal toxicity observed at a nearly lethal dose, it is surprising that more evidence of developmental toxicity was not seen. No developmental effects were observed at the middle dose (300 mg/kg/day), a dose which still produced maternal toxicity, albeit less than was observed at the high dose.

NTP Reference 38, Morrissey *et al*., (1987), reported an increase in fetal resorptions in a developmental study of BPA in the mouse. According to the NTP-CERHR Expert Panel, "One or 2 of 29-34 dams died in each of the 3 lowest doses [500, 750, and 1000 mg/kg bw/day] and 6 of 33 dams [18%] died in the 1250 mg/kg bw/day group." Clinical signs reported in mice treated with BPA included arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss, and wheezing. Statistically significant increases in relative liver weight were observed at all doses. An increase in resorptions and a decrease in fetal body weight was observed at the high dose, 1250 mg/kg bw/day. No signs of developmental toxicity were observed at doses below 1250 mg/kg bw/day. The study authors concluded that BPA is not teratogenic in mice at doses that result in maternal toxicity. [85]

As the NTP-CERHR Expert Panel noted, administration of the high dose (1250 mg/kg bw/day), which was the only dose that produced increased fetal resorptions, produced maternal death among 18% of the pregnant mice. A maternal death rate above 10% is not only enough to explain an increase in fetal resorptions, it is also considered to be an unacceptably high level of maternal toxicity to interpret the results of a developmental toxicity study Regulatory agencies generally require that the high dose level in a developmental toxicity study be sufficiently high to cause some maternal toxicity. If the dose is too high, however, it can cause excessive maternal toxicity, which makes it extremely difficult, if not impossible, to interpret the results of the study.

Thus, the US EPA Guidelines for Developmental Toxicity Risk Assessment (1991) state: "The high dose is selected to produce some minimal maternal toxicity or adult toxicity (*i.e.,* a level that at least produces marginal but significantly reduced body weight, reduced weight gain, or specific organ toxicity, and at most produces no more than 10% mortality). At doses that cause excessive maternal toxicity (that is, significantly greater than the minimal toxic level) information on developmental effects may be difficult to interpret and of limited value."

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[84] NTP-CERHR Expert Panel Report at 238.

[85] NTP-CERHR Expert Panel Report at 237.

Therefore, according to the US EPA criteria, the effect observed at the high dose in NTP Reference 38 is of virtually no value for human hazard identification, because the only dose that produced developmental toxicity caused excessive maternal toxicity, such that any developmental effects are "difficult to interpret and of limited value." Indeed, the increased incidence of resorptions per litter is attributed to seven litters at the high dose that were completely resorbed. BPA had ***no*** significant effect on the number of live fetuses per litter for those litters that were not completely resorbed. It is not surprising that a dose that killed 18% of the pregnant females was so maternally toxic that seven of the surviving dams resorbed their entire litter. Virtually any substance that is given at such a high dose to pregnant rats that it kills 18% of the mothers would be expected to cause an increase in resorptions. As noted by US EPA, such a result is of limited value for human hazard identification.

Finally, NTP Reference 43, Tinwell *et al*., (2002), a developmental toxicity study in the rat, made no attempt to monitor for maternal toxicity. This was not a conventional developmental toxicity study. The US EPA Guidelines for Developmental Toxicity Risk Assessment (1991) contain at page 10 a description of the minimal amount of information considered useful for evaluating maternal toxicity; this study did not monitor any of these minimal endpoints. Because no observations of maternal toxicity were made at all, it is not possible to (1) take maternal toxicity into consideration, and (2) conclude that any adverse effects observed in this study were due to the direct action of BPA on the embryo or fetus (and not due to maternal toxicity).

In summary, consideration of maternal toxicity among the three studies with pre-natal only exposure indicates that there is insufficient evidence to satisfy the listing requirement of Section 25306(g). In two studies, there was excessive or serious maternal toxicity at the only dose that produced developmental effects. The developmental effects are easily explained by the degree of maternal toxicity because, in both studies, a lower dose also produced maternal toxicity, but no evidence of developmental toxicity. These studies thus indicate that developmental toxicity is secondary to maternal toxicity. In the third study, the authors did not even look for maternal toxicity.

(2) *Maternal Toxicity in the Five Studies Considered Relevant by OEHHA*

It is our understanding that OEHHA considers five of the eight studies relied upon by NTP, NTP References 36-40, to be relevant, because these are the studies that reported a decrease in litter size or an increase in resorptions. As discussed above, three of these studies are not relevant; the reported effect cannot be attributed to pre-natal exposure with certainty, because exposure to BPA occurred both pre-natally and post-natally. Nevertheless, assuming for the sake of argument that all five of these studies demonstrate developmental effects due to pre-natal exposure (which they do not), it is instructive to examine the evidence of maternal toxicity observed in these five studies, as summarized in Table 3.

In all five studies, developmental effects were observed only in the presence of significant maternal toxicity. In fact, the LOAEL for maternal toxicity was less than the LOAEL for developmental toxicity in all five studies. The degree of maternal toxicity observed was more

than enough to account for the developmental effects reported in these studies. In all cases, the developmental effects were secondary to maternal toxicity.

The evidence of maternal toxicity in NTP References 36 and 38 is summarized above. The evidence of maternal toxicity in the remaining three studies, NTP References 37, 39 and 40, is discussed below.

NTP Reference 37 (Tyl *et al*., 2002b) is a state-of-the-art, three-generation reproductive toxicity study in rats. The Expert Panel Report summarizes: "The study authors identified an offspring and reproductive NOAEL of 750 ppm (~50 mg/kg bw/day). A systemic NOAEL for adult rats was identified at 75 ppm (~5 mg/kg bw/day) by the study authors; therefore, bisphenol A was not considered a selective developmental toxicant."[86]

In more detail, BPA was administered to male and female rats in the diet at levels to provide doses of 0, 0.001, 0.02, 0.3, 5, 50, and 500 mg/kg bw/day. Developmental effects were observed at the high dose only (500 mg/kg bw/day); these effects included decreased litter size, decreased pup body weight, and delayed puberty. Therefore, the LOAEL for developmental toxicity was 500 mg/kg bw/day. At this dose, substantial maternal toxicity was observed. Signs of maternal toxicity at 500 mg/kg bw/day included decreased maternal body weight (approximately 30% decrease) and body weight gain. No consistent effect on food consumption was reported. The investigators also reported a decrease in absolute and increase in relative organ weights (liver, kidneys, adrenals, spleen, pituitary, brain). Mild histological changes in female kidneys and livers were observed at the high dose.

The degree of maternal toxicity reported at the high dose in NTP Reference 37 was more than sufficient to account for the observations of developmental effects. Less pronounced maternal toxicity was evident at the next lower dose, 50 mg/kg bw/day, but no developmental effects were seen at this dose level. As such, the LOAEL for maternal toxicity was less than the LOAEL for developmental effects. The results of this study show that the developmental effects are secondary to maternal toxicity.

NTP Reference 39 (Tyl *et al.,* 2002a) is an abbreviated one-generation reproductive toxicity study in mice. BPA was administered in the diet in amounts to provide doses of 0, 870, and 1716 mg/kg bw/day. Developmental effects were reported at the high dose only. According to NTP, the developmental effects that were observed included a decrease in litter size and a decrease in pup body weight. At the only dose that produced developmental effects, BPA caused significant maternal toxicity, including a decrease in body weight gain, an increase in absolute liver and kidney weight, an increase in the incidence and severity of hepatocyte hypertrophy and an increase in kidney lesions (renal tubular epithelial necrosis degeneration, and regeneration). Thus, the only dose associated with developmental effects in this study caused significant maternal toxicity. The lower dose (870 mg/kg bw/day) also caused some maternal toxicity, but no developmental effects were reported at this dose. The degree of maternal toxicity observed at the high dose is sufficient to have caused the developmental effects reported in this study.

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[86] NTP-CERHR Expert Panel Report at 249.

NTP Reference 40 (NTP, 1985) is a continuous-breeding reproduction and fertility study in mice. Male and female mice were given 0, 437.5, 875, and 1750 mg/kg bw/day of BPA through dietary administration. Mice were exposed continuously throughout the experiment (7 days of pre-mating and 98 days of mating), which included multiple matings and pregnancies. The mice were exposed prior to mating, during mating, during pregnancy, and during the lactation period until the pups were sacrificed. At the two higher dose levels, exposure to BPA produced a decrease in the number of litters per mated pair of mice, a decrease in the number of live pups per litter, and an increase in live pup weight. Measurements of adult systemic toxicity were limited. The investigators reported a significant decrease in postpartum body weights at the high dose, "indicating generalized maternal toxicity." According to the investigators, "Since F0 maternal postpartum weights tended to decrease at doses of 0.5% [875 mg/kg bw/day], and were significantly less than controls in the 1.0% BPA group, the observed toxicity to the conceptus may be all or in part due to generalized maternal toxicity." Organ weights and histopathology were evaluated only in the control and high dose groups. Liver weight was significantly increased in the high dose dams. Histopathological evaluation revealed "significant hepatic and renal toxicity." The authors concluded: "It is possible, therefore, that some or all of the adverse effects on reproductive performance observed in the present study may be secondary to the generalized toxicity of BPA."

TABLE 3
EVIDENCE OF MATERNAL TOXICITY IN THE FIVE DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CONSIDERED RELEVANT BY OEHHA

NTP REFERENCE NO. (AUTHOR & DATE)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL,
36 (Kim *et al.,* 2001)	Decrease in litter size; decrease in fetal body weight	Abnormal clinical signs (severe diarrhea and urination throughout the study, decrease in locomotor activity, emaciation, sedation, piloerection, dull fur, reddish tear, perineal soiling; expansion and/or congestion of the stomach and intestines); decrease in body weight(15% decrease in corrected body weight) and body weight gain (52% decrease); decrease in food consumption; increase in pregnancy failure; maternal death at dose of 1200 mg/kg bw/day in preliminary study	300 mg/kg bw/day 1000 mg/kg bw/day
37 (Tyl *et al.,* 2002b)	Decrease in litter size; decrease in pup body weight; delayed puberty (male and female)	Decrease in body weight (~ 30%) and body weight gain; decrease in absolute and increase I relative organ weight (liver, kidneys, adrenals, spleen, pituitary, brain); mild histologic changes in female kidney and liver	50 mg/kg bw/day 500 mg/kg bw/day

TABLE 3
EVIDENCE OF MATERNAL TOXICITY IN THE FIVE DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CONSIDERED RELEVANT BY OEHHA

NTP REFERENCE NO. (AUTHOR & DATE)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL,
38 (Morrissey *et al*., 1987)	Increase in resorptions and litter size; decrease in fetal body weight	Maternal death (18% death rate); decrease in weight gain; increase relative liver weight, clinical signs, including arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss, and wheezing	500 mg/kg bw/day 1250 mg/kg bw/day
39 (Tyl *et al.*, 2002a)	Decrease in litter size; decrease in pup body weight	Decrease in body weight gain; increase in absolute and relative liver and kidney weight, incidence and severity of hepatocyte hypertrophy and kidney lesions (renal tubular epithelial necrosis, degeneration, and regeneration)	870 mg/kg bw/day 1716 mg/kg bw/day
40 (NTP, 1985)	Decrease in litter size	Decrease in food consumption (13% decrease); increase in relative liver and kidney weight and significant hepatic and renal toxicity at high dose; not measured at 437 or 875 mg/kg bw/day	437 mg/kg bw/day 875 mg/kg bw/day

(3) *Maternal Toxicity in All Eight Studies Evaluated by NTP*

Even if one were to consider all eight studies of BPA relied upon by NTP, it is apparent that the amount of evidence of developmental toxicity does not satisfy the requirements of Section 25306(g) after consideration of maternal toxicity. Setting aside the issue that most of these studies do not provide evidence of developmental toxicity, as that term is defined by Proposition 65, it is helpful to examine the relationship between doses required to produce developmental effects and those that cause maternal toxicity. Two studies did not evaluate maternal toxicity; in one case, the investigators simply did not monitor for maternal toxicity, and in the other there was no pre-natal exposure so no mothers were exposed to BPA. Among the six studies that evaluated maternal toxicity, all showed that developmental effects were always associated with significant or even excessive maternal toxicity, and all show types of developmental effects (e.g., reduced weight, not malformations) consistent with maternal toxicity. Of note, in all cases, the dose required to produce maternal toxicity was always lower than the dose required to produce developmental toxicity. In every case, the degree of maternal toxicity observed was more than sufficient to explain the developmental effects.

In the previous two sections, we described all of these studies but two (NTP References 41 and 42). In this section, the two remaining studies are summarized with respect to the relationship between developmental effects and maternal toxicity. Table 4 provides a summary of the evidence of maternal toxicity in all eight studies relied upon by NTP.

NTP Reference 41 (Tyl, *et al.,* 2008b) is a state-of-the-art, two-generation reproductive toxicity study of BPA in mice. The Expert Panel Report summarizes: "The study authors identified bisphenol A NOELs of 30 ppm (~ 5 mg/kg bw/day) for systemic effects and 300 ppm (50 mg/kg bw/day) for developmental toxicity."[87] This study was conducted subsequent to the abbreviated one-generation reproductive toxicity study of BPA in mice (Tyl *et al.,* 2002a), by the same investigators. BPA was administered to mice in the diet at dose levels of 0, 0.003, 0.03, 0.3, 5, 50 and 600 mg/kg bw/day. Some developmental effects were reported at the high dose (600 mg/kg bw/day); these effects included a decrease in pup weight on PND 7-21 among F1 pups (but not among F2 pups) and a slight delay in male puberty that the authors did not consider to be biologically significant. At 600 mg/kg bw/day, maternal toxicity included an increase in absolute and/or relative liver and kidney weights, as well as histopathological changes in the liver. The investigators concluded that the delay in puberty was secondary to systemic toxicity: "It is likely that these transient effects were secondary to (or caused by) systemic toxicity." At the second highest dose, 50 mg/kg bw/day, some maternal toxicity was observed, but no developmental effects were reported. Thus, the results of NTP Reference 41 are consistent with the other studies. Developmental effects were observed only at a dose that produced significant maternal toxicity. In fact, the authors attributed the developmental effects to maternal toxicity.

NTP Reference 42 (Tan *et al.*, 2003) is a reproductive toxicity that evaluated the effect of post-natal exposure to BPA on the timing of the onset of puberty. There was no pre-natal or maternal exposure to BPA in this study. Obviously, there was no observation of maternal toxicity in this study since the study design did not include exposing pregnant rats. This study, by definition, cannot be evidence of adverse developmental effects for purposes of Proposition 65.

TABLE 4
EVIDENCE OF MATERNAL TOXICITY IN THE EIGHT DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CITED IN THE NTP BRIEF

STUDY (NTP REFERENCE & AUTHOR)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
36 (Kim *et al.,* 2001)	Decrease in litter size; decrease in fetal body weight	Abnormal clinical signs (severe diarrhea and urination throughout the study, decrease in locomotor activity, emaciation, sedation, piloerection, dull	300 mg/kg bw/day 1000 mg/kg bw/day

[87] NTP-CERHR Expert Panel Report at 302.

TABLE 4
EVIDENCE OF MATERNAL TOXICITY IN THE EIGHT DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CITED IN THE NTP BRIEF

STUDY (NTP REFERENCE & AUTHOR)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
		fur, reddish tear, perineal soiling; expansion and/or congestion of the stomach and intestines); decrease in body weight (15% decrease in corrected body wt.) and body weight gain (52% decrease); decrease in food consumption; increase in pregnancy failure. In a preliminary study, a dose of 1200 mg/kg bw/day caused maternal death.	
37 (Tyl *et al*., 2002b)	Decrease in litter size; decrease in pup body weight; delayed puberty (male and female)	Decrease in body weight (~ 30%) and body weight gain; decrease in absolute and increase relative organ weight (liver, kidneys, adrenals, spleen, pituitary, brain); mild histologic changes in female kidney and liver	50 mg/kg bw/day 500 mg/kg bw/day
38 (Morrissey *et al*., 1987)	Increase in resorptions and litter size; decrease in fetal body weight	Maternal death (18% death rate); decrease in weight gain; increase relative liver weight, clinical signs, including arched back, lethargy, piloerection, rough coat, vaginal bleeding, vocalization, alopecia, weight loss, and wheezing	500 mg/kg bw/day 1250 mg/kg bw/day
39 (Tyl *et al*., 2002a)	Decrease in litter size; decrease in pup body weight	Decrease in body weight gain; increase in absolute and relative liver and kidney weight; increase in incidence and severity of hepatocyte hypertrophy and increase in kidney lesions (renal tubular epithelial necrosis, degeneration, and regeneration)	870 mg/kg bw/day 1716 mg/kg bw/day
40 (NTP, 1985)	Decrease in litter size	Decrease in food consumption (13% decrease); increase in relative liver and kidney weight and significant hepatic and renal toxicity at high dose; not measured at 437 or 875 mg/kg bw/day	437 mg/kg bw/day 875 mg/kg bw/day
41 (Tyl *et al.,* 2008b)	Decrease in pup body weight; delayed	Increase in absolute and/or relative liver and kidney weight;	50 mg/kg bw/day 600 mg/kg bw/day

TABLE 4
EVIDENCE OF MATERNAL TOXICITY IN THE EIGHT DEVELOPMENTAL OR REPRODUCTIVE TOXICITY STUDIES CITED IN THE NTP BRIEF

STUDY (NTP REFERENCE & AUTHOR)	REPORTED DEVELOPMENTAL EFFECT(S)	REPORTED MATERNAL EFFECT(S) AT LOAEL FOR DEVELOPMENTAL EFFECTS	MATERNAL LOAEL/ DEVELOPMENTAL LOAEL
	puberty	histopathological change in liver (centrilobular hepatocyte hypertrophy of minimal severity)	
42 (Tan *et al*., 2003)	Delayed puberty	Not measured (no pre-natal exposure)	Not Available
43 (Tinwell *et al.,* 2002)	Delayed female puberty (vaginal patency) in one of two strains of rats; no effect on estrous cycle in either strain.	Not measured	Not Available

2. *The Animal Data Do Not Show That an Association Between the Effects Observed in Animals and Adverse Developmental Effects in Humans Is Biologically Plausible*

Even in their totality, the eight studies relied upon by the NTP do not show that an association between exposure to BPA and the observed effects in humans is biologically plausible. Again, Section 25306(g)(2) sets the standard and, in full, requires a determination that there are "***sufficient data***" from animal studies, taking into account such factors as "***route of administration,***" "***frequency and duration of exposure***," "***choice of dosage levels,***" "***consideration of maternal toxicity***," ***and others***, to indicate "an association between adverse reproductive effects in humans and the toxic agent in question" that is "biologically plausible."

The full articulation of this standard, taken directly from Section 25306(g)(2), raises two objections to any proposal to list BPA. Either is cause for OEHHA to halt the listing process.

First, it appears the Request is premised on a finding that does not meet the correct regulatory standard. At page one, under the heading "Background on listing via the authoritative bodies mechanism," the Request correctly recites that "[a] chemical must be listed under the Proposition 65 regulations when OEHHA determines that two conditions are met: . . . 1. The evidence considered by the authoritative body meets the sufficiency criteria contained in [Section] 25306(g)." The only information offered in the Request to indicate that the "sufficiency criteria" are satisfied, however, is the following statement at page two: "The NTP-CERHR report concludes that there is clear evidence of adverse developmental effects in

laboratory animal at "high" levels of exposure. Developmental effects include fetal death and reduced litter size in rats and mice exposed prenatally."

As noted above, the definitional standard under Section 25306(g) requires a showing of "biological plausibility" in an association between exposure to BPA and adverse developmental effects in humans. The observation that "there is clear evidence of adverse developmental effects in laboratory animals" is merely an indication that ***one*** of the factors enumerated under Section 25306(g) has been recognized. Without more, however, it is not a statement that the correct regulatory standard is being followed, much less satisfied. Clear evidence of developmental toxicity in animals in the absence of a biologically plausible threat of a developmental hazard to humans is not sufficient. Unless the agency is prepared to establish that Section 25306(g) is satisfied, *i.e.,* that an association between those effects and exposure to BPA in humans is "biologically plausible," then the listing process should be halted.

Second, the correct regulatory standard cannot be met. Assuming that the Request merely mis-states the Section 25306(g) standard, and OEHHA believes that all of the factors identified therein have been addressed, the animal data do not demonstrate that an association between exposure to BPA and developmental effects ***in humans*** is biologically plausible. Thus, the all-important end-point under Section 25306(g), referred to herein simply as a "biologically plausible association," has not been reached.

There are at least four reasons why a biologically plausible association has not been established. First, as discussed previously, the animal studies demonstrate that maternal toxicity in animals is consistently observed at dose levels lower than those required to produce developmental toxicity. Second, also discussed above, maternal toxicity is sufficient to cause the developmental effects observed at high doses in developmental toxicity studies of BPA in mice and rats. Third, it is clear that humans are not exposed at levels even remotely close to maternally toxic levels of BPA. Fourth, pharmacokinetic differences between rodents and humans are substantial, and even if humans were exposed to the same high doses of BPA used in the laboratory animal studies, developmental effects would not be expected in humans due to differences in pharmacokinetic handling.

As the articulation of these four reasons indicates, the issue of dose is extremely important, not only in its own right, but also in the consideration of maternal toxicity and pharmacokinetics. According to the NTP Brief, the doses that produced "high" dose developmental effects in rodents were over ***3500 times higher*** than "worst-case" doses in infants and children and ***160,000 times higher*** than estimated daily intakes in children ages 6 - 11 and adult women.[88] In other words, the dose that was required to induce adverse developmental

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[88] NTP Brief at p. 36 (The "high" dose effects of bisphenol A that represent clear evidence for adverse effects on development, *i.e.,* reduced survival (≥ 500 mg/kg bw/day) (36 – 40), reduced birth weight and growth of offspring early in life (≥ 300 mg/kg bw/day) (36 – 39, 41), and delayed puberty in female rats and male rats and mice (≥ 50 mg/kg bw/day) (37, 41 – 43), are observed at dose levels that are ***more than 3,500- times higher than "worst case" daily intakes of bisphenol A in infants and children*** less than 6 years of age (≥ 50 mg/kg bw/day versus 0.008 – 0.0147 mg/kg bw/day). The differences in exposures are much greater, more than 160,000- times different, when the high oral dose level is compared to estimated daily intakes for children ages 6 – 11 and adult women (as an indicator

(footnote continued on next page)

effects in rats and mice was over 3500 times more the exposure of the subset of the human population with the highest exposure relative to body weight.

It is clear from the NTP-CERHR Monograph, and extremely important for purposes of any proposal to list BPA under the authoritative bodies mechanism, that NTP took this into account when it declined to conclude that BPA is a reproductive toxicant. This is clear because, as noted previously, NTP concluded that it has only "negligible concern" that BPA might produce the same adverse developmental effects in humans that were seen in laboratory animals. (In fact, NTP took into account both the choice of dose levels and maternal toxicity. Indeed, the NTP's reasoning was practically identical to that of the DART IC when it considered maternal toxicity and other relevant factors made by the DART IC at the July 15, 2009 public meeting on BPA, as noted earlier.)

It is important that NTP took this into account because OEHHA is prohibited from "substituting its judgment" for that of the authoritative body. *See* Section IV.F, below. As discussed at length in Section IV.A. above, NTP-CERHR did not formally identify BPA as a reproductive toxicant within the meaning of Proposition 65, and did not conclude that BPA causes developmental toxicity for purposes of the Act. With that issue resolved, it is not OEHHA's role to examine the data independently to see if the agency would reach a different conclusion.

Even if it were to do so, however, OEHHA should not reach a different conclusion. Section 25306(g)(2) expressly recognizes the importance of "dose-response" in identifying reproductive and developmental toxicants. Indeed, the US EPA Guidelines, on which OEHHA is known at times to rely, also take dose-response relationships into account, indicating that hazard identification (in this case, the identification of chemical agents that produce adverse developmental effects) should be conducted in conjunction with an evaluation of dose-response relationships. In relevant part, the US EPA Guidelines state: "[h]azard identification for developmental toxicity is usually done in conjunction with an evaluation of dose-response relationships, since the determination of a hazard is often dependent on whether a dose-response relationship is present. One advantage of this approach is that it reflects ***hazard*** within the context of ***dose***, ***route*** and ***duration*** and ***timing*** of exposure, all of which are important in comparing the toxicity information available to potential human exposure scenarios."[89]

Again, if NTP had concluded there that an association between exposure to BPA and developmental effects in humans were biologically plausible, NTP would never have concluded that there is "negligible concern" for developmental effects in humans from BPA. By the same reasoning, it would make no sense for the State of California to designate BPA as a "chemical that causes birth defects or other reproductive harm" on the basis of the conclusions expressed in the NTP Brief, when NTP so plainly concluded that the chemical poses no more than a "negligible concern for adverse effects" for "[r]eproductive toxicity in adult men and women[,] [f]etal or neonatal mortality, birth defects, or reduced birth weight and growth."

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of exposure for pregnant women) at the 95th percentile of 0.311 and 0.271 μg/kg bw/day, respectively (35). (Emphasis added.)

[89] US EPA Guidelines for Developmental Toxicity Risk Assessment, at ix.

Finally, there are differences in the pharmacokinetics of BPA between rodents and humans that make it biologically implausible that BPA causes developmental effects in humans. The NTP-CERHR Expert Panel Report (Chapin *et al.,* 2008) reviewed in detail the many pharmacokinetic studies of BPA in rodents and humans, and the differences between rodents and humans in how the body handles BPA. In fact, the NTP-CERHR Expert Panel Report devoted a full 24 pages to the review of the pharmacokinetic data. Similarly, the European Food Safety Authority (2006, 2008) noted toxicokinetic data showing "major species differences" in the way that BPA is handled in the bodies of rodents and humans, including "major differences in disposition of BPA-glucuronide due to different pathways of elimination from the liver in rodents and primates."

When administered orally to humans and other primates, BPA "is rapidly transformed to BPA-glucuronide during first pass metabolism in the gut wall and the liver." Accordingly, "[d]ue to this rapid biotransformation and excretion and plasma protein binding in humans, peak BPA-concentrations after dietary exposures to BPA available for receptor binding are predicted to be very low even in worst case exposure scenarios." By contrast, BPA-glucuronide formed in rats "is excreted from the liver into the gut in the bile" where it "is then cleaved into BPA and glucuronic acid and BPA is reabsorbed as such into the bloodstream," resulting in "slow elimination of BPA in rodents." As to mice, the EFSA Panel observed that "oxidation products of BPA have been identified after low-dose administration, suggesting possible formation of metabolites with higher oestrogenic potency," but noted "major species differences between the mouse and the human, both in the physiology of gestation and in their toxicodynamic sensitivity to oestrogens, the mouse being particularly sensitive to weak oestrogens such as BPA." BPA, which is regarded as the active toxicological moiety, is conjugated rapidly with glucuronide in humans in the GI tract of humans, even before it can be absorbed into the body. Glucuronidation effectively "deactivates" BPA by converting it into a different substance, which has no estrogenic activity and is rapidly eliminated from the body.

The differences in the pharmacokinetics of BPA in rodents and humans are directly relevant to the issue of biological plausibility. Even if humans received the same high level of exposure to BPA as the rodents received in the high-dose studies of BPA where developmental effects were reported in rodents, developmental effects would not be expected in humans due to pharmacokinetic differences in the disposition of BPA between rodents and humans. In other words, developmental effects in humans from BPA are not biologically plausible based on pharmacokinetic differences alone.

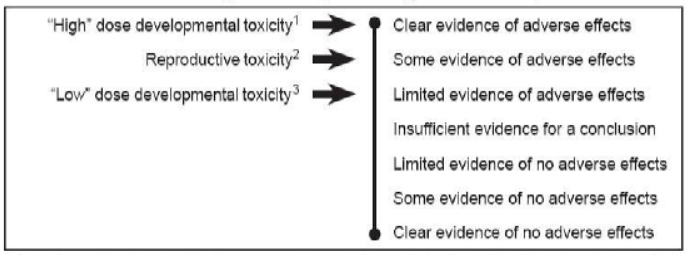
In summary, after taking into account the pharmacokinetic differences between rodents and humans, as well as consideration of maternal toxicity, dose-response relationships and other factors, an association between adverse reproductive effects in humans and BPA is biologically implausible and highly unlikely.

E. *The Studies That Are Relevant for Purposes of Proposition 65 Would Not Satisfy the "Weight of the Evidence" Test*

In evaluating the "high" dose data, NTP followed the well-known "weight of the evidence" approach. This is implicit throughout the NTP Brief and explicit in Figure 2b,

reproduced again below, with its heading "The ***weight of evidence*** that bisphenol A causes adverse developmental or reproductive effects in laboratory animals," and the top-most arrow, which points to the words "Clear evidence of adverse effects." (Emphasis added.)

Figure 2b. The weight of evidence that bisphenol A causes adverse developmental or reproductive effects in laboratory animals



[1]Based on reduced survival in fetuses or newborns (≥500 mg/kg bw/day) *(36–40)*, reduced fetal or birth weight or growth of offspring early in life (≥300 mg/kg bw/day) *(36, 37, 41)*, and delayed puberty in female rats (≥50 mg/kg bw/day) and male rats and mice (≥50 mg/kg bw/day) *(37, 41–43)*.

[2]Based on possible decreased fertility in mice (≥875 mg/kg bw/day) *(40)*; altered estrous cycling in female rats (≥600 mg/kg bw/day) *(110)*, and cellular effects on the testis of male rats (235 mg/kg bw/day) *(111)*.

[3]Based a variety of effects related to neural and behavior alterations (≥10 µg/kg bw/day) *(44–50)*, lesions in the prostate (10 µg/kg bw/day) *(51)* and mammary glands (0.0025–1 mg/kg bw/day) *(52, 53)*; altered prostate gland and urinary tract development (10 µg/kg bw/day) *(54)*, and early onset of puberty (2.4 and 200 µg/kg bw/day) *(48, 55)*.

Again, it is noteworthy that the studies cited to support this designation are the eight studies discussed above, NTP References 36 – 43. As a general matter, the "weight-of-the-evidence" approach is taken when no single study and no single modality of studies (*e.g.*, human, animal, *in vitro, etc.*) is conclusive in itself to demonstrate a causal relationship. Under this approach, the "weight of the evidence" is the eight studies which, in their totality, which show "clear evidence of adverse developmental effects" at "high" doses in laboratory animals.

For the reasons discussed above, however, not all of these eight studies can be considered to support a conclusion that exposure to BPA causes "developmental" effects within the meaning of Proposition 65. As discussed above, only three studies (NTP Reference 36, 38 and 43) demonstrate adverse effects as a result of pre-natal exposure alone (and the relevance of even these three studies is questionable, when maternal toxicity is considered). The remaining studies should be removed from consideration.

It is not possible to determine from the NTP CERHR Monograph whether NTP would have considered that there is "clear evidence" of high dose developmental toxicity (in laboratory animals) if NTP had removed from consideration those studies that are irrelevant for purposes of Proposition 65. It is clear that three studies, none of which reported developmental toxicity in the absence of significant maternal toxicity, present less weight than eight.

Hypothetically, a single study might constitute "clear evidence." But that obviously is not the case here. NTP did not state that ***each*** of the eight studies, or that any one of the eight, provided "clear evidence." Nor did NTP state that any given subset of the eight studies was sufficient to constitute "clear evidence." To the contrary, NTP explicitly cited all eight studies collectively as the "weight" of the evidence. And, despite the obvious opportunity, NTP did not state that it would have been satisfied with less. In this context, the fact that one study (NTP Reference 42) was based exclusively on post-natal exposure, and thus clearly is not relevant under Proposition 65, is extremely important: removal of that one study from consideration quite

logically might have caused NTP to have reached a different result. Removal of all studies that included post-natal exposure likely would have tipped balance in the other direction. Further, one cannot deduce what NTP would have concluded if it had limited its evaluation to the studies with developmental toxicity, as defined by Proposition 65.

F. *In Reaching a Conclusion That the Studies Above Satisfy the "Sufficient Data" Requirement of Section 25306(g), OEHHA Would Substitute Its Judgment for That of the Authoritative Body*

For all of the reasons above, it is clear that NTP did not "conclude" that BPA is a developmental toxicant. Rather, OEHHA has interpreted these studies itself, concluded on its own that BPA is a developmental toxicant, and has determined that these studies would be "sufficient" to support such a conclusion for purposes of Section 25306(g).

This distinction is extremely important: by interpreting the data to reach its own conclusions (which NTP did not reach), OEHHA would substitute its judgment for that of the authoritative body, NTP-CERHR. The authoritative body regulations clearly do not allow this. To the contrary, in promulgating those regulations, OEHHA's predecessor agency recited no less than four times in the Final Statement of Reasons that "[i]t is not the intention of the Agency to substitute its scientific judgment for that of the authoritative body."[90]

G. *Scientifically Valid Data Not Considered by NTP Further Demonstrate That BPA Does Not Cause Adverse Developmental Effects in Humans*

Even if the statements referred to in the Request could be interpreted validly as an NTP "conclusion" that BPA "causes . . . reproductive toxicity" within the meaning of Section 25306(d) (and we maintain that they cannot), the analysis would not end there. Rather, it would proceed to Section 25306(h), which requires OEHHA to "find that a chemical does not satisfy the definition of 'as causing reproductive toxicity' if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of [Section 25306(g)(2).]" That analysis is appropriate here, because significant data have been developed since the publication of the NTP-CERHR Monograph (that NTP obviously did not consider) that go to the heart of NTP's expression of "some concern for adverse [developmental] effects," which, as noted above, was based not on the "high dose" studies but on the numerous and controversial "low dose" studies.

An article published in Toxicological Sciences in October 2009, entitled *In Utero and Lactional Exposure to Bisphenol A, In Contrast to Ethinyl Estradiol, Does Not Alter Sexually Dimorphic Behavior, Puberty, Fertility, and Anatomy of Female LE Rats,* reported on a recent

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[90] Final Statement of Reasons at 16, 18, 19, 22.

study conducted by scientists from the United States Environmental Protection Agency (another "authoritative body" for purposes of Proposition 65), among others.[91]

The abstract of the article appears verbatim below:

> "Many concerns have been raised about the potential effects of BPA. ***The National Toxicology Program rated the potential effects of low doses of BPA on behavior and central nervous system (CNS) as an area of "Some concern,"*** whereas most of the effects were rated as of "negligible" or "minimal" concern. However, the number of robust studies in this area was limited. ***The current study was designed to determine if maternal exposure to relatively low oral doses of EE2 or BPA in utero and during lactation would alter the expression of well-characterized sexually dimorphic behavior of alter the age of puberty or reproductive function in the Female Long-Evans rat offspring.*** Pregnant rats were gavaged with vehicle, EE2 (0.05-50 µg/kg/day), or BPA (2,20 and 200 µg/kg/day) from day 7 of gestation to post-natal day (PND) 18, and the female offspring were studied. EE2 (50 µg/kg/day) increases anogenital distance and reduced pup body weight at PND2, accelerated the age at vaginal opening, reduced F1 fertility and F2 litter sizes, and induced malformations of the external genitalia (5 µg/kg/day). F1 females exposed to EE2 also displayed a reduced (male-like) saccharin preference (5 µg/kg/day) and absence of lordosis behavior (15 µg/kg/day), indications of defeminization of the CNS. ***BPA had no effect on any of the aforementioned measures***. . . ."[92]

These new data have reduced greatly the concerns in the toxicological community regarding potential estrogenic effects of BPA. Indeed, another article in Toxicological Sciences appropriately raises in its title the following question: *"Is it Time to End Concerns over the Estrogenic Effects of Bisphenol A?"* The author, Richard M. Sharpe, from the Medical Research Council Human Reproductive Science Unit, Center for Reproductive Biology, The Queen's Medical Research Institute, and one of the world's preeminent experts in reproductive toxicology, writes as follows:

> "For more than a decade, there has been a heated controversy whether or not the environmental chemical bisphenol A exerts adverse estrogenic effects in animal studies, ***and by extrapolation, in humans***. . . . Ryan, *et al*. (2009) publish a detailed study that throws cold water on this controversy by showing complete absence of effect of a range of bisphenol A exposures perinatally on reproductive development, function and behavior in female rats."[93]

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[91] Ryan, B.C., Hotchkiss, A.K., Crofton, K.M., and Gray,Jr., E.L (2009). In Utero and Lactional Exposure to Bisphenol A, In Contrast to Ethinyl Estradiol, Does Not Alter Sexually DiMorphic Behavior, Puberty, Fertility, and Anatomy of Female LE Rats. *Toxicol. Sci.* 114(1), 133-148 (2010).

[92] Ryan, *et. al.,* at 133.

[93] Sharpe RM. 2010. Is it time to end concerns over the estrogenic effects of Bisphenol A. Toxicol Sci. 114:1-4, at 1.

The author continues:

> "The results from Ryan, *et al*., (2009) are unequivocal and robust and are based on a valid and rational scientific foundation.[94] . . ."

The author concludes:

> "Therefore, based on the results of Ryan, *et al.,* (2009) and other similarly detailed studies that examined effects of bisphenol A on different end points (Ema *et al*, 2001; Howdeshall *et al*., 2008; Tinwell *et al*., 2002; Tyl *et al.,* 2002), ***the only scientifically logical conclusion is that bisphenol A, at doses considerably in excess of human exposure levels, does not reliably affect parameters of development and function in male or female rats/mice that are estrogen sensitive***."[95]

The importance of Ryan, *et al*., (2009) in the debate as to whether BPA causes adverse estrogenic effects is obvious, for the reasons Sharpe explains. For those same reasons, they are vital to the concerns expressed in the NTP Brief, and specifically the statement that "NTP has ***some concern*** for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A."[96] Ryan *et al.,* (2009) and Sharpe address directly the data that gave NTP reasons to have "some concern for adverse effects," and explain convincingly why those data now have far less importance, in light of the Ryan *et al.,* (2009) findings. In other words, Ryan *et al.,* (2009) and Sharpe demonstrate that the hypothesis that was supported by the data that gave NTP cause for "some concern" has been disproved. Thus, those studies would no longer support an expression by NTP of "some concern" or a "conclusion" that the possibility of adverse effects in humans "cannot be dismissed."

In addition, new information has been published recently regarding the potential for BPA to cause neurodevelopmental toxicity. Stump *et al*. (2010) reported the results of an important new developmental neurotoxicity study of BPA in rats, to which BPA was administered in the diet at concentrations of 0, 0.15, 1.5, 75, 750, and 2250 ppm from gestation day 0 through lactation day 21. Significantly, there was no evidence of that BPA is a developmental neurotoxicant in rats in this large, state-of-the-art developmental neurotoxicity study. This study is important because there were no neurological or neurobehavioral effects at either high or low doses. Consequently, this study did not confirm, and tends to disprove, allegations that low doses of BPA cause neurodevelopmental effects.

The relevance of Ryan *et al.* (2009) and Stump *et al.* (2010) in responding to OEHHA's Request is this: if OEHHA were to restrict itself to determining whether the NTP-CERHR Monograph, in the words of Section 25306(d)(1), "concludes that [BPA] causes . . . reproductive toxicity," then the NTP conclusion that shows its highest level of concern for developmental effects ("some concern," in the NTP lexicon) would no longer stand. Rather, the highest "level

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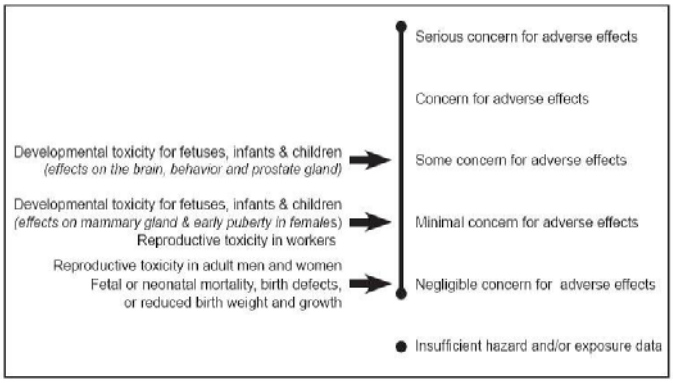
94 Sharpe RM, at 1.

95 Sharpe RM, at 2 (emphasis added).

96 NTP Brief at 8, Fig. 3 (emphasis added).

of concern" that NTP would express regarding the "possibilities that human development or reproduction might be effected by exposure to bisphenol A," as depicted in the above-mentioned Figure 3, reproduced below, would be a "minimal concern," for developmental toxicity for fetuses, infants and children," derived from the "low-dose" data that OEHHA does not address in the Request, or a "negligible concern" for "[r]eproductive toxicity in adult men and women," [f]etal or neonatal mortality, birth defects, or reduced birth weight and growth," derived from the data that OEHHA does address in the Request.

Figure 3. NTP conclusions regarding the possibilities that human development or reproduction might be effected by exposure to bisphenol A



Neither of these "conclusions" would warrant listing under the Authoritative Bodies Mechanism. In this regard, the following cases are instructive.

In *AFL-CIO v. Deukmejian*, the Health & Welfare Agency (OEHHA's predecessor agency) defended its judgment that certain "animal carcinogens" (chemicals for which there was data to show evidence of carcinogenicity in animals, but not humans) should not be placed on the "initial list" of chemicals "known to cause cancer or reproductive toxicity" pursuant to Section 25249.8(a) of the Act, which provided that "[s]uch list shall include at a minimum those substances identified by reference in Labor Code Section 6382(b)(1) and those substance identified additionally by Labor Code Section 6382(d)." The controversy centered on whether the list was required to include chemicals that came within the "scope" of the Hazard Communication Standard, because they were designated by the International Agency for Research on Cancer ("IARC") as "Group 2B" ("probable" or "possible" human carcinogens under IARC's carcinogenicity classification system). Defending its decision, the OEHHA's predecessor argued:

> "a literal construction of Section [25249.8(a) would] lead to absurd results, requiring the listing of substances not known to cause cancer [because the Hazard Communication Standard] referred to in Labor Code Section 6382 includes thousands of substances that are not carcinogens or reproductive toxins. A literal construction of the statute, [the State argued], would require the initial list to include these substances . . . ."

The Court of Appeal responded:

> "It is true that 'any substance within the scope of the federal [Hazard Communication Standard]' includes chemicals other than known carcinogens. Section [25249.8(a)] and the Act itself, however, are concerned only with those substances that authoritative bodies have concluded are known to cause cancer or reproductive toxicity. ***Thus, the initial list, and subsequent lists published thereafter, need not include all substances listed under [the federal Hazard Communication Standard] but only known carcinogens and reproductive toxins*** listed there**.**"[97]

More recently, in *Styrene Information and Research Center v. OEHHA,* the Superior Court for Sacramento issued an order enjoining OEHHA from listing the chemicals styrene and vinyl acetate monomer under the Labor Code Listing Mechanism. OEHHA proposed to list the styrene because a monograph published by IARC classified the chemical in Group 2B and, as such was "within the scope of the federal Hazard Communication Standard." Nevertheless, classification in Group 2B meant only that that styrene is "possibly carcinogenic to humans," within the IARC classification system.

In moving for judgment on the pleadings and a permanent injunction to prohibit the listing of styrene, the plaintiff Styrene Information and Research Center argued that chemicals may not be listed under Proposition 65 unless they are "known to cause" cancer or reproductive toxicity, and that in order for a chemical to be "known to cause cancer," there must be "sufficient evidence" of carcinogenicity.[98] The fact that IARC classified styrene in Group 2B did not, in itself, establish "sufficient evidence" of carcinogenicity for purposes of Proposition 65. To the contrary, SIRC pointed out that "recent studies 'show no causal link' between styrene exposure and human cancer. New mechanistic evidence and animal exposure studies show that the 'limited evidence' of carcinogenicity in mice does not apply to human beings."[99]

These arguments run parallel to the facts here. As to styrene, OEHHA argued that the chemical must be listed under the Labor Code Mechanism because it had been "classified" as a potential carcinogen when IARC placed the chemical in its Group 2B. As to BPA, OEHHA similarly indicates that the chemical must be listed under the Authoritative Bodies Mechanism because it has been "formally identified" as a reproductive toxin, when NTP concluded only that "the possibility that bisphenol A may alter human development cannot be dismissed," and recent studies (*i.e*., Ryan *et al.* (2009)) show that the basis of that concern now can be discounted.

The Sacramento Court resolved the matter as follows: citing the same passage from *Deukmejian*, the Court noted that "only those chemicals that are known, and not merely

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97 *AFL-CIO v. Deukmejian* (1989) 212 Cal.App.3d 425 ["Deukmejian"] at 437, 438 (emphasis added).

98 *See Deukmejian* at 434, n. 3 (stating that although the IARC does not use the term "known carcinogen" for the purpose of interpreting the IARC monographs, "sufficient evidence" of carcinogenicity is the equivalent of "known" carcinogenicity).

99 *Styrene Information and Research Center v. OEHHA (2009)*, Minute Order Granting Preliminary Injunction at 3.

suspected, of causing cancer or reproductive toxicity must be on the list. The IARC Group 1 substances, made up of chemicals for which there is sufficient evidence of carcinogenicity to humans, clearly are subject to the Act. Beyond that, the question is not whether a chemical is "probably' carcinogenic to humans, but where it is in fact a known carcinogen or reproductive toxin."

Deukmejian, recently interpreted and applied to enjoin the listing of styrene, thus instructs that the ultimate test for listing any substance is whether it is "known to cause cancer or reproductive toxicity." To the extent that OEHHA's implementing regulations would provide for a different result, whether based on "classifications" or "formal identifications," they are inconsistent with the statute. To the extent that Sections 25306(d) or Section 25306(g) would allow for the listing of BPA, when NTP has concluded only that the "possibility that the chemical causes adverse developmental effects cannot be dismissed," the listing would be arbitrary, capricious, and contrary to law.

V. CONCLUSION

On July 15, 2009, the DART IC concluded that BPA has not been "clearly shown to cause developmental toxicity," and thus should not be listed pursuant to Section 25249.8(b) of the Act. Any proposal to list the chemical now under the Authoritative Bodies Mechanism on the basis of the NTP-CERHR Monograph is unlawful under Section 25259.8(b) and Section 25306 of the implementing regulations, because the Monograph does not "formally identify" BPA as a developmental toxin, and neither the Act nor the regulations authorize OEHHA to overrule the DART IC or list the chemical on the basis of its own evaluation of the same data that the DART IC already considered. If OEHHA were to continue nevertheless to consider BPA for listing, the chemical should not be listed, because the data identified in the Request as the basis for listing are not "sufficient" within the meaning of Section 25306(g)(2). Moreover, OEHHA would be required under Section 25306(h) to acknowledge the existence of new data not available to NTP-CERHR at the time it published the Monograph, which mitigate the concerns that NTP expressed regarding both estrogenic and neurodevelopmental effects. Although these data do not relate directly to the studies identified in the Request, it appears they would reduce NTP-CERHR's "level of concern" that BPA is a reproductive or developmental toxicant from "some concern" to only a "negligible" concern.

For all of these reasons, OEHHA should conclude that it is inappropriate and unlawful to list BPA as a chemical "known to the state to cause . . . reproductive toxicity" under Section 25249.8(a) of the Act. We respectfully request that OEHHA issue a public notice consistent with this conclusion and cease any further activity to list the chemical under the Authoritative Bodies Mechanism on the basis of the NTP-CERHR Monograph.

Respectfully submitted,

AMERICAN CHEMISTRY COUNCIL

BY:

STEVEN G. HENTGES, PH.D.
EXECUTIVE DIRECTOR
POLYCARBONATE/BPA GLOBAL GROUP

MURRAY & ASSOCIATES

By:_____
F. JAY MURRAY, PH.D.

MCKENNA LONG & ALDRIDGE LLP

By:_____
CHRISTIAN VOLZ

_____
STANLEY W. LANDFAIR

TECHNOLOGY SCIENCES GROUP INC.

By:_____
ARTHUR L. LAWYER, PH.D.

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