January 22, 2013

This is to be emailed to
Dr. Leon Earl Gray Jr.
emgray@mindspring.com

Dear Dr. Gray:

Thank you for your email submission of May 14, 2010, responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65 (California Health and Safety Code section 25249.5 et seq.). You submitted two recent papers from your laboratory on the transgenerational effects of estradiol and BPA for inclusion in our evaluation of BPA. You also included a paper discussing the significance of your work. We appreciate your sending these publications to us.

BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies provision of Proposition 65 (Health and Safety Code section 25249.8(b)), based on findings by the National Toxicology Program (NTP). NTP made its findings in a report by the NTP Center for the Evaluation of Risks to Human Reproduction that BPA causes developmental toxicity at “high” doses (NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NIH Publication No. 08 – 5994).

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 on the OEHHA website at www.oehha.ca.gov and in the California Regulatory Notice Register in the near future. Following its publication, there will be a 30-day public comment period regarding the possible listing. Comments should focus on whether or not the criteria for listing the chemical under Proposition 65 have been met (Title 27, Cal. Code of Regulations, section 25306). In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification...
Dr. Leon Earl Gray Jr.
January 22, 2013
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Committee (DARTIC) for its consideration as required by regulation (Title 27, Cal. Code of Regulations, section 25306(i)).

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
January 22, 2013

Julie Silas, JD
Director, Health Care Projects

Tom Lent
Policy Director
Healthy Building Network
390 49th Street
Oakland, California 94606

Dear Ms. Silas and Mr. Lent:

Thank you for your letter of April 27, 2010, responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65 (California Health and Safety Code section 25249.5 et seq.). BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies’ provision of Proposition 65 (Health and Safety Code section 25249.8(b) et seq.), based on findings by the National Toxicology Program (NTP). NTP made its findings in a report by the NTP Center for the Evaluation of Risks to Human Reproduction that BPA causes developmental toxicity at “high” doses (NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NIH Publication No. 08 – 5994).

You provided information regarding the use of BPA as a component of epoxy resin in building materials, including paints and adhesives. While the information is not relevant to deciding whether or not BPA meets the criteria for listing under Proposition 65, OEHHA nonetheless acknowledges your interest in the listing process and your stated support of the addition of BPA to the Proposition 65 list.

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 on the OEHHA website at www.oehha.ca.gov and in the California Regulatory Notice Register in the near future. Following its publication, there will be a 30-day public comment period regarding the possible listing.
Comments should focus on whether or not the criteria for listing the chemical under Proposition 65 have been met (Title 27, Cal. Code of Regulations, section 25306). In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation (Title 27, Cal. Code of Regulations, section 25306 (i)).

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
January 22, 2013

Drew Johnson  
Acting Division Chief  
Division of Chronic Disease and Injury Control  
California Department of Public Health  
P.O. Box 997377 MS 7200  
Sacramento, California 95899-7377

Dear Mr. Johnson:

This letter is in response to a memorandum Dr. Donald Lyman sent on April 30, 2010 responding to the Office of Environmental Health Hazard Assessment's (OEHHA) Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65.¹ BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies provision² of Proposition 65, 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 (NTP-CERHR) that BPA causes developmental toxicity at “high” doses.

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 on the OEHHA website at www.oehha.ca.gov and in the California Regulatory Notice Register in the near future. Following its publication, there will be a 30-day public comment period regarding the possible listing. Comments should focus on whether or not the criteria for listing the chemical under Proposition 65 have been met (Title 27, Cal. Code of Regulations, section 25306). In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation (Title 27, Cal. Code of Regulations, section 25306 (i)).

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.  
Your comments concern the importance of dental sealants in the protection of public health in California, and you request that OEHHA consider the public health benefits of dental sealants as we consider the listing of BPA. The listing of BPA under Proposition 65 would not prohibit use of BPA in any product and, consequently, would not require replacement of BPA in dental sealants. Rather, warnings would be required if levels of BPA released from dental sealants were above a Maximum Allowable Dose Level (MADL). If the chemical were to be listed, we would make it a priority to develop a MADL for BPA. This would reduce the likelihood of unnecessary litigation and warnings. In cases where the average use of a product by the average consumer does not result in exposure to a listed chemical that exceeds the MADL, no warning is required.

OEHHA's general practice, when feasible, is to propose a MADL within one year of the listing of a chemical. In many cases, we have been able to finalize a MADL at or near the time the warning requirement for a newly listed chemical takes effect. As you may be aware, Proposition 65 provides a “grace period” of 12 months after the chemical is listed before any interested party can sue for alleged violations of the Act. During that time, product manufacturers can evaluate their product exposures against the MADL and determine whether or not a warning is necessary. In some instances, OEHHA has been able to propose MADLs concurrent with or even prior to the listing of a chemical. If OEHHA makes a final determination to add BPA to the Proposition 65 list, we will consider whether it is feasible to release a draft MADL concurrent with the listing. At a minimum, we would make it a priority to develop and adopt a MADL for BPA at the earliest possible date following the chemical's listing.

OEHHA also can develop interpretive guidelines and safe use determinations to provide further guidance to businesses and the public concerning the applicability of Proposition 65 to specific products or uses of a chemical. OEHHA will consider developing these materials as appropriate if BPA is listed.

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

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4 Health and Safety Code section 25249.10(c) and Title 27, Cal Code of Regs., section 25821(c)(2).
5 Health and Safety Code section 25249.5(10)(b).
January 22, 2013

Geoffrey Cullen  
Vice President of Government Relations  
Can Manufacturers Institute  
1730 Rhode Island Avenue NW, Suite 1000  
Washington, DC 20036

Dear Mr. Cullen:

Thank you for your letter of May 10, 2010, responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65.1 BPA is a candidate for listing as known to cause reproductive toxicity. The 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).3

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 regulatory criteria for listing have been met.4 In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation.5

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2 Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regulations, section 25306.
4 Title 27, Cal. Code ofRegs., section 25306.
5 Title 27, Cal. Code ofRegs., sections 25306(i).
Your comments were submitted in opposition to the possible Proposition 65 listing of BPA. The comments endorsed other comments submitted by the Grocery Manufacturers Association, which raised technical issues related to the criteria provided above. A copy of our response to the Grocery Manufacturers Association is enclosed.

Your comments primarily discuss potential economic and public health consequences of the possible listing of BPA. You suggest that a Proposition 65 warning would undermine the U.S. Food and Drug Administration’s (U.S. FDA’s) goal of limiting warnings on food labels to only those deemed necessary to protect the public health and must be based on credible scientific evidence. Your comments state that a Proposition 65 warning would convey a threat to human health that is unsupported by appropriate scientific evidence and is not consistent with the conclusions about the safety of BPA drawn by U.S. FDA and other federal and international public health bodies.

The listing of BPA under Proposition 65 would be based on formal identification of the chemical as causing reproductive toxicity by the National Toxicology Program, a highly respected entity whose status as an authoritative body for purposes of Proposition 65 listings was reaffirmed by the DARTIC in 2011. Warnings would be required only if exposures to the public to the chemical from a given product exceeded the levels exempted in the statute from this requirement.\(^6\) The Proposition 65 statute and its regulations are directed toward helping California consumers make informed choices regarding the products that they purchase. In doing so, Proposition 65 promotes public health protection. The law and regulations do not allow OEHHA to consider the potential economic impact of chemical listings.

Your comments note that U.S. FDA has begun working with the food industry to reduce or eliminate BPA exposure and state that Proposition 65 activity would undermine the authority of the U.S. FDA and Obama Administration to effectively regulate the safety of food, including packaging.

OEHHA is aware that federal agencies such as U.S. FDA are currently involved in risk assessment and risk characterization of BPA. Any potential conflict between U.S. FDA and Proposition 65’s warning requirements are speculative. In the event of an actual conflict between the federal requirements and Proposition 65, OEHHA will work with FDA to resolve the issue. Further, Proposition 65 expressly states that to the extent it conflicts with federal law, it does not apply.\(^7\)

Where levels of BPA exposure are sufficiently low, warnings will not be required. If the chemical is listed, we will provide compliance assistance to businesses to reduce the

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\(^6\) Health and Safety Code section 25249.10(c).

\(^7\) Health and Safety Code section 25249.10(a).
likelihood of unnecessary warnings or litigation. For example, in cases where the average use of a product by the average consumer does not result in exposure to a listed chemical that exceeds a maximum allowable dose level (MADL), no warning is required. OEHHHA can assist interested parties by adopting a MADL.

OEHHHA's general practice, when feasible, is to propose a MADL within one year of the listing of a chemical. In many cases, we have been able to adopt the MADL at or near the time the warning requirement for a newly listed-chemical takes effect. In some instances, OEHHHA has been able to propose MADLs concurrent with or even prior to the listing of a chemical. If OEHHHA makes a final determination to add BPA to the Proposition 65 list, we will consider whether it is feasible to release a draft MADL concurrent with the listing. At a minimum, we would make it a priority to develop and adopt a MADL for BPA at the earliest possible date following the chemical's listing. As you may be aware, Proposition 65 provides a "grace period" of 12 months after the chemical is listed before any interested party can sue for alleged violations of the Act. During that time, product manufacturers can evaluate their product exposures against the MADL and determine whether or not a warning is necessary.

OEHHHA also can develop interpretive guidelines and safe use determinations to provide further guidance to businesses and the public concerning the applicability of Proposition 65 to specific products or uses of a chemical. OEHHHA would consider developing these materials in the event BPA is listed.

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@oehh.ca.gov.

Sincerely,

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

Enclosure:

Response to comments from Michelle Corash on behalf of the Grocery Manufacturers Association.

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8 Health and Safety Code section 25249.10(b).
9 Title 27, Cal Code of Regulations, section 25203.
10 Title 27, Cal Code of Regulations, section 25204.
January 22, 2013

Michele B. Corash
Morrison & Foerster LLP
425 Market Street
San Francisco, California 94105-2482

Dear Ms. Corash:

Thank you for your letter of May 13, 2010, on behalf of the Grocery Manufacturers Association (GMA), responding to the Request for Relevant Information on bisphenol A (BPA) as a chemical under consideration for listing as known to cause reproductive toxicity under Proposition 65\(^1\). The potential listing is based on the authoritative bodies provision\(^2\) of the Proposition 65 implementing regulations as applied to findings by the National Toxicology Program (NTP) on the basis of 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)\(^3\).

Under the formal authoritative bodies listing process set out in the regulation, a chemical must be listed under Proposition 65 when the Office of Environmental Health Hazard Assessment (OEHHA) determines that the following criteria are met:

1. **Formal Identification**: An authoritative body formally identifies the chemical as causing reproductive toxicity (Title 27, Cal. Code of Regs., section 25306(d)\(^4\)).
2. **Sufficiency of Evidence**: The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulation (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)).

GMA’s comments address both public policy and legal issues. GMA’s comments assume that all manufacturers will stop using BPA in their products if the chemical is listed.

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

\(^2\) Title 27, Cal. Code of Regulations, section 25306.


\(^4\) All further references are to sections of Title 27 of the California Code of Regulations unless otherwise stated.
However, Proposition 65 does not ban the use of listed chemicals. It simply requires that consumers be given a warning prior to certain exposures to the chemical and prohibits the release of significant amounts of the chemical into sources of drinking water. It is not clear whether or not a warning might be required for exposures to BPA from food packaging and, in fact, GMA maintains that the manufacturers will be able to prove that any exposure is below the safe harbor level and therefore will not require a warning. Further, policy arguments about the potential impact on the food industry in California are not relevant to whether or not the chemical meets the listing criteria in the regulation. Proposition 65 does not allow consideration of economic impacts, a chemical’s merits or the availability of alternative chemicals when making listing decisions.

OEHHA also disagrees with GMA’s contention that the law creates a “hierarchy” of listing mechanisms where the “state’s qualified experts” mechanism trumps the three others. Proposition 65 provides four mechanisms for listing of chemicals, all of which are independent of each other. In fact, the Labor Code listing mechanism is established in a separate subsection from the other three. The Labor Code mechanism is set forth in Health and Safety Code section 25249.8(a) and the other three are listed in the disjunctive in Health and Safety Code section 25249.8(b). The only connection in the statute between the state’s qualified expert’s mechanism and the authoritative bodies’ mechanism is the requirement that the authoritative bodies be identified by the state’s qualified experts. No hierarchical structure, consensus requirement or other provision is made in the statute or regulations for establishing interdependent operation of the different mechanisms. The 2009 determination of the Developmental and Reproductive Toxicant Identification Committee (DARTIC) that BPA does not meet the criteria for listing pursuant to the state’s qualified experts mechanism does not address the entirely separate question of whether BPA meets the criteria for listing pursuant to an alternative listing mechanism. Thus, the state’s qualified experts cannot “overrule” the authoritative body process, and vice-versa. If the criteria for listing by any of the four mechanisms are met, the chemical is added to the list because it is “known to the state” to cause reproductive toxicity.

The fact that the Health and Welfare Agency originally expressed its opinion that the state’s qualified experts would be the “primary approach to listing” at the time the authoritative bodies regulations were being adopted, does not change this analysis. Neither the Proposition 65 statute nor its implementing regulations refer to any hierarchy in which the state’s qualified experts mechanism is the “primary approach to listing” chemicals.

OEHHA agrees with cited text from the statement of reasons for Section 25306, stating that the purpose of the authoritative bodies provision is to conserve the resources (time and effort) of the state’s qualified experts. This is because the DARTIC (which serves as the state’s qualified experts for reproductive toxicity) does not need to re-evaluate chemicals for which a thorough scientific evaluation has already been conducted. Generally, the chemicals that are brought to the DARTIC are there for a de novo review because the chemical has not been considered by an authoritative body. In the case of BPA, the NTP-CERHR report was published during the pendency of BPA’s review by the DARTIC. OEHHA could have removed the chemical for DARTIC consideration, but chose not to do
so. However, OEHHA can and indeed must consider whether BPA meets the authoritative bodies listing criteria, whether or not it has been previously reviewed by the DARTIC. Nothing in the statute or regulations allows OEHHA to ignore a chemical that may qualify for listing under one of the four listing mechanisms, simply because it has already been considered under another mechanism.

Finally, we acknowledge GMA’s request that a regulatory Maximum Allowable Dose Level (MADL) be proposed prior to the potential listing of BPA and agree that a safe harbor level would provide valuable compliance assistance to the food industry. It is OEHHA’s practice to propose a safe harbor level, where sufficient data are available to do so, within one year of the listing of a chemical. Often these safe harbors become effective at or near the time the warning requirements of the law are effective and well before the time that discharges of the chemical to sources of drinking water are prohibited. In some instances, it has proved feasible to propose a MADL concurrent with or even prior to listing of a chemical. OEHHA will consider whether it is feasible to do so for BPA but would, at a minimum, make it a priority to timely propose such a level for BPA, should the chemical be listed. OEHHA also has regulatory authority to develop interpretive guidelines and safe use determinations to provide further guidance to businesses and the public concerning the applicability of Proposition 65 to specific products as well as uses of a chemical. OEHHA would consider developing these materials as appropriate if BPA were listed.

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 (NOIL) BPA will be published in the near future. Following publication of the NOIL, there will be a further 30-day period for submission of comments on this proposed action.

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,

[Signature]

Lauren Zeise, Ph.D.
Deputy Director for Scientific Affairs
January 22, 2013

Dear interested parties and Institute for Liberty submitters:

In May 2010, the California Office of Environmental Health Hazard Assessment (OEHHA) received approximately 3,000 e-mails from individuals who said they had been contacted by the Institute for Liberty about the chemical bisphenol A (BPA). The e-mails were sent during a public-comment period on the potential listing of BPA as a reproductive toxicant under California’s Proposition 65. We appreciate your interest in BPA, and are writing to respond to and provide clarification on issues you raised.

Proposition 65, officially known as the Safe Drinking Water and Toxic Enforcement Act, was passed by California voters in 1986. Under this law, OEHHA maintains and updates a list of chemicals that cause cancer or reproductive toxicity. There are four different ways that chemicals are added to the list. One way is when certain federal agencies identify a chemical as causing reproductive toxicity. The federal National Toxicology Program (NTP) in a 2008 report identified BPA as harming the development of laboratory animals exposed to high doses of BPA. The NTP report is available at http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/bisphenol.pdf. The possible listing of BPA is based on this report.

We carefully reviewed the e-mails and all other comments on the possible listing of BPA that we received in 2010. We have now determined that BPA meets the criteria for addition to the Proposition 65 list. Accordingly, we are posting a Notice of Intent to List BPA on our web site at www.oehha.ca.gov. The posting starts a 30-day public comment period on the proposed listing. Comments should focus on whether or not the criteria for listing the chemical have been met. The criteria are contained in Section 25306 of the Proposition 65 regulations, which is accessible at www.oehha.ca.gov/prop65/law/pdf_zip/RegsArt3.pdf. If OEHHA finds the criteria have not been met after review of the comments received during this new comment period, BPA will be referred to an expert scientific panel, the Developmental and Reproductive Toxicant (DART) Identification Committee, for a final listing decision.

I appreciate the strong viewpoints expressed in the e-mails from Institute for Liberty submitters, and would like to offer the following responses to those comments:
The addition of BPA to the Proposition 65 list would not ban the production or use of the chemical. Proposition 65 would require that businesses provide a warning when they expose consumers to significant levels of BPA. Rather than limiting consumer choice as indicated in your comment letters, the warnings allow consumers to make informed choices about whether they wish to buy or use products that will expose them to chemicals that are known to be reproductive toxicants and carcinogens.

Your comment letters state that several government agencies – including NTP and the U.S. Environmental Protection Agency (U.S. EPA) – have determined that BPA is safe. In fact, recent statements by these agencies reflect some concern about BPA.

For example, NTP in its 2008 report not only said there is “clear evidence” of developmental effects in laboratory animals at high doses, but also said there is “some concern” for effects on fetuses, infants and children at current human exposures to BPA.

Similarly, the U.S. Food and Drug Administration (FDA), in its 2010 document, “Update on Bisphenol A for Use in Food Contact Applications,” says, “FDA shares the perspective of the National Toxicology Program that recent studies provide reason for some concern about the potential effects of BPA on the brain, behavior and prostate gland of fetuses, infants and children.” The same sentence appears in FDA’s March 30, 2012 update of this document.


Only the NTP’s “clear evidence” statement provides the basis for adding BPA to the Proposition 65 list. However, we are sharing these statements with you to help clarify what these federal entities have said about BPA.

I would also like to clarify the action that the DART Committee took in July 2009. The DART Committee determined that available scientific information on BPA had not “clearly shown” that BPA causes reproductive or developmental effects. In making this determination, the DART Committee did not make any finding that BPA is safe, as indicated in your comment letters.

It is fair to ask why BPA is being proposed for the Proposition 65 list at this time when the DART Committee voted against adding the chemical to the list in 2009. Proposition 65 requires chemicals to be listed when NTP’s identification of a chemical meets the listing criteria, even if the DART Committee had decided earlier not to list it. In fact, the DART Committee in 2011 reaffirmed that NTP’s
identifications of reproductive toxicants must be used as a basis for making listing decisions, including the potential listing of BPA. Proposition 65 was written to ensure that chemicals could be listed based on the findings of expert entities like NTP and the DART Committee. It is not necessary for NTP and the DART Committee to concur on a chemical’s toxicity in order for it to be listed.

- Your comment letters state that the current proposal to list BPA was triggered by an environmental advocacy group after the DART Committee’s 2009 meeting. The Natural Resources Defense Council (NRDC) did request in writing that BPA be listed, based on the NTP document. However, Proposition 65 requires that BPA be considered for listing based on the NTP document, irrespective of the request by the NRDC or any other interested party.

- Lastly, your emails expressed concern about the costs to taxpayers for the BPA listing process, particularly the cost of public hearings. Public meetings on proposed Proposition 65 listings based on the findings of NTP only occur when they are requested by a member of the public. The cost of such public meetings is minimal. Comments are generally made by the public by mail or e-mail. Public meetings are seldom requested.

Thank you for your interest in Proposition 65. If you have any questions or concerns, please email P65Public.Comments@oehha.ca.gov.

Sincerely,

Lauren Zeise, Ph.D.
Deputy Director for Scientific Affairs
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 65. BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies provision of Proposition 65 and based on findings by the National Toxicology Program (NTP). NTP made its findings in a report 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. In the event that OEHHA finds the criteria have not been met after review of the comments,

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2 Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regulations, section 25306.
4 Title 27, Cal. Code of Regulations, section 25306.
the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation. 

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,

[Signature]

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.

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5 Title 27, Cal. Code of Regulations, section 25306(i).
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. The listing would be based on the authoritative bodies provision 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)).

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
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:


  “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:


January 22, 2013

Rochelle W. Tyl, Ph.D., DABT
Distinguished Fellow
RTI International
Center for Pharmacology & Toxicology
Discovery Sciences Unit
3040 Cornwallis Road
P.O. Box 12194
Research Triangle Park, North Carolina 27709-2194

Dear Dr. Tyl:

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 65\(^1\). BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies provision\(^2\) of Proposition 65 and based on findings by the National Toxicology Program (NTP). NTP made its findings in a report\(^3\) by the NTP Center for the Evaluation of Risks to Human Reproduction that BPA causes developmental toxicity at “high” doses.

OEHHA has carefully reviewed the comments 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.

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Comments should focus on whether or not the criteria for listing have been met. In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation.

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,

[Signature]

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

Enclosure:

Response to Comments from Rochelle W. Tyl on the Request for Relevant Information on Bisphenol A as a Chemical under Consideration for listing under Proposition 65.

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4 Title 27, Cal. Code of Regulations, section 25306.
5 Title 27, Cal. Code of Regulations, section 25306(i)
Response to Comments from Rochelle W. Tyl 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 was proposed under the authoritative bodies provision of the regulations² based on findings by the National Toxicology Program’s 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 Rochelle W. Tyl of Research Triangle Institute (RTI) International, supported by the American Chemistry Council. This document provides a response to those comments.

For authoritative bodies listings, 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)).

Dr. Tyl’s comments primarily address OEHHA’s role in examining **sufficiency of evidence**, specifically considerations of maternal toxicity as stated in the regulations, section 25306(g)(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

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¹ The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 et seq.).
² Title 27, Cal. Code of Regulations, section 25306.
³ All referenced sections are from Title 27 of the Cal. Code of Regulations.
adverse reproductive effects in humans and the toxic agent in question is biologically plausible.”

Detailed responses are provided below using headers from Dr. Tyl’s comments.

Comment:

I. Definition of Maternal Toxicity:

The comments provide a definition of maternal toxicity, as follows:

“Maternal systemic toxicity has been classically defined (U.S. EPA guidelines, 1991) as one or more of the following effects:

- Dose-related maternal mortality (no greater than 10%)
- Dose-related reduced body weight(s)
- Dose-related reduced body weight gain(s)
- Dose-related reduced feed and/or water consumption (especially if associated with reduced body weights)
- Adverse clinical observations or clinical observations known to be associated with adverse outcomes
- Necropsy observations such as changes in organ weights (increased or decreased), especially if there is confirmatory evidence of histopathology (e.g., liver, kidneys, adrenal glands, etc.), both absolute and relative to terminal body weight or brain weight, to correct for any confounding from changes in body weight (U.S. EPA Guidelines, 1991; pp. 7-9).”

Response: The comments appear to be Dr. Tyl’s opinion and interpretation of the U.S. Environmental Protection Agency (U.S. EPA, 1991) Guidelines for Developmental Toxicity Risk assessment, as the exact wording of the comments does not appear in the guidelines document. The Guidelines provide a list of endpoints of maternal toxicity, along with guidance as to their interpretation. The list of endpoints is as follows (U.S. EPA 1991, pp 8-9):

“Mortality
Mating index [(no. with seminal plugs or sperm/no. mated) × 100]
Fertility index [(no. with implants/no. of matings) × 100]
Gestation length (useful when animals are allowed to deliver pups)
Body weight
  Day 0
  During gestation
  Day of necropsy
Body weight change
  Throughout gestation
  During treatment (including increments of time within treatment period)
  Post-treatment to sacrifice
Corrected maternal (body weight change throughout gestation minus gravid uterine weight or litter weight at sacrifice)

Organ weights (in cases of suspected target organ toxicity and especially when supported by adverse histopathology findings)
  - Absolute
  - Relative to body weight
  - Relative to brain weight

Food and water consumption (where relevant)

Clinical evaluations
  - Types, incidence, degree, and duration of clinical signs
  - Enzyme markers
  - Clinical chemistries

Gross necropsy and histopathology

There are a number of important differences between the definition provided in the comments and that provided by U.S. EPA. In several bullets the comments include the wording “dose-related”, which is not found in the U.S. EPA Guidelines. The incidence of maternal mortality is not addressed in the U.S. EPA list of endpoints; rather, the parenthetical phrase “no greater than 10%” is used in the Guidelines in connection with selection of doses in experimental studies that do not exceed a “minimal” level of maternal toxicity. The parenthetical “especially if associated with reduced body weight” is not found in the Guidelines. The phrase “known to be associated with adverse outcomes” is not used in the Guidelines in reference to clinical observations. The phrase “especially if there is confirmatory evidence of histopathology” is not found in the Guidelines. Thus, OEHHA considers the definition of maternal toxicity in the comments to be Dr. Tyl's opinion and interpretation of the Guidelines, rather than a direct quote from the guidance document.

Comment:

II. Background:

A series of comments concerning maternal toxicity are presented under this header. The general theme of these comments is that maternal toxicity caused by a chemical could influence the fetus. The comments state that “[t]he current consensus is that maternal toxicity in toxicology studies is the major cause of embryo fetal effects observed,” and provides a series of quotations addressing the possible relationship between extreme maternal toxicity and adverse developmental outcome. For example,

“…[e]xtreme maternal toxicity may result in embryo-fetal loss in utero…”

“[s]ometimes, the toxicity toward the pregnant animal, including her embryos/fetuses… is severe enough to result in the resorption of the embryo or absorption of the fetus. Therefore, it is possible that embryo lethality and other
indications of developmental toxicity, produced by some drugs and chemicals, may be the result of mechanism(s) other than selective toxicity toward the embryo”.

A second theme of the comments is that, if this occurs, the chemical cannot be identified as causing developmental toxicity.

Response: Although the comments state “[t]he current consensus is that maternal toxicity in toxicology studies is the major cause of embryo fetal effects observed,” no documentation supporting this statement is included in the comments. All of the quotations provided in the comments address only the possibility that extreme maternal toxicity might influence developmental outcome.

As regards the relationship between maternal and developmental toxicity, OEHHA relies on generally accepted scientific principles as expressed by regulatory agencies. Two examples are given below:

“Agents that produce developmental toxicity at a dose that is not toxic to the maternal animal are especially of concern because the developing organism is affected but toxicity is not apparent in the adult. However, the more common situation is when adverse developmental effects are produced only at doses that cause minimal maternal toxicity; in these cases, the developmental effects are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity” U.S. EPA (1991) Guidelines for Developmental Toxicity Risk Assessment

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

This same principle is also expressed by individual reviews of the issue, such as the review by Carney (1997) cited in the comments:

“[T]here currently remains a considerable burden of proof lying with the investigator if developmental effects are suspected to be secondary to altered maternal physiology. This burden is justifiable in that maternal toxicity is not always associated with developmental toxicity. Thus a cause and effect relationship between the two is not automatic.”

Comment:

III. Bisphenol A
This section of the comments reviews the maternal and developmental toxicity data from six of the eight studies cited by NTP-CERHR to support their finding of “clear” evidence of the developmental toxicity of BPA at “high” doses. The comments reiterate various findings related to maternal and developmental toxicity in the studies discussed in the NTP-CERHR document. In each case the comments discuss the co-occurrence of maternal and developmental effects, and conclude that BPA is not a selective developmental toxicant. The comments also discuss a recent developmental neurotoxicity study by Stump et al. (Stump et al, 2010) that was not considered by the authoritative body.

Response: As described above, OEHHA relies on the generally accepted scientific principle that developmental toxicity occurring at the same doses as maternal toxicity is not to be dismissed as secondary to maternal toxicity. The comments provide the opinion of the commenter about the relationship between maternal and developmental effects; however, no evidence is provided in the comments that the developmental toxicity of BPA was secondary to maternal toxicity. The comments also do not provide any information beyond that which was considered by the authoritative body.

The study by Stump et al. includes oral doses of BPA greater than 50 mg/kg/d (identified as “high dose” by NTP-CERHR) and administered during gestation and lactation in rats. No effects were reported on survival of newborns, or birth weight. However, this study was conducted under a protocol that differed from those of the studies where effects were reported. For example, the dosing period is not as long as in studies with dietary administration cited by NTP-CERHR.

Section 25306(h) specifies that “[t]he lead agency shall 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 [specified in regulations]”. However, this single study conducted under a different experimental protocol does not meet this criterion.

Comment:

IV. Additional Comments and Concerns

This section contains comments concerning oral vs. parenteral administration, noting the

“profound difference in metabolism of BPA when administered orally (by gavage or dosed feed) versus parenterally. Non-oral routes of administration (e.g., subcutaneous or intravenous injection, intracisternal [brain] injections, subcutaneous implants, etc.) bypass the rapid and essentially complete first pass presystemic metabolic conjugation of BPA observed with oral exposures”.
The section also comments on differences in metabolism between humans and rodents. In humans, the comments note, oral administration of BPA results in essentially 100% metabolism of the parent to BPA glucuronide. In rats, oral administration of BPA results in glucuronidation of BPA in the intestine and liver (less efficiently than in humans), but there is enterohepatic recirculation after hydrolysis of the conjugated BPA metabolites in the intestines and reabsorption of parent BPA. The comments state that there is a longer half-life and higher bioavailability in rodents compared to humans and conclude that, since the weight of evidence indicates that BPA is not a selective reproductive or developmental toxicant in rodents, it is highly unlikely that BPA could be a reproductive or developmental toxicant in humans. Finally, this section discusses the variable response of mouse and rat strains to estrogen.

Response: As regards oral vs. parenteral administration, all of the studies cited by NTP-CERHR in connection with its “clear evidence” conclusion used oral administration. Thus, consideration of differences in metabolism resulting from differences in route of administration is not relevant to the listing stage of the Proposition 65 process since the route of exposure in the relevant animal studies is the same as the expected route of exposure in humans.

As regards species differences in metabolism, the relevance of these differences in metabolism to Proposition 65 listing is not clearly spelled out by the commenter. OEHHA reviewed the discussion of metabolism in the NTP-CERHR document and did not find any information that conflicted with the finding of adverse developmental effects at high doses. The comments do cite one study not reviewed by NTP-CERHR (Calafat et al. 2009). However, this report concerns BPA exposure of premature infants from medical devices, which is not relevant to Proposition 65 since post-natal exposures are not considered when assessing the toxicity of a chemical under Proposition 65’s criteria.

Regarding differences in response to estrogen, the NTP-CERHR document notes that:

“Bisphenol A is most commonly described as being “weakly” estrogenic; however, an emerging body of molecular and cellular studies indicate the potential for a number of additional biological activities. These range from interactions with cellular receptors that have unknown biological function to demonstrated effects on receptor signaling systems known to be involved in development.” (NTP-CERHR, p. 1)

“The NTP does not necessarily consider it appropriate to consider the reported biological effects of bisphenol A exclusively within the context of estrogen receptor α or β binding. An increasing number of molecular or cell-based (“in vitro”) studies suggest that attributing the effects of bisphenol A solely to a classic estrogenic mechanism of action, or even as a selective estrogen receptor modulator (SERM), is overly simplistic.” (NTP-CERHR, p. 10)
Thus, it is apparent that NTP considered the estrogenic activity of BPA in reaching its weight of evidence conclusion based on studies of several mouse and rat strains.

Comment:

V. Summary and conclusions:

The comments summarize four reasons why the commenter “strongly believes, based on scientific data, that embryo-fetal offspring toxicity from exposure to high doses of BPA is caused by maternal toxicity”. The comments also note that

“[t]he importance and central role of maternal toxicity in the causation and evaluation of embryo-fetal and postnatal offspring toxicity are explicitly acknowledged in all the national and international regulatory test guidelines for developmental toxicity. All of them specifically require demonstrable maternal toxicity at the top dose.”

1. “…BPA is not a selective developmental toxicant.”

Response: The term “selective developmental toxicant” is not specifically defined in the comments, nor is the term contained in Proposition 65 regulations, in the NTP-CERHR conclusions concerning BPA, or in the regulatory guidelines for performing and evaluating developmental toxicity studies. No “selective developmental toxicants” are named to provide examples. From the context of the comments it may be inferred that the intended meaning of the term “selective developmental toxicant” is a chemical that causes developmental toxicity in the absence of any discernible toxicity in the dam. As discussed above, developmental toxicity that co-occurs with maternal toxicity is generally regarded as developmental toxicity unless the maternal toxicity is excessive.

Comment:

2. “BPA is not a developmental neurotoxicant…”

Response: Developmental neurotoxicology studies were not among the studies cited by NTP-CERHR in connection with their conclusion concerning “clear evidence” for BPA developmental toxicity at “high” doses. Neither the Proposition 65 “Request for relevant information” nor the NTP-CERHR “clear evidence” conclusions mention developmental neurotoxicity. Thus OEHHA is unable to take this statement into account in evaluating the adequacy of the data which supports the identification of bisphenol A as a developmental toxicant by the authoritative body.

Comment:

3. “…BPA is not a selective reproductive toxicant.”
Response: This point is not relevant to the Request for Information which is limited to the developmental toxicity of BPA.

Comment:

4. “Since intentional feed restriction results in maternal toxicity and subsequent embryo-fetal toxicity in rats and rabbits, it is likely that maternal toxicity is the critical determinant of embryo-fetal toxicity in BPA studies.”

Response: This comment suggests that reduced food intake was a prominent component of the maternal toxicity produced by BPA in the studies cited by NTP-CERHR in reaching their weight of evidence conclusion concerning developmental toxicity. OEHHA’s review of the maternal toxicity data found minimal reports of effects on maternal food intake during gestation. Three of the studies (Morrissey et al. 1987; NTP 1985; Tinwell et al. 2002) cited by NTP-CERHR did not present, analyze or describe gestational food intake. One developmental toxicity study (Kim et al. 2001) reported lower food intake on gestation day (gd) 4 in terms of g/day, but no effects on food intake on gd 1, 11, 15 or 18. The three-generation rat study (Tyl et al. 2002b) reported no treatment related effects on food intake. The one-generation mouse studies (Tyl et al. 2002a) reported reduced food intake from gd 14 to 17 in terms of g/day but not g/kg/day(corrected for body weight), with no effects reported for gd 7-10, gd 10-24 or overall gestation (gd 0-17). A similar finding was reported in the second generation of the two-generation mouse study (Tyl et al. 2008b) with no food intake effects in the first generation. In no case was food intake reduced by 20% relative to controls as in the study cited in the comments (Waalkens-Berendsen et al. 1990).

The comments cite recent literature concerning the relationship between maternal food intake and developmental toxicity (Beyer et al. 2011; Chernoff et al. 1987; Chernoff et al. 2008). This literature is very clear in recommending that a pair-fed group is necessary to determine the possible role of reduced maternal food intake in causing developmental toxicity for any individual chemical. No such pair-fed control groups were included in the studies cited by NTP-CERHR to support their conclusion concerning developmental toxicity. Thus, there is no empirical basis for concluding that reduced maternal food intake had any influence on the developmental outcomes reported in these studies.

With regard to national and international regulatory test guidelines for developmental toxicity specifically requiring demonstrable maternal toxicity at the top dose, OEHHA agrees that this is the case. OEHHA also notes that it is generally recognized that “[i]n order to interpret the data fully, an integrated evaluation must be performed considering all maternal and developmental endpoints” (U.S. EPA, 1991). Although the commenter has offered her opinion of the relationship between maternal and developmental effects in the studies relied upon by NTP, she has provided no factual information to demonstrate either that NTP failed to consider maternal toxicity in concluding that there
is clear evidence that BPA causes developmental toxicity, or that NTP made factual errors in doing so.

References


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


January, 2013

Mr. Thomas E. Tremble  
Vice President, State Government Relations  
Advanced Medical Technology Association  
701 Pennsylvania Avenue, Suite 800  
Washington, DC 20004-2654

Dear Mr. Tremble:

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

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 proposed listing. Comments should focus on whether or not the criteria in OEHHA’s regulations for listing chemicals under Proposition 65 have been met. In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to

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2 Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regulations, section 25306.  
4 Title 27, Cal. Code of Regulations, section 25306.
the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration for possible listing as required by regulation.5

Your comments state that there is current scientific debate regarding the toxicity of BPA at low levels. It is important to note in this regard that the authoritative body, the NTP in the NTP-CERHR report, found that BPA causes developmental toxicity at “high” doses. The listing of BPA under Proposition 65 would be based on this high-dose finding. Your comments also note that the U.S. Food and Drug Administration has taken steps to reduce infants' exposure but has not called for restriction of BPA use, and you urge that BPA’s availability not be limited. In this regard, the listing of a chemical under Proposition 65 does not ban or otherwise restrict its use. It simply requires that a warning be provided to Californians prior to their exposure to the chemical.

You also commented that, “the length and amount of exposure to affected populations is critical in light of the need to preserve patient access to needed therapies, particularly when there is a notable absence of demonstrably safer alternatives for medical applications.” While the listing process under Proposition 65 is concerned solely with identification of a reproductive hazard, there are other parts of the Proposition 65 process that address the level of exposure. For example, in cases where the average use of a product by the average consumer does not result in exposure to a listed chemical that exceeds a maximum allowable dose level (MADL), the product is exempt from the warning requirement under Proposition 65 (Health and Safety Code section 25249.10(c)).

We acknowledge your concerns regarding the listing of BPA. If the chemical is listed, we will provide compliance assistance to businesses to reduce the likelihood of unnecessary litigation and warnings. OEHHA can assist interested parties by providing a MADL in regulation. OEHHA’s general practice, when feasible, is to propose a MADL within one year of the listing of a chemical. In many cases, we have been able to finalize a MADL at or near the time the warning requirement for a newly listed chemical takes effect. In some instances, OEHHA has been able to propose MADLs concurrent with or even prior to the listing of a chemical. If OEHHA makes a final determination to add BPA to the Proposition 65 list, we will determine whether it is feasible to release a draft MADL concurrent with the listing. At a minimum, we will make it a priority to develop and adopt a MADL for BPA at the earliest possible date following the chemical’s listing. As you may be aware, Proposition 65 provides a “grace period” of 12 months after the chemical is listed before any interested party can sue for alleged violations of the Act. During that time, product manufacturers can evaluate their product exposures against the proposed MADL and determine whether or not a warning is necessary.

5 Title 27, Cal. Code of Regulations, sections 25306(h) and (i)
OEHHA also can develop interpretive guidelines and, upon request, safe use determinations to provide further guidance to businesses and the public concerning the applicability of Proposition 65 to specific products or uses of a chemical. OEHHA would consider developing these materials as appropriate if BPA were listed. Our website at www.oehha.ca.gov has more information concerning these compliance assistance activities.

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
January 22, 2013

Sharon Rubalcava
Alston & Bird LLP
333 South Hope Street, 16th Floor
Los Angeles, California 90071-1410

Dear Ms. Rubalcava:

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

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

You comment that the possible listing of BPA under Proposition 65 is both controversial and subject to different opinions. You also note that MPAA lacks the expertise to comment on the underlying scientific studies. Rather, the MPAA comments focused on concerns about

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2 Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regulations, section 25306.
4 Title 27, Cal. Code of Regulations, section 25306.
5 Title 27, Cal. Code of Regulations, section 25306(i).
the possible economic impacts of the listing of BPA. Those concerns include the potential for warnings on CDs and DVDs as well as other entertainment-related merchandise. Because of the potential economic impacts, you urged OEHHA to explore every avenue to avoid casting the net too widely under Proposition 65 and limit the application of the listing, or to adopt a maximum allowable dose level (MADL) concurrently with the listing of BPA, should that listing occur.

We acknowledge your concerns regarding the listing of BPA. If the chemical is listed, we will provide compliance assistance to businesses to reduce the likelihood of unnecessary litigation and warnings. In cases where the average use of a product by the average consumer does not result in exposure to a listed chemical that exceeds the MADL, no warning is required. OEHHA can assist interested parties by providing a MADL, as you have requested.

OEHHA's general practice, when feasible, is to propose a MADL within one year of the listing of a chemical. In many cases, we have been able to finalize a MADL at or near the time the warning requirement for a newly listed chemical takes effect. In some instances, OEHHA has been able to propose MADLs concurrent with or even prior to the listing of a chemical. If OEHHA makes a final determination to add BPA to the Proposition 65 list, we will consider whether it is feasible to release a draft MADL concurrent with the listing. At a minimum, we would make it a priority to develop and adopt a MADL for BPA at the earliest possible date following the chemical’s listing. As you may be aware, Proposition 65 provides a “grace period” of 12 months after the chemical is listed before any interested party can sue for alleged violations of the Act. During that time, product manufacturers can evaluate their product exposures against the MADL and determine whether or not a warning is necessary.

OEHHA also can develop interpretive guidelines and safe use determinations to provide further guidance to businesses and the public concerning the applicability of Proposition 65 to specific products or uses of a chemical. OEHHA would consider developing these materials as appropriate if BPA were listed.

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,

[Signature]

Lauren Zeise, Ph.D.
Deputy Director for Scientific Affairs
January 22, 2013

Luis R. Cabrales  
Deputy Director of Campaigns  
Coalition for Clean Air

Pam Palitz  
Toxics Advocate and Staff Attorney  
Environment California

David W. Campbell  
Secretary-Treasurer  
United Steelworkers Local 675

Matt Prindiville  
Clean Production Project Director,  
Legislative Coordinator  
Natural Resources Council of Maine

Charity Carbine  
Environmental Health Advocate  
Vermont Public Interest Research Group

Jeanne Rizzo, R.N.  
President and CEO  
Breast Cancer Fund

Sheila Davis  
Executive Director  
Silicon Valley Toxics Coalition

Mark Rossi, PhD  
Research Director  
Clean Production Action

Rick Hind  
Legislative Director  
Greenpeace

Gretchen Lee Salter  
Breast Cancer Fund

Kimberly Irish, J.D.  
Program Manager  
Breast Cancer Action

Erin Switalski  
Executive Director  
Women’s Voices for the Earth

Tom Lent  
Policy Director  
Healthy Building Network

Dear Members of Environmental and Public Health Organizations:

Thank you for your letter of May 13, 2010, responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65 (California Health and Safety Code section 25249.5 et seq.). BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies' provision of Proposition 65 (Health and Safety Code section 25249.8(b)), based on findings

California Environmental Protection Agency

The energy challenge facing California is real. Every Californian needs to take immediate action to reduce energy consumption.
Members of Environmental and Public Health Organizations
January 22, 2013
Page 2

by the National Toxicology Program (NTP). NTP made its findings in a report by the NTP Center for the Evaluation of Risks to Human Reproduction that BPA causes developmental toxicity at “high” doses (NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NIH Publication No. 08 – 5994).

You note that there have been a number of additional studies published in the peer-reviewed scientific literature that demonstrate harm from low doses of BPA. OEHHA acknowledges the large amount of work undertaken to understand the toxicity of BPA. However, the proposed authoritative body listing is based on NTP conclusions regarding clear evidence of developmental toxicity at “high” doses of BPA. We acknowledge your concern for low-dose effects, and that there have been a number of studies generated since the release of the NTP report. Since NTP did not consider this evidence, however, OEHHA has not reviewed it in support of the authoritative body listing since it falls outside of the administrative record for the action by the authoritative body.

You also note activities of regulatory agencies in the United States to address concerns regarding BPA, and provide as examples some actions of the U.S. Food and Drug Administration and the U.S. Environmental Protection Agency. These entities are Proposition 65 authoritative bodies and scientific findings they make are directly relevant to adding BPA to the Proposition 65 list. OEHHA is following and will continue to follow the efforts of these organizations in their characterization of the hazards of BPA.

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 on the OEHHA website at www.oehha.ca.gov and in the California Regulatory Notice Register in the near future. Following its publication, there will be a 30-day public comment period regarding the proposed listing.

Comments should focus on whether or not the criteria for listing the chemical under Proposition 65 have been met (Title 27, Cal. Code of Regulations, section 25306). In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation (Title 27, Cal. Code of Regulations, section 25306 (i)).

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,

[Signature]
Lauren Zeise, Ph.D.
Deputy Director for Scientific Affairs
January 22, 2013

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

Dear Dr. Lamb:

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

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

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

2 Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regulations, section 25306.
4 Title 27, Cal. Code of Regulations, section 25306.
the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation.\textsuperscript{5}

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

Sincerely,

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

Enclosure:

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

\textsuperscript{5} Title 27, Cal. Code of Regulations, section 25306(1).
Response to Comments from Exponent on the 
Request for Relevant Information on 
Bisphenol A as a Chemical under Consideration 
for Listing under Proposition 65

Office of Environmental Health Hazard Assessment

January 2013

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

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

1) **Formal Identification**: An authoritative body formally identifies the chemical as causing reproductive toxicity (Section 25306(d)).

2) **Sufficiency of Evidence**: The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulations (Section 25306(g)). However, the chemical is not listed if scientifically valid data which were not considered by the authoritative body clearly establish that the sufficiency of evidence criteria were not met (Section 25306(h)).

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

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

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

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

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

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

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

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

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

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

“Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.” (Section 25306(g)(2), emphasis added).

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

Response: At the July 12, 2011 meeting of the DART Identification Committee, Dr. John Bucher, Associate Director of the NTP, described how NTP-CERHR regularly considers maternal toxicity in reaching its conclusions:

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

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

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

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

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

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

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

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

“Agents that produce developmental toxicity at a dose that is not toxic to the maternal animal are especially of concern because the developing organism is affected but toxicity is not apparent in the adult. However, the more common situation is when adverse developmental effects are produced only at doses that cause minimal maternal toxicity; in these cases, the developmental effects are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity. At doses causing excessive maternal toxicity (that is, significantly greater than the minimal toxic dose), information on developmental effects may be difficult to interpret and of limited value. Current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity; rather, when the LOAEL is the same for the adult and developing organisms, it may simply indicate that both are sensitive to that dose level. Moreover, whether developmental effects are secondary to maternal toxicity or not, the maternal effects may be reversible while effects on the offspring may be permanent.” (U.S. EPA, 1991, Guidelines
“Developmental effects, which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case by case basis that the developmental effects are secondary to maternal toxicity.” (United Nations Economic Commission for Europe Globally Harmonized System of Classification and Labeling of Chemicals, Part 3, Section 3.7.2.4.2, 2009, at page 176)

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

Morrisey et al. 1987

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

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

Comment:

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

Response: OEHHA agrees that severe maternal toxicity occurred in the mouse study in that 18% mortality occurred in the high dose group. In regard to this issue, OEHHA referred to the research literature on the relationship between occurrence of maternal mortality in a dose group and fetal outcomes in the litters of surviving dams. In a paper by Kavlock et al. (Kavlock et al., 1985), lethal doses of 10 agents were given to pregnant mice. Maternal deaths ranged from 5 to 53% in 30 dose groups in the study. Neither the percent of maternal deaths nor the pregnancy weight gain of the surviving dams in the dose groups was clearly associated with developmental toxicity as
measured by fetal mortality and fetal weight. The authors did find a correlation between maternal weight gain and incidence of supernumerary ribs in the fetuses. The authors concluded that “there was no relationship between the incidence of maternal mortality in treated groups and any endpoints in the fetuses of surviving females.” No research with a contrary conclusion was located. Thus, limited relevant scientific information does not suggest that fetal endpoints in mice need to be interpreted differently on the basis that maternal mortality is increased in the same dose group.

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

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

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

Kim et al., 2001

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

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

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

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

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

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

The relationship between maternal and fetal toxicity in 56 rat studies was analyzed (Chernoff et al., 2008). From these studies, the authors selected dose groups in which
a significantly lower maternal weight occurred at some point during gestation and found a significant positive correlation between corrected maternal weight gain and fetal weight. However, a positive correlation between these two variables was also seen in control groups from these studies and thus cannot be attributed to toxic actions of the agents. The authors further state that maternal weight reductions were associated with significant fetal weight reduction in only 40% of the studies. They further conclude that “the complexities involved in both maternal toxicity and fetal development preclude the identification of a single relationship of these factors for all test agents.”

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

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

Reel et al. 1985

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

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

In reviewing the study OEHHA notes that there was no effect of BPA on mortality in the male or female breeders. The dose that produced increased mortality in the dose-finding study (Task 1), described in the comment, was not used in the reproductive assessment (Task 2). As regards body weights, there were no effects of BPA on body weights in the dose-finding study at the doses selected for the reproductive assessment. The high dose for the reproductive assessment (1.0%) was selected “such that it would not depress weight gain in either sex by more than 10%”. As stated
in the comment, postpartum weights (day of birth) were 8-9% lower in the high dose group than in controls in Task 2. However, developmental toxicity was also seen at the 0.5% dose which did not influence postpartum weights. Further, there were no BPA effects on postpartum body weights in Task 3 or Task 4 at any dose, and no effects on female body weights measured weekly during the 18 weeks of Task 2. At the conclusion of the study, after 21 weeks of dosing, female body weights were 4% lower in the high dose group and not affected at any other dose. Based on the mortality and body weight data, OEHHA concludes that the maternal toxicity produced by BPA was not “severe” at any dose.

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

Tyl et al. 2002a

Comment:

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

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

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

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

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

Corrected body weight gains were not provided. OEHHA notes that body weight gain during pregnancy includes both the body weight gain of the mother and the weight of fetuses and placentas. Because litter size was lower in the high dose group it would be anticipated that the weight of the fetuses and placentas contributing to pregnancy weight gain would be lower. In fact the difference in pregnancy weight gain was 18% between the control and high dose group, while the difference in weight of the offspring
(number of offspring x average weight) at term was also 18%. The difference from control in corrected maternal body weight of 6.6% (after the delivery), representing toxicity to the dam, is not considered by OEHHA to represent “severe” toxicity and was not so described by the study authors or CERHR reviewers.

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

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

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

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

Tyl et al. 2008b

Comment:

“Adult systemic toxicity in the F0 animals included centrilobular hepatocyte hypertrophy at 300 and 3500 ppm, renal nephropathy in males only at 3500 ppm, and reduced body weight, increased kidney and liver weight at 3500 ppm. Gestation length was slightly but significantly delayed (0.3 days) in both the F0 and F1 maternal animals. Effects on reproduction and offspring were seen only
at 3500 ppm and included reduced weanling body weight, spleen and testis weight, delayed preputial separation and undescended testes in weanlings. The effects on reproductive organs did not result in adverse effects on adult reproductive structures or functions, so were considered a developmental delay."

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

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

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

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

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

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

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

Tyl et al. 2002b

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

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

Results of the study were also tabulated.

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

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

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

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

Comment:

“We have reviewed the critical studies cited by the NTP CERHR report and have summarized the key findings above. In every case, effects on offspring seen were at dose levels that also produced maternal/adult systemic toxicity greater than what would be considered minimal toxicity. In addition, the levels of
exposure at which the maternal/adult toxicity and reproductive and developmental toxicity occurred are far above those exposure levels that might plausibly occur in humans. We believe that the developmental effects reported as a result of BPA exposure are part of the pattern of general toxicity caused by BPA and are not specific or selective for developmental toxicity."

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

Response:

Although the commenter’s opinion of these studies differs from the interpretation of the studies by the authoritative body, OEHHA is relying on the NTP interpretation of these studies. Proposition 65 does not allow OEHHA to substitute its judgment for NTP’s judgment in the interpretation of these studies. NTP stated that there is clear evidence that BPA causes developmental toxicity at “high” doses in laboratory animals. This conclusion is sufficient for the report to provide a basis for listing the chemical via the authoritative bodies provision of Proposition 65.

References:


January 22, 2013

David Rothman, DDS
President
Paur Reggiardo, DDS
Public Policy Advocate
California Society of Pediatric Dentistry
P.O. Box 221608
Carmel, California 93922

Dear Drs. Rothman and Reggiardo:

Thank you for your letter of May 11, 2010, on behalf of the California Society of Pediatric Dentistry, responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65. BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies provision of Proposition 65 and based on findings by the National Toxicology Program (NTP). NTP made its findings in a report by the NTP Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) that BPA causes developmental toxicity at “high” doses.

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. In the event that OEHHA finds the criteria have not been met after review of the comments,

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1 The Safe Drinking Water and Toxic Enforcement Act of 1986, California Health and Safety Code section 25249.5 et seq.
4 Title 27, Cal. Code of Regs., section 25306.
the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee for its consideration as required by regulation.\(^5\)

Your comments do not address the basis for listing BPA under Proposition 65, but do express concerns about the potential impact of the listing on the dental health of young children such as kindergarteners and first-graders. You also discuss the absence of BPA as an ingredient in dental sealants, that intraoral exposure to BPA that occurs in the sealant process is a byproduct of the degradation of other components of sealant materials, and that levels of exposure resulting from application of sealants is likely to be very low.

If BPA is added to the Proposition 65 list, you should be aware of the following:

- Proposition 65 expressly exempts businesses with fewer than 10 employees from its requirements, including the warning requirement.\(^6\) Many pediatric dentists may fall within this exemption.

- Proposition 65 provides an exemption to the warning requirement if the exposure is not significant.\(^7\) In cases where the average use of a product by the average consumer does not result in exposure to a listed chemical that exceeds a maximum allowable dose level (MADL)\(^8\), no warning is required. OEHHA can assist interested parties by providing a MADL.

OEHHA’s general practice, when feasible, is to propose a MADL within one year of the listing of a chemical. In many cases, we have been able to finalize a MADL at or near the time the warning requirement for a newly listed chemical takes effect. If OEHHA makes a final determination to add BPA to the Proposition 65 list, we will consider whether it is feasible to release a draft MADL concurrent with the listing. At a minimum, we would make it a priority to develop and adopt a MADL for BPA at the earliest possible date following the chemical’s listing. As you may be aware, Proposition 65 provides a “grace period” of 12 months after the chemical is listed before any interested party can sue for alleged violations of the Act. During that time, product manufacturers can evaluate their product exposures against the MADL and determine whether or not a warning is necessary.

Your letter indicates that BPA is not an ingredient in dental sealants but that some intraoral exposure to BPA occurs due to the degradation of other components in dental sealants. If your association would find it helpful, you may request that OEHHA provide

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\(^5\) Title 27, Cal. Code of Regs., section 25306(i).  
\(^6\) Health and Safety Code section 25249.11(b).  
\(^7\) Health and Safety Code section 25249.10(c) and Title 27, Cal. Code of Regs., section 25821(c)(2).  
\(^8\) Title 27, Cal. Code of Regs., section 25801.
assistance to you on evaluating whether the level released and nature of exposure would require warning, if BPA were listed.

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@oeeha.ca.gov.

Sincerely,

[Signature]

Lauren Zeise, Ph.D.
Deputy Director for Scientific Affairs
January 22, 2013

John M. Rost, Ph.D.
Chair
North American Metal Packaging Alliance, Inc.
1203 19th Street NW, Suite 300
Washington, DC 20036-2401

Dear Dr. Rost:

Thank you for your letter of May 13, 2010 responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65.1 BPA is a candidate for listing as known to cause reproductive toxicity. The potential listing would be by the authoritative bodies provision2 of Proposition 65, based on findings by the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) that BPA causes developmental toxicity at “high” doses.3

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 regulatory criteria for listing have been met.4 In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation.5

2 Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regulations, section 25306.
4 Title 27, Cal. Code of Regulations, section 25306.
5 Title 27, Cal. Code of Regulations, sections 25306(i).
Your comments discuss the decision by the DARTIC not to list BPA as an argument against authoritative body listing of the chemical. Proposition 65 identifies multiple methods for listing of chemicals but does not put in place a hierarchical or consensus structure, instead each listing mechanism functions independently. Thus, a decision not to list a chemical under one of the listing mechanisms does not preclude its consideration for listing via one of the other mechanisms.

On the issue of formal identification, your comments also note that NTP-CERHR states that its report is not a quantitative risk assessment and is not intended to supersede risk assessments conducted by regulatory agencies. You indicate that listing BPA would be inconsistent with NTP’s advice and therefore inappropriate. Proposition 65 and the implementing regulations for the authoritative bodies mechanism require the listing of chemicals based solely on formal identification of a reproductive hazard by the authoritative body, and do not require a full risk assessment. Elements of risk assessment other than hazard identification (e.g., dose response assessment) are taken into account at future points in the Proposition 65 process but not at the listing stage. Listing does not depend on whether or not the authoritative body has completed all the steps in risk assessment, or whether or not the authoritative body contemplates the use of a document under Proposition 65.

Your comments state that a person would have to consume food or beverages from 14 million cans a day in order to achieve the BPA exposure of ≥50 mg/kg-d described by NTP-CERHR as a “high” dose. You indicate that this is not physically or biologically possible. Without endorsing or detracting from the calculations you provide, we note that this type of calculation is relevant to a different part of the Proposition 65 process, and not to the listing process. The matter you are addressing is relevant to the issue of whether a warning would be required if BPA were placed on the list. For information concerning calculating an exposure to a listed chemical that requires a warning, see Title 27 of the California Code of Regulations, section 25801 et seq.

The issue of whether an association between an adverse reproductive effect in humans and a chemical is “biologically plausible” is addressed in the Proposition 65 regulation for listing via the authoritative bodies mechanism:

“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

The "biologically plausible" phrase in this regulation does not pertain to actual levels of exposure that may be occurring in the human population from any given source. Rather, the phrase "biologically plausible" applies to extrapolation of findings from animal studies to humans in a biological framework. NTP found that there was clear evidence of developmental toxicity in animals from BPA at high doses, and specifically found that it is possible that BPA can affect human development. The data relied upon by the NTP in the NTP-CERHR report were reviewed by OEHHA against the sufficiency of evidence criteria cited above. OEHHA found they met the criteria in the regulation, including biological plausibility.

Elsewhere in your comments you refer to reviews by other bodies of the potential hazards posed by current uses of BPA. You note for example that the US Food and Drug Administration "clearly stated that BPA has not been proven to be harmful to children or adults in any of its current uses." Under Proposition 65, even if current exposures have not been proven to cause reproductive or developmental harm in humans, the chemical must be listed if there are sufficient data in laboratory animals to support the formal identification by the authoritative body. That is the case for BPA.

You also describe new studies from the U.S. Environmental Protection Agency providing evidence that BPA at extremely low doses has no effect on female development and fertility. In this regard, we note that the proposed authoritative body listing of BPA is based on NTP-CERHR conclusions concerning evidence of developmental toxicity at "high" doses (greater than or equal to 50 mg/kg-d), and not at low doses.

Elsewhere in your comments you provide a summary of the use and value of BPA in the metal packaging industry, its use as an epoxy resin and the difficulties involved in replacing BPA. Please note that that listing of BPA under Proposition 65 would not prohibit use of BPA in any product and, consequently, would not require replacement of BPA in metal packaging. Rather, warnings about exposures caused by use of a product are required unless there would be no observable effect given an exposure 1,000 times greater than that resulting from use of the product by the average consumer. If levels of BPA exposure are sufficiently low, warnings would not be required. If the chemical is listed, we will provide compliance assistance to businesses to reduce the likelihood of unnecessary litigation and warnings. For example, in cases where the average use of a product by the average consumer does not result in exposure to a listed chemical that exceeds a maximum allowable dose level (MADL), no warning is required. OEHHA can assist interested parties by adopting a MADL.

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7 NTP-CERHR Monograph pp. 6-8
8 HSC section 25249.10(c) and Title 27, Cal Code of Regs., section 25821(c)(2).
OEHHA's general practice, when feasible, is to propose a MADL within one year of the listing of a chemical. In many cases, we have been able to adopt the MADL at or near the time the warning requirement for a newly listed chemical takes effect.\(^9\) In some instances, OEHHA has been able to propose MADLs concurrent with or even prior to the listing of a chemical. If OEHHA makes a final determination to add BPA to the Proposition 65 list, we will consider whether it is feasible to release a draft MADL concurrent with the listing. At a minimum, we would make it a priority to develop and adopt a MADL for BPA at the earliest possible date following the chemical’s listing. As you may be aware, Proposition 65 provides a “grace period” of 12 months after the chemical is listed before any interested party can sue for alleged violations of the Act. During that time, product manufacturers can evaluate their product exposures against the MADL and determine whether or not a warning is necessary.

OEHHA also can develop interpretive guidelines\(^10\) and safe use determinations\(^11\) to provide further guidance to businesses and the public concerning the applicability of Proposition 65 to specific products or uses of a chemical. OEHHA would consider developing these materials in the event BPA is listed.

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@oeinha.ca.gov.

Sincerely,

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

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\(^9\) Health and Safety Code section 25249.10(b).
\(^10\) Title 27, Cal Code of Regulations, section 25203.
\(^11\) Title 27, Cal Code of Regulations, section 25204.
January 22, 2013

Gene Livingston
Greenberg Traurig LLP
1201 K Street, Suite 1100
Sacramento, California 95814

Dear Mr. Livingston:

This is in response to a letter of May 12, 2010 from Ms. Lisa Halko on behalf of the California Dental Association (CDA) and the CDA Foundation, responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) under Proposition 65.1 We are addressing this to you since we understand that Ms. Halko is no longer with your firm.

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 (NTP-CERHR) that BPA causes developmental toxicity at “high” doses.

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 public comment period regarding the possible listing. Comments should focus on whether or not the regulatory criteria for listing have been met.4 In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical

2 Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regs., section 25306.
4 Title 27, Cal. Code of Regs., section 25306.
will be referred to the Developmental and Reproductive Toxicant Identification Committee for its consideration as required by regulation.\(^5\)

Ms. Halko’s comments were submitted in opposition to the possible Proposition 65 listing of BPA, and stated that dental sealants are no longer made with BPA and do not cause exposures that require a warning. She further commented that it is rare for dental sealants to cause any exposure to BPA, and indicated concern that a Proposition 65 listing of BPA could discourage use of dental sealants in children. Ms. Halko is correct that where there is no exposure or insignificant exposure to BPA, a warning is not required. Regarding the current lack of use of BPA in dental sealants, OEHHA will not indicate in future notices that BPA is used in making dental sealants. We appreciate the clarification.

Ms. Halko also predicted that a listing of BPA would likely lead dentists and other oral health professionals to use warnings to avoid baseless litigation, and that that result would be inconsistent with the Court of Appeal decision in *Nicole-Wagner vs. Deukmejian*.

Proposition 65\(^6\) expressly exempts businesses with fewer than 10 employees from its requirements. Many dentists and oral health professionals may fall within this exemption, reducing the likelihood that they would be the targets of litigation. For all other businesses, warnings would only be required if exposures to BPA were sufficiently high.\(^7\) You gave a number of reasons why you thought this would be very unlikely. If the chemical is listed, we will provide compliance assistance to businesses to reduce the likelihood of unnecessary litigation and warnings. For example, where the average use of a product by the average consumer does not result in an exposure to a listed chemical that exceeds a maximum allowable dose level (MADL), no warning is required. OEHHA can assist interested parties by providing a MADL.

OEHHA’s general practice, when feasible, is to propose a MADL within one year of the listing of a chemical. In many cases, we have been able to finalize a MADL at or near the time the warning requirement for a newly listed chemical takes effect. In some instances, OEHHA has been able to propose MADLs concurrent with or even prior to the listing of a chemical. If OEHHA makes a final determination to add BPA to the Proposition 65 list, we will consider whether it is feasible to release a draft MADL concurrent with the listing. At a minimum, we will make it a priority to develop and adopt a MADL for BPA at the earliest possible date following the chemical's listing. As you may be aware, Proposition 65 provides a “grace period” of 12 months after the chemical is listed before any interested party can sue for alleged violations of the warning requirement. During that time, product manufacturers can evaluate their

\(^{5}\) Title 27, Cal. Code of Regs., sections 25306(i).
\(^{6}\) Health and Safety Code section 25249.11(b).
\(^{7}\) Health and Safety Code section 25249.10(c) and Title 27, Cal. Code of Regs., section 25821(c)(2).
product exposures against the MADL and determine whether or not a warning is necessary.

OEHHA also can develop interpretive guidelines\(^8\) and safe use determinations\(^9\) to provide further guidance to businesses and the public concerning the applicability of Proposition 65 to specific products or uses of a chemical. This type of guidance might be especially helpful in deterring unnecessary litigation against dentists and oral-health professionals. OEHHA would consider developing these materials as appropriate if BPA is listed.

Ms. Halko’s comments also included arguments concerning the formal identification of BPA as causing reproductive toxicity. These comments incorrectly identify the statements in the NTP-CERHR document used by OEHHA as the basis of formal identification. As stated in the Request for Relevant Information, OEHHA relied on the conclusion by NTP that there is clear evidence of developmental toxicity in laboratory animals at “high” doses. These developmental effects include fetal death and reduced litter size in rats and mice exposed prenatally. The text that Ms. Halko cited refers to NTP’s conclusion about a level of concern for human populations taking into account what is known about current human exposures. It is important to note that Proposition 65’s listing process is based exclusively on hazard identification. Anticipated human exposure is taken into account later in the Proposition 65 process. It is not considered during the listing phase. The statute and implementing regulations focus on whether or not the authoritative body identifies the chemical as posing a reproductive toxicity hazard. Under Proposition 65, listing is based solely on hazard identification resulting from scientific studies in either animals or humans. Thus, the risk characterization conclusions related to “level of concern” were not used in OEHHA’s determination that BPA has been formally identified by NTP as causing reproductive toxicity.

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

\(^8\) Title 27, Cal Code of Regulations, section 25203.
\(^9\) Title 27, Cal Code of Regulations, section 25204.
January 22, 2013

Michele B. Corash
Morrison & Foerster LLP
425 Market Street
San Francisco, California 94105-2482

Dear Ms. Corash:

Thank you for your letter of May 13, 2010, on behalf of the Grocery Manufacturers Association (GMA), responding to the Request for Relevant Information on bisphenol A (BPA) as a chemical under consideration for listing as known to cause reproductive toxicity under Proposition 65\(^1\). The potential listing is based on the authoritative bodies provision\(^2\) of the Proposition 65 implementing regulations as applied to findings by the National Toxicology Program (NTP) on the basis of 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)\(^3\).

Under the formal authoritative bodies listing process set out in the regulation, a chemical must be listed under Proposition 65 when the Office of Environmental Health Hazard Assessment (OEHHA) determines that the following criteria are met:

1) **Formal Identification**: An authoritative body formally identifies the chemical as causing reproductive toxicity (Title 27, Cal. Code of Regs., section 25306(d)\(^4\)).

2) **Sufficiency of Evidence**: The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulation (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)).

GMA’s comments address both public policy and legal issues. GMA’s comments assume that all manufacturers will stop using BPA in their products if the chemical is listed.

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4. All further references are to sections of Title 27 of the California Code of Regulations unless otherwise stated.

California Environmental Protection Agency

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However, Proposition 65 does not ban the use of listed chemicals. It simply requires that consumers be given a warning prior to certain exposures to the chemical and prohibits the release of significant amounts of the chemical into sources of drinking water. It is not clear whether or not a warning might be required for exposures to BPA from food packaging and, in fact, GMA maintains that the manufacturers will be able to prove that any exposure is below the safe harbor level and therefore will not require a warning. Further, policy arguments about the potential impact on the food industry in California are not relevant to whether or not the chemical meets the listing criteria in the regulation. Proposition 65 does not allow consideration of economic impacts, a chemical’s merits or the availability of alternative chemicals when making listing decisions.

OEHHA also disagrees with GMA’s contention that the law creates a “hierarchy” of listing mechanisms where the “state’s qualified experts” mechanism trumps the three others. Proposition 65 provides four mechanisms for listing of chemicals, all of which are independent of each other. In fact, the Labor Code listing mechanism is established in a separate subsection from the other three. The Labor Code mechanism is set forth in Health and Safety Code section 25249.8(a) and the other three are listed in the disjunctive in Health and Safety Code section 25249.8(b). The only connection in the statute between the state’s qualified expert’s mechanism and the authoritative bodies’ mechanism is the requirement that the authoritative bodies be identified by the state’s qualified experts. No hierarchical structure, consensus requirement or other provision is made in the statute or regulations for establishing interdependent operation of the different mechanisms. The 2009 determination of the Developmental and Reproductive Toxicant Identification Committee (DARTIC) that BPA does not meet the criteria for listing pursuant to the state’s qualified experts mechanism does not address the entirely separate question of whether BPA meets the criteria for listing pursuant to an alternative listing mechanism. Thus, the state’s qualified experts cannot “overrule” the authoritative body process, and vice-versa. If the criteria for listing by any of the four mechanisms are met, the chemical is added to the list because it is “known to the state” to cause reproductive toxicity.

The fact that the Health and Welfare Agency originally expressed its opinion that the state’s qualified experts would be the “primary approach to listing” at the time the authoritative bodies regulations were being adopted, does not change this analysis. Neither the Proposition 65 statute nor its implementing regulations refer to any hierarchy in which the state’s qualified experts mechanism is the “primary approach to listing” chemicals.

OEHHA agrees with cited text from the statement of reasons for Section 25306, stating that the purpose of the authoritative bodies provision is to conserve the resources (time and effort) of the state’s qualified experts. This is because the DARTIC (which serves as the state’s qualified experts for reproductive toxicity) does not need to re-evaluate chemicals for which a thorough scientific evaluation has already been conducted. Generally, the chemicals that are brought to the DARTIC are there for a de novo review because the chemical has not been considered by an authoritative body. In the case of BPA, the NTP-CERHR report was published during the pendency of BPA’s review by the DARTIC. OEHHA could have removed the chemical for DARTIC consideration, but chose not to do
so. However, OEHHA can and indeed must consider whether BPA meets the authoritative bodies listing criteria, whether or not it has been previously reviewed by the DARTIC. Nothing in the statute or regulations allows OEHHA to ignore a chemical that may qualify for listing under one of the four listing mechanisms, simply because it has already been considered under another mechanism.

Finally, we acknowledge GMA’s request that a regulatory Maximum Allowable Dose Level (MADL) be proposed prior to the potential listing of BPA and agree that a safe harbor level would provide valuable compliance assistance to the food industry. It is OEHHA’s practice to propose a safe harbor level, where sufficient data are available to do so, within one year of the listing of a chemical. Often these safe harbors become effective at or near the time the warning requirements of the law are effective and well before the time that discharges of the chemical to sources of drinking water are prohibited. In some instances, it has proved feasible to propose a MADL concurrent with or even prior to listing of a chemical. OEHHA will consider whether it is feasible to do so for BPA but would, at a minimum, make it a priority to timely propose such a level for BPA, should the chemical be listed. OEHHA also has regulatory authority to develop interpretive guidelines and safe use determinations to provide further guidance to businesses and the public concerning the applicability of Proposition 65 to specific products as well as uses of a chemical. OEHHA would consider developing these materials as appropriate if BPA were listed.

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 (NOIL) BPA will be published in the near future. Following publication of the NOIL, there will be a further 30-day period for submission of comments on this proposed action.

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@oeah.ca.gov.

Sincerely,

Lauren Zeise, Ph.D.
Deputy Director for Scientific Affairs
January 22, 2013

Avinash Kar, JD
Staff Attorney

Sarah Janssen, M.D., M.P.H., Ph.D.
Staff Scientist
Natural Resources Defense Council
111 Sutter Street, 20th Floor
San Francisco, California 94104

Renee Sharp
Director, California Office
Environmental Working Group
2201 Broadway Street, Suite 308
Oakland, California 94612

Dear Mr. Kar, Dr. Janssen, and Ms. Sharp:

Thank you for your letter of May 13, 2010, responding to the Request for Relevant Information on the possible listing of bisphenol A (BPA) as known to cause reproductive toxicity under Proposition 65 (California Health and Safety Code section 25249.5 et seq.). The potential listing would be by the authoritative bodies’ provision of Proposition 65 (Health and Safety Code section 25249.8(b)), based on findings in a report by the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) that BPA causes developmental toxicity at “high” doses (NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NIH Publication No. 08 – 5994).

You commented that the state’s qualified expert and authoritative body listing mechanisms are completely independent and cited documents to support the statement. OEHHA agrees with this conclusion and the documentation cited in the comments to support it. You indicated that other chemicals have been listed under Proposition 65 via the authoritative bodies mechanism based on NTP findings in NTP-CERHR reports. OEHHA agrees with this observation.
You also state that other entities “designate BPA as a reproductive and developmental toxicant.” You name classifications and designations by the European Chemicals Bureau, the Canadian government and the U.S. Environmental Protection Agency (U.S. EPA). While the findings of the European and Canadian institutions are noteworthy, these entities are not Proposition 65 authoritative bodies as designated in Title 27, California Code of Regulations, section 25306(l)\(^1\) and so their findings are not directly relevant to adding BPA to the Proposition 65 list based on the NTP formal identification.

You also cite U.S. EPA’s 2010 Action Plan.\(^2\) U.S. EPA conducted a “screening level review” of hazard and exposure information for the Action Plan. That review refers to the chemical as a developmental and reproductive toxicant in animal studies, and generally concurs with the NTP findings, and discusses the uncertainties regarding low dose effects. These findings are also reflected in U.S. EPA’s Advance Notice of Proposed Rulemaking\(^3\) to develop data under section 4(a) of the Toxic Substances Control Act. While U.S. EPA is an authoritative body, the Action Plan states that it “does not constitute a final Agency determination or other final Agency action”; thus, this document does not meet the criteria for formal identification specified in Section 25306(d) and cannot serve as a basis for listing BPA.

You noted that since the NTP-CERHR report was published, there have been additional studies published which support the conclusions of the report that there is “some concern” for the impacts of low dose exposure to BPA on brain and behavior. The proposed authoritative body listing is based on NTP conclusions regarding clear evidence of developmental toxicity at “high” doses of BPA. We acknowledge your concern for low dose effects, and that there have been a number of studies generated since the release of the NTP report. Since NTP did not consider this evidence, however, OEHHA has not reviewed it in support of the listing since it falls outside of the administrative record for the action by the authoritative body.

You also assert that “[h]uman exposure to BPA is widespread.” While this topic is not directly related to the authoritative body listing of BPA, OEHHA acknowledges the information provided.

You commented that BPA meets the listing requirements under the authoritative bodies mechanism. 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

\(^1\) All further citations are to Title 27, Cal. Code of Regs., unless otherwise indicated.


Intent to List BPA will be published on the OEHHA website at www.oehha.ca.gov and in the California Regulatory Notice Register in the near future. Following its publication, there will be a 30-day public comment period regarding the proposed listing.

Comments should focus on whether or not the criteria for listing the chemical under Proposition 65 have been met (Section 25306). In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation (Section 25306 (i)).

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
January 22, 2013

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

Dear Dr. Hentges:

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

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

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

2 Health and Safety Code section 25249.8(b) Title 27, Cal. Code of Regulations, section 25306.
4 Title 27, Cal. Code of Regulations, section 25306.
event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation.\(^5\)

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

Sincerely,

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

Enclosure:

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

\(^5\) Title 27, Cal. Code of Regulations, section 25306(i).
On February 12, 2010, the Office of Environmental Health Hazard Assessment (OEHHA) published in the California Regulatory Notice Register (CRNR) a Request for Relevant Information for Bisphenol A (BPA) for possible listing as a chemical known to cause reproductive toxicity under Proposition 65.\(^1\) The listing would be based on the authoritative bodies provision\(^2\) relying on findings by the National Toxicology Program (NTP) in a final report from the NTP Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) that BPA causes developmental toxicity at “high” doses (NTP-CERHR, 2008).

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

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

1) **Formal Identification**: An authoritative body formally identifies the chemical as causing reproductive toxicity (Section 25306(d)\(^3\))

2) **Sufficiency of Evidence**: The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulations (Section 25306(g)). However, the chemical is not listed if scientifically valid data which were not considered by the authoritative body clearly establish that the sufficiency of evidence criteria were not met (Section 25306(h)).

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\(^1\) The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 \textit{et seq.}).

\(^2\) Title 27, Cal. Code of Regulations, section 25306.

\(^3\) All referenced sections are from Title 27 of the Cal. Code of Regulations.
Formal Identification
Sections IV.A, IV.B, IV.C and parts of section G of the comments are relevant to formal identification.

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

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

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

Further, there is no requirement in the law or regulations that the authoritative body must determine that effects have occurred in humans, or that effects that have been demonstrated in animals are biologically plausible in humans. Section 25306(c) states that “the lead agency [OEHHA] shall determine which chemicals have been formally identified by an authoritative body as causing cancer or reproductive toxicity” (emphasis added). Section 25306(g) specifies the criteria that the lead agency must apply in determining whether the chemical is identified “as causing reproductive toxicity”. This interpretation of the regulation has been upheld by the courts. Section 25306(g)(2) requires OEHHA to consider whether the chemical’s effects in animals are indicative of...
a biologically plausible adverse effect in humans. As discussed below, OEHHA has
made this determination for BPA. In addition, in this case the authoritative body also
concluded, based explicitly on data in animals, that it is possible that bisphenol A can
affect human development or reproduction. That conclusion is equivalent to concluding
that such effects are biologically plausible in humans.

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

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

The NTP-CERHR monograph states:

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

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

In section IV.A the commenters compare the format of the NTP-CERHR monograph on
BPA to some previous NTP-CERHR monographs as a reason for disregarding the
conclusions of the BPA monograph. OEHHA agrees that the formats of these
documents can differ, and that the conclusions in the BPA document were formatted
specifically for that chemical, including different weight-of-evidence conclusions for
“high” dose effects on some endpoints and “low” dose effects on others. By discounting these weight-of-evidence conclusions because of variations in formatting when compared with previous documents, the commenters identify the level-of-concern conclusions as the only conclusions of the report. Since the level-of-concern conclusions take into account what is known about levels of human exposure, not just the weight-of-evidence for reproductive and developmental toxicity, they are not relevant to formal identification for listing under the Proposition 65 authoritative bodies provision. Levels of human exposure are, of course, important. If BPA is listed, human exposures can be considered under Section 25821 to determine whether or not a given exposure requires a warning.

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

“CERHR evaluated selected chemicals, agents, mixtures, or exposure circumstances based on production volume, the potential for human exposure and the extent of public concern, and the extent of available literature with data that were applicable to an evaluation of reproductive and developmental hazard.

“These have been published as NTP-CERHR monographs that assess the evidence, whether the environmental substance causes adverse effects on reproduction and development, which as you heard earlier, is the Phase 1, the hazard identification phase of the document.

“And secondly, the second phase is to provide an opinion on whether these substances may be of concern, given what is known about current human exposure levels. And these are the levels of concern statements that are developed…

“As you saw in one of the slides previously, the hazard identification portion of this used a seven point hazard identification scale, weighting the evidence from both human and experimental animal data. And these were considered independently. And then the
conclusions are reached on a case-by-case basis” (emphasis added).

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

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

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

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

Section IV.B
Comment 2.  Section IV.B

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

Response: See response to Section IV.A above.

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

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

The fact that the Health and Welfare Agency expressed its opinion that the state’s qualified experts would be the “primary” approach to listing at the time the authoritative bodies regulations were being adopted does not change this analysis. That statement of opinion does not create a hierarchy. Further, the Proposition 65 implementing
regulations cannot impose such a hierarchy where none exists in the statute, since such an action would not conform with or further the purposes of the statute.  

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

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

**Sufficiency of Evidence**

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

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

Response: Regarding these eight studies:

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7 Health and Safety Code section 25249.12
Only one of the studies includes only postnatal exposure. The endpoint identified by NTP-CERHR from this study, delayed puberty, is not mentioned in the Request for Relevant Information. In studies including prenatal and postnatal exposure, many endpoints are determined prior to postnatal exposure. The endpoints named in the Request for Relevant Information, fetal death and reduced litter size, were observed prior to postnatal exposure.

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

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

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

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

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

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

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

8 OEHHA did not find mention of cleft palate in Nishimura et al. 1969
Comment: The ACC states that “[t]hese [subcutaneous] dose levels of table salt are only slightly higher than the oral dose levels of BPA that were associated with less severe developmental effects and greater maternal toxicity”.

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

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

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

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

“Agents that produce developmental toxicity at a dose that is not toxic to the maternal animal are especially of concern because the developing organism is affected but toxicity is not apparent in the adult. However, the more common situation is when adverse developmental effects are produced only at doses that cause minimal maternal toxicity; in these cases, the developmental effects are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity. At doses causing excessive maternal toxicity (that is, significantly greater than the minimal toxic dose), information on developmental effects may be difficult to interpret and of limited value. Current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity; rather, when the LOAEL is the same for the adult and developing organisms, it may simply indicate that both are sensitive to that dose level. Moreover, whether developmental effects are secondary to maternal toxicity or not, the maternal effects may be reversible while effects on the offspring may be permanent.” U.S. EPA (1991) Guidelines for Developmental Toxicity Risk Assessment.
“Developmental effects, which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case by case basis that the developmental effects are secondary to maternal toxicity.” United Nations Economic Commission for Europe Globally Harmonized System of Classification and Labeling of Chemicals (Section 3.6.2.4.2, 2009)

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

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

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

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

- “Both of these studies demonstrated that the degree of maternal toxicity observed is more than sufficient to account for developmental effects” ACC, p.44
- “The degree of maternal toxicity observed in this study is more than enough to explain the decrease in litter size observed at the high dose in this study.” ACC, p.46
- “The developmental effects are easily explained by the degree of maternal toxicity…” ACC, p. 47
• "The degree of maternal toxicity observed was more than enough to account for the developmental effects reported in these studies. In all cases the developmental effects were secondary to maternal toxicity." ACC, p.47-48
• "The degree of maternal toxicity reported at the high dose in NTP Reference 37 was more than sufficient to account for the observations of developmental effects." ACC, p. 48
• "The results of this study show that the developmental effects are secondary to maternal toxicity." ACC, p. 48
• "The degree of maternal toxicity observed at the high dose is sufficient to have caused the developmental effects reported in this study." ACC, p. 48
• "In every case, the degree of maternal toxicity observed was more than sufficient to explain the developmental effects." ACC, p.50

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

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

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

effects include fetal death and reduced litter size in rats and mice exposed prenatally.’ ”

Response: The sufficiency of evidence criteria are as follows:

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

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

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

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

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10 Section 25306(g)(2)
Table 1. Information from studies cited by NTP in concluding that BPA had clear evidence for high dose developmental toxicity.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Observations at the LOAEL</th>
<th>Maternal Toxicity</th>
<th>Developmental Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morrissey et al., 1987</td>
<td>CD-1 mice N=21–26</td>
<td>LOAEL: 1250 mg/kg-day</td>
<td>↑ mortality</td>
<td>↑ % resorptions/litter</td>
</tr>
<tr>
<td>Exposures - Period: GD 6–15 Route: gavage Doses: 0, 500, 750, 1000, or 1250 mg/kg-day</td>
<td>↑ body weight gain</td>
<td>↓ fetal body weight</td>
<td></td>
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<td></td>
<td>↑ liver weight</td>
<td>Not reported: Food intake Kidney weight Histopathology</td>
<td></td>
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<tr>
<td>Kim et al., 2001</td>
<td>SD rats N=14–20</td>
<td>LOAEL: 300 mg/kg-day</td>
<td>↑ clinical observations</td>
<td>↓ fetal body weight/litter</td>
</tr>
<tr>
<td>Exposures - Period: GD 1–20 Route: gavage Doses: 0, 100, 300, 1000 mg/kg-day,</td>
<td>↓ body weight gain</td>
<td>↓ live fetuses/litter</td>
<td></td>
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<tr>
<td></td>
<td>↑ food intake GD4</td>
<td>Not reported: Organ weights Histopathology</td>
<td></td>
<td></td>
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<tr>
<td>NTP, 1985</td>
<td>CD-1 mice N=19</td>
<td>LOAEL: 1920 mg/kg-day</td>
<td>No ↑mortality</td>
<td>↓ live pups/litter</td>
</tr>
<tr>
<td>Female exposure only, beginning one week prior to mating, for 14 weeks Route: Diet Dose: 1920 mg/kg-day</td>
<td>↑ liver and kidney weights</td>
<td>↓ live male pups/litter</td>
<td></td>
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<tr>
<td></td>
<td>↑ liver/kidney histopathology</td>
<td>Not reported: Clinical observations Food intake (reported for mating pairs)</td>
<td>↓ live female pups/litter</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Observations at the LOAEL</td>
<td></td>
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<tr>
<td><strong>Maternal Toxicity</strong></td>
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<tr>
<td>Tyl et al., 2002b</td>
<td>SD rats</td>
<td>LOAEL: 500 mg/kg-day</td>
<td></td>
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<tr>
<td></td>
<td>3-Generation Study</td>
<td>No mortality</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>F₀ N=30</td>
<td>Clinical observations not statistically analyzed</td>
<td></td>
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<tr>
<td></td>
<td>Male and female exposures</td>
<td>↑ food intake during gestation</td>
<td></td>
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<tr>
<td></td>
<td>Period: premating through lactation Route:</td>
<td>↓ postpartum body weight</td>
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<tr>
<td></td>
<td>Diet Doses: 0, 0.001, 0.02, 0.3, 5, 50, 500</td>
<td>↑ kidney, liver, brain weight</td>
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<td></td>
<td>mg/kg-day</td>
<td>↓ ovary weight</td>
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<td></td>
<td></td>
<td>↑ liver/kidney histopathology</td>
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<td></td>
<td></td>
<td>LOAEL: 500 mg/kg-day</td>
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<td></td>
<td></td>
<td>↓ live pups/litter</td>
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<td></td>
<td></td>
<td>↓ pups/litter</td>
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<td></td>
<td></td>
<td>↓ implantation sites</td>
<td></td>
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<td></td>
<td></td>
<td>↓ pup body weight pnd 4, 7, 14, 21</td>
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<td>LOAEL: (Fi generation) 50 mg/kg-day</td>
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<td></td>
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<td>↑ age at vaginal opening</td>
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<td></td>
<td></td>
<td>↑ age at preputial separation</td>
<td></td>
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<tr>
<td>Tyl, 2008</td>
<td>CD-1 mice</td>
<td>LOAEL: 600 mg/kg-day</td>
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<tr>
<td></td>
<td>2-Generation Study</td>
<td>No mortality</td>
<td></td>
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<tr>
<td></td>
<td>N=55 (control)</td>
<td>Clinical observations not statistically analyzed</td>
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<td></td>
<td>19–25 (BPA)</td>
<td>No reduced food intake</td>
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<td></td>
<td>Exposures:</td>
<td>No body weight effects</td>
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<td></td>
<td>Period: premating through lactation Route:</td>
<td>↑ liver and kidney weight;</td>
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<tr>
<td></td>
<td>Diet Doses: 0, 0.003, 0.03, 0.3, 5, 50, 600</td>
<td>↑ liver/kidney histopathology</td>
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<tr>
<td></td>
<td>mg/kg-day</td>
<td>LOAEL: 600 mg/kg-day</td>
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<td>↓ pup body weight pnd 7, 14, 21</td>
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<td></td>
<td></td>
<td>↑ age at preputial separation</td>
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<tr>
<td>Tyl et al., 2002a</td>
<td>CD-1 mice, 1-Generation Study</td>
<td>LOAEL: 1750 mg/kg-day</td>
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<td></td>
<td>N=20</td>
<td>No mortality</td>
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<tr>
<td></td>
<td>Exposure:</td>
<td>Clinical observations not statistically analyzed</td>
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<tr>
<td></td>
<td>Period: premating through birth Route: Diet</td>
<td>No reduced food intake (g/kg)</td>
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<tr>
<td></td>
<td>Diet Doses: 0, 875, 1750 mg/kg-day during gestation</td>
<td>↓ postpartum body weight</td>
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<td></td>
<td></td>
<td>↑ postpartum liver kidney weights</td>
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<td>↑ gestation length</td>
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<td>↑ liver, kidney histopathology</td>
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<td></td>
<td></td>
<td>LOAEL: 1750 mg/kg-day</td>
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<td></td>
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<td>↓ live pups/litter</td>
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<td>↓ total pups/litter</td>
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<td>Significant trend test; no pairwise effects ↓female pup weight</td>
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<tr>
<td>Tinwell et al., 2002</td>
<td>SD and Wistar rats, male and female N=7</td>
<td>LOAEL: 50 mg/kg-day</td>
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<tr>
<td></td>
<td>Exposure:</td>
<td>No mortality</td>
<td></td>
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<td></td>
<td>Period: GD 6–21</td>
<td>Not reported:</td>
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<tr>
<td></td>
<td>Route: gavage</td>
<td>Body weight</td>
<td></td>
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<tr>
<td></td>
<td>Doses: 20, 100 μg/kg, 50 mg/kg.</td>
<td>Liver/kidney weight</td>
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<td></td>
<td></td>
<td>Food intake</td>
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<td></td>
<td></td>
<td>Clinical observations</td>
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<td></td>
<td></td>
<td>Histopathology</td>
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<td></td>
<td></td>
<td>LOAEL: 50 mg/kg-day</td>
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<td></td>
<td></td>
<td>No effects litter size, sex ratio, birth weight</td>
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<td></td>
<td></td>
<td>↑ age at vaginal opening (Wistar)</td>
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</tbody>
</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposure Details</th>
<th>Endpoint Effect</th>
<th>LOAEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan et al., 2003</td>
<td>SD rats, Male</td>
<td>Not applicable</td>
<td>LOAEL: 100 mg/kg ↓ number with preputial separation by day 53</td>
</tr>
<tr>
<td></td>
<td>N=12</td>
<td></td>
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<tr>
<td></td>
<td>Exposure:</td>
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<tr>
<td></td>
<td>Period days 23-53 postnatal</td>
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<td></td>
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<tr>
<td></td>
<td>Route: gavage</td>
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<td></td>
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<tr>
<td></td>
<td>Dose: 100 mg/kg</td>
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</tbody>
</table>

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

Statistically significant results are presented with the exception of clinical observations and histopathology incidence, which were not statistically analyzed. Organ weights are relative to body weight. Maternal weight effects are reported as corrected gestational weight/weight gain or postpartum weight (weights that do not include fetuses). For multigeneration studies, data are from the F₀ generation parents and offspring.

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

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

The comments state that “NTP took [lack of biological plausibility in humans] into account when it declined to conclude that BPA is a reproductive toxicant”, and note that “it is important that NTP took this into account because OEHHA is prohibited from
The comments also offer four reasons in support of the commenter’s conclusion stated in the title of the section:

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

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

The arguments regarding maternal toxicity have been discussed above. The levels of exposure that humans may currently be experiencing have no bearing on the biological...
plausibility that some levels of exposure may cause developmental toxicity in humans.\textsuperscript{13} The final argument regarding pharmacokinetic differences does not address biological plausibility of effects in humans but instead addresses levels of exposure at which such effects might occur.

**New Evidence**

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

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

**References**


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

\textsuperscript{13} Exxon Mobil Corporation v Office of Environmental Health Hazard Assessment, (2009) 169 Cal.App.4\textsuperscript{th} 1264 at page 1291-1292


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


January 22, 2013

Hugh N. Tucker, Ph.D.
Distinguished Research Fellow
Global Research and Development
Mead Johnson Nutrition
2400 West Lloyd Expressway
Evansville, Indiana 47721-0001

Dear Dr. Tucker:

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

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 on the OEHHA website at [www.oehha.ca.gov](http://www.oehha.ca.gov) and in the California Regulatory Notice Register in the near future. Following its publication, there will be a 30-day public comment period regarding the proposed listing. In order to be relevant to the listing process, comments should focus on whether or not the criteria for listing the chemical under Proposition 65 have been met (Title 27, Cal. Code of Regulations, section 25306). In the event that OEHHA finds the criteria have not been met after review of the comments, the chemical will be referred to the Developmental and Reproductive Toxicant Identification Committee (DARTIC) for its consideration as required by regulation (Title 27, Cal. Code of Regulations, section 25306(i)).

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\(^1\) 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.

In your comments you object to the possible listing by stating that “the authoritative body listed in the petition has not determined that BPA is hazardous to health”. This statement is based on conclusions in the NTP-CERHR document regarding the “level of concern” for current human exposures to the chemical. NTP’s conclusions regarding level of concern for fetal exposures to BPA ranged from negligible concern to some concern, depending on the type of endpoints. However, it is important to note that Proposition 65’s listing process is based exclusively on hazard identification from scientific studies in animals or humans. The implementing regulations focus on whether or not the authoritative body identifies the chemical as posing a reproductive toxicity hazard. In contrast, NTP’s conclusions regarding “level of concern” are based in part on information regarding known human levels of exposure to BPA. Anticipated human exposure is taken into account later in the Proposition 65 processes, and is not considered during the listing phase.

The formal identification criteria in the Proposition 65 regulation are met by the NTP-CERHR's report that concludes that there is clear evidence of adverse developmental effects in laboratory animals at “high” levels of exposure to BPA. These developmental effects include fetal death and reduced litter size in rats and mice exposed prenatally.

NTP’s conclusions regarding “weight of evidence” also meet the criteria for formal identification as provided in regulation because BPA “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)).

Your comments also list several international groups that have considered the safety of BPA, and also provide a quote from a U.S. Food and Drug Administration (FDA) representative at a press conference. While this information attests to the ongoing focus on BPA by government regulatory agencies, it does not provide a basis for withdrawing BPA from consideration for listing under Proposition 65. Several governmental bodies have expressed concern about BPA (e.g., the French Agency for Food, Environmental and Occupational Health & Safety, Health Canada), and some have taken steps to reduce human exposures.

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