

Office of Environmental Health Hazard Assessment



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Edmund G. Brown Jr.
Governor

January 22, 2013

Anthony R. Scialli, M.D.
Senior Scientist
Tetra Tech Sciences
2200 Wilson Boulevard, Suite 400
Arlington, Virginia 22201-3397

Dear Dr. Scialli:

Thank you for your letter of May 12, 2010, responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65¹. BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies provision² of Proposition 65 and based on findings by the National Toxicology Program (NTP). NTP made its findings in a report³ by the NTP Center for the Evaluation of Risks to Human Reproduction that BPA causes developmental toxicity at “high” doses.

OEHHA has carefully reviewed the comments you submitted. A document providing our responses to your comments is enclosed.

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

¹ The California Safe Drinking Water and Toxic Enforcement Act of 1986, California Health and Safety Code section 25249.5 et seq.

² Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regulations, section 25306.

³ National Toxicology Program – Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR, 2008). *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A*. NIH Publication No. 08 – 5994.

⁴ Title 27, Cal. Code of Regulations, section 25306.

California Environmental Protection Agency

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Anthony R. Scialli, M.D.

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the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation.⁵

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

Sincerely,



Lauren Zeise, Ph.D.

Deputy Director for Scientific Affairs

Enclosure:

Response to Comments from Anthony R. Scialli on the Request for Relevant Information on Bisphenol A as a Chemical under Consideration for Listing under Proposition 65.

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

**Response to Comments from Anthony R. Scialli on the
Request for Relevant Information on
Bisphenol A as a Chemical under Consideration
for Listing under Proposition 65**

Office of Environmental Health Hazard Assessment

January 2013

On February 12, 2010, the Office of Environmental Health Hazard Assessment (OEHHA) published in the California Regulatory Notice Register (CRNR) a Request for Relevant Information for Bisphenol A (BPA) for possible listing as a chemical known to cause reproductive toxicity under Proposition 65.¹ The listing would be based on the authoritative bodies provision² relying on findings by the National Toxicology Program (NTP) in a final report from the NTP Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) that BPA causes developmental toxicity at “high” doses (NTP-CERHR, 2008).

On May 12, 2010, OEHHA received comments concerning the listing of BPA under Proposition 65 from Anthony R. Scialli of Tetra Tech Sciences, developed with the financial support of the American Chemistry Council. This document provides a response to these comments.

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

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

Responses are provided to comments related to these aspects of the possible listing of BPA under Proposition 65 via the authoritative bodies listing process. Dr. Scialli’s

¹ The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq.*).

² Title 27, Cal. Code of Regs., section 25306.

³ All referenced sections are from Title 27 of the California Code of Regulations unless otherwise indicated

comments address Formal Identification in the section of his comment letter entitled, “The CERHR approach” and Sufficiency of Evidence, specifically as regards consideration of maternal toxicity, in the section, “The studies”.

Formal Identification

Comment:

CERHR differs from Proposition 65 in that “CERHR characterizes the conditions under which reproductive or developmental toxicity occur and determines a level of concern for human exposure based on a comparison of anticipated human exposure conditions and those represented in experimental studies.” The comments then quote from a template from a paper providing guidance for stating the weight of the evidence for data that the chemical does or does not cause reproductive toxicity.

Response:

While NTP-CERHR does provide conclusions concerning a *level of concern*, it also provides a conclusion regarding the *weight of evidence* for the occurrence of developmental toxicity, as illustrated by the template language cited in the letter. The NTP found “clear evidence” for the developmental toxicity of BPA at high doses. Some confusion is caused in the comment by quoting the template for the *weight of evidence* conclusion to support a description of the *level of concern* conclusion.

The *weight of evidence* conclusion is based on evaluation of scientific evidence from human and/or animal studies, while the *level of concern* statement includes consideration of human exposure, as described in the comments.

Proposition 65 listing involves evaluation of scientific evidence that a chemical causes reproductive toxicity.

“The lead agency shall determine which chemicals have been identified by an authoritative body as causing cancer or reproductive toxicity.” (Section 25306(c))

Consideration of human exposure is considered at later stages in the Proposition 65 process, after listing of a chemical has occurred. It is the *weight of evidence* conclusion and not the *level of concern* conclusion of NTP-CERHR that is relevant to Proposition 65 listing. As stated in OEHHA’s Request for Relevant Information, the *weight of*

evidence conclusion of NTP-CERHR for BPA provides the basis for formal identification and possible Proposition 65 listing of the chemical.

Comment:

“The CERHR process by its design could not have listed bisphenol A as a reproductive or developmental toxicant because it does not create lists. “

Response:

Proposition 65 does not require that an authoritative body create lists in order to identify an agent as a reproductive toxicant. Instead, a chemical is known to cause reproductive toxicity if an authoritative body “has formally identified it as causing... reproductive toxicity.” (Health and Safety Code section 25249.8(b))

As explained above, the implementing regulations provide criteria for OEHHA to use to determine whether an authoritative body has formally identified a chemical. The relevant language is as follows:

“For purposes of this section a chemical is “formally identified” by an authoritative body when the lead agency determines that: (1) the chemical has been included on a list of chemicals causing cancer or reproductive toxicity issued by the authoritative body: *or is the subject of a report which is published by the authoritative body and which concludes that the chemical causes cancer or reproductive toxicity; or has otherwise been identified as causing cancer or reproductive toxicity by the authoritative body in a document that indicates that such identification is a final action....*” (Section 25306(d)(1)), emphasis added)

Sufficiency of Evidence: Maternal Toxicity

Comment:

The comments review the studies cited by NTP-CERHR in support of its conclusion that there is clear evidence that “high” doses of BPA cause developmental toxicity in laboratory animals, to support the commenter’s contention that “...parental or adult toxicity explains the reproductive or developmental effects” in the studies cited by NTP-CERHR, and that “[r]eproductive or developmental effects due to parental or adult toxicity do not warrant consideration of a chemical as a reproductive or developmental toxicant.”

Response:

In considering the relationship between maternal and developmental toxicity, OEHHA relies on generally accepted principles as expressed in regulatory documents and in the peer-reviewed literature. For example, the U.S. Environmental Protection Agency’s (U.S. EPA, 1991) Guidelines for Developmental Toxicity Risk Assessment state:

- “Agents that produce developmental toxicity at a dose that is not toxic to the maternal animal are especially of concern because the developing organism is affected but toxicity is not apparent in the adult. However, the more common situation is when adverse developmental effects are produced only at doses that cause minimal maternal toxicity; in these cases, the developmental effects are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity.” (pp 18)
- “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.” (pp 18)

Three situations must be distinguished in connection with the relationship between maternal toxicity and developmental toxicity:

1. Maternal toxicity and developmental toxicity occur at the same doses.
2. Maternal toxicity causes developmental toxicity.
3. Maternal toxicity precludes clear interpretation of the study.

While the comments describe associations between maternal and developmental toxicity, no evidence is presented that maternal toxicity causes the developmental toxicity observed or precludes interpretation of the study. The comments express the opinion that:

“...the effects occurred with exposure levels that produced clear parental/adult toxicity of a degree sufficient to explain the reproductive or developmental effects; moreover the developmental effects were those expected to occur from the adult toxicity.”

The study descriptions provided in the comments outline the parental/adult toxicity and the developmental toxicity for each study cited by NTP-CERHR, without providing any indication how the former explains the latter, or why the developmental effects would be the ones expected to occur from the adult toxicity.

For example, the comments state that a transient delay of testes descent in weanlings in the Tyl *et al.* (2008) study was “attributed to maternal toxicity”. It goes on to state that parental toxicity was “manifested by abnormal kidney and liver organ weights and histopathology.” The report itself does not connect the liver and kidney weight and histopathological changes in the parents to weanlings’ delayed testes descent. No information on a causal biological link is provided in the comments.

Two articles cited by the author to support the statement that embryo development is sensitive to maternal toxicity deal only with associations between maternal and developmental endpoints, not causal relationships. As pointed out in the following examples provided in the comments, there is also evidence for *lack* of association between maternal toxicity and developmental toxicity in the same documents.

- “The highest dose level produced a 14% decrease in maternal body weight gain over the course of the pregnancy. In spite of this substantial toxicity, there was no developmental toxicity at any dose in the rat.” (comments page 7)
- “...post implantation exposure to BPA (gavage) did not cause external, visceral, or skeletal malformations at doses that caused significant maternal toxicity (rats) or mortality (mice).” (comments page 8)
- “This study is remarkable for the lack of reproductive or developmental toxicity over three generations in the face of prominent adult toxicity in the high dose group.” (comments page 8)

Thus, the examples provided by the author do not support the conclusion that parental/adult toxicity caused the developmental toxicity, or that associations between maternal and developmental toxicity are predictable and consistent.

Further, it is important to note that existing authoritative guidelines do not preclude the identification of developmental toxicity when associated with maternal toxicity or even when it is caused by maternal toxicity:

- The U.S. EPA (1991) Guidelines for Developmental Toxicity Risk Assessment state:

“Current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity: rather, when the LOAEL is the same for the adult and developing organisms, it may simply indicate that both are sensitive to that dose level.”

“Moreover, whether developmental effects are secondary to maternal toxicity or not, the maternal effects may be reversible while effects on the offspring may be permanent.”

- The U.S. EPA Toxic Substances Control Act (TSCA), Section 8(e) guidance Frequent Questions state:

“Q. 18. How should reproductive or developmental toxicity data be evaluated for possible TSCA 8(e) submission if maternal toxicity is also present?”

A. 18. Statistically or biologically significant increases in reproductive or developmental toxicity should be reported under TSCA 8(e) regardless of the level of maternal toxicity observed in the study.” (U.S. EPA 2006; available at <http://www.epa.gov/oppt/tsca8e/pubs/frequentlyaskedquestionsfaqs.html#2010>).

- The United Nations Economic Commission for Europe Globally Harmonized System of Classification and Labeling of Chemicals states:

“Developmental effects, which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case by case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification should be

considered where there is significant toxic effect in the offspring, e.g. irreversible effects such as structural malformation, embryo/foetal lethality, significant post-natal functional deficiencies.” (GHS, Section 3.7.2.4.2, 2009)

Comment:

“There is a well-established tradition in the field of avoiding excessive parental or adult toxicity in study design in order to avoid obtaining findings that cannot be interpreted.”

Response:

As regards the ability to interpret the study, all six studies were described and interpreted by the authoritative body (NTP), by the study authors and by the commenter. Interpretation of the data was possible in all the studies cited in the NTP-CERHR document.

References:

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

United Nations Economic Commission for Europe (2009). Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Third Revised Edition. (available at http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev03/English/03e_part3.pdf).

U.S. Environmental Protection Agency. (U.S. EPA, 2006). Toxic Substances Control Act (TSCA), Section 8(e) guidance Frequent Questions. Q.18. (available at <http://www.epa.gov/oppt/tsca8e/pubs/frequentlyaskedquestionsfaqs.html>)

U.S. Environmental Protection Agency. (U.S. EPA, 1991). “Guidelines for Developmental Toxicity Risk Assessment.” Fed Reg **56** (234):63798-63826.