September 1, 2011

VIA U.S. MAIL AND EMAIL

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

Re: SUPPLEMENTAL RESPONSE TO REQUEST FOR RELEVANT INFORMATION ON BISPHENOL A

Dear Dr. Alexeeff:

On behalf of the Polycarbonate/BPA Global Group of the American Chemistry Council ("ACC"), I am submitting this supplemental response to OEHHA's February 12, 2010 Request for Relevant Information on bisphenol A ("BPA"). This supplemental response addresses a series of related in-depth studies that have been published in recent months, with the most recent study published in August 2011. These recent studies, along with other scientific literature previously identified by ACC, show that BPA does not satisfy the definition of causing reproductive toxicity and thus cannot be listed under the authoritative bodies mechanism. This supplemental response should be considered with ACC's prior written submittals dated September 15, 2009, May 13, 2010, and August 10, 2011.

Since the publication of the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of BPA ("NTP-CERHR Monograph") in September 2008, BPA has continued to be a popular subject for additional research. As stated by NTP, "*the scientific literature on the toxic effects of bisphenol A in laboratory animals is extensive and expanding*."[1] ACC's May 13, 2010 submittal detailed significant data that had been developed after the publication of the NTP-CERHR Monograph. This supplemental response provides additional important studies that have been published more recently.

[1] NTP Brief on Bisphenol A, part of the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of BPA, September 2008, page 16 (available at http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/bisphenol.pdf).

All of the studies highlighted in this supplemental response and our May 13, 2010 submittal are relevant to OEHHA's decision whether to designate BPA as a reproductive toxicant under the "authoritative bodies" mechanism pursuant 25306, subsection (h). This section of the implementing regulations provides: "[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 of subsection (g), paragraph (1) or subsection (g), paragraph (2)."

Both the NTP-CERHR expert panel, in its final report on BPA,[2] and NTP itself, in its Brief on BPA,[3] acknowledged the need for additional research to better understand the potential for BPA to cause adverse health effects. The expert panel itemized a list of Critical Data Needs at the end of its report and NTP interspersed a series of data gaps and research needs throughout its Brief. In addition, after consideration of the NTP-CERHR Monograph, FDA also acknowledged the need for additional research, stating that in cooperation with NTP, "FDA's National Center for Toxicological Research is carrying out in-depth studies to answer key questions and clarify uncertainties about the risks of BPA."[4]

Many of the studies designed by NTP and FDA to address identified research needs are now being completed and published in the peer-reviewed scientific literature. Without question these studies are relevant to the conclusions of the NTP-CERHR Monograph and, thus, of substantial importance to OEHHA's decision whether to designate BPA as a reproductive toxicants based on the NTP-CERHR Monograph.

One of the key areas for additional research relates to the NTP-CERHR conclusion that it had "some concern" for potential effects on the brain and behavior from current human exposures in fetuses, infants and children. As stated by the NTP-CERHR expert panel, "*A concerted effort is needed to better understand the effects of gestational and lactational exposure to bisphenol A on maternal behavior and offspring brain structure and behavior*."[5] The NTP fully agreed with this recommendation, stating "*The NTP also concurs with the CERHR Expert Panel on Bisphenol A*

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[2] NTP-CERHR Report on the Reproductive and Developmental Toxicity of Bisphenol A, November 26, 2007 (available at http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/BPAFinalEPVF112607.pdf).

[3] NTP Brief on Bisphenol A, September 2008.

[4] See http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm.

[5] NTP-CERHR Report on the Reproductive and Developmental Toxicity of Bisphenol A, November 26, 2007, page 383.

that additional research is needed to more fully assess the functional, long-term impacts of exposures to bisphenol A on the developing brain and behavior. Overall, the current literature cannot yet be fully interpreted for biological or experimental consistency or for relevance to human health."[6] The inability to interpret the literature existing at that time was the primary basis for the "some concern" conclusion, which essentially was a signal for additional research.

Most recently, researchers at FDA's National Center for Toxicological Research have published initial results from their study on the potential for developmental exposure to BPA to cause effects on the brain and behavior.[7] Although effects were observed for ethinyl estradiol, a known potent estrogen used as a reference compound, no effects were found for BPA. As concluded by the authors, "*These results add to the literature indicating developmental BPA treatment at these doses has no effects on gestational or lactational body weight, offspring anogenital distance, preweaning behaviors or hormone levels and whole and regional brain weights measured at weaning*."

These new results, combined with the results of the Ryan et al. (2010)[8] and Stump et al. (2010)[9] studies that were highlighted in our May 13, 2010 submittal, substantially address the NTP-CERHR Monograph conclusion of "some concern" for effects on the brain and behavior. Had all of these results been available to the NTP-CERHR expert panel and to NTP when their reports were being generated, it is quite likely that the "some concern" conclusion would have been downgraded to a lower level.

This downgrade is made more likely and reinforced by the new findings, summarized below, on the metabolism of BPA.

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[6] NTP Brief on Bisphenol A, September 2008, page 20.

[7] Ferguson, S. A., Law, C. D., and Abshire, J. S. 2011. Developmental treatment with bisphenol A or ethinyl estradiol causes few alterations on early preweaning measures. Toxicological Sciences. In Press. Available at http://dx.doi.org/10.1093/toxsci/kfr201.

[8] Ryan, B. C., Hotchkiss, A. K., Crofton, K. M., and Gray Jr., L. E. 2010. In utero and lactational exposure to bisphenol A, in contrast to ethinyl estradiol, does not alter sexually dimorphic behavior, puberty, fertility and anatomy of female LE rats. Toxicological Sciences. 114(1):133-148. Available at http://dx.doi.org/10.1093/toxsci/kfp266).

[9] Stump, D. G., Beck, M. J., Radovsky, A., Garman, R. H., Freshwater, L. L., Sheets, L. P., Marty, M. S., Waechter, J. M., Dimond, S. S., Van Miller, J. P., Shiotsuka, R. N., Beyer, D., Chappelle, A. H., and Hentges, S. G. 2010. Developmental neurotoxicity study of dietary bisphenol A in Sprague-Dawley rats. Toxicological Sciences. 115(1):167-182. Available at http://dx.doi.org/10.1093/toxsci/kfq025.

As stated by NTP in its Brief on BPA, "*Understanding the degree to which bisphenol A is metabolized is very important in determining whether bisphenol A poses a potential risk to human reproduction and development. While free bisphenol A and its major metabolites (bisphenol A-glucuronide and bisphenol A-sulfate) can all be measured in humans, only free bisphenol A is considered to be biologically active*."[10] The importance of this comment cannot be overstated. All of the concern level conclusions expressed in the NTP-CERHR Monograph are dependent on understanding how BPA is processed in the human body. If BPA is effectively metabolized and eliminated from the human body, in particular relative to the laboratory animals used for toxicity testing, the potential for adverse human health effects decreases substantially. Understanding the metabolism of BPA is critical to understanding the biological plausibility of adverse human health effects.

Because of the importance of this question, both NTP and the NTP-CERHR expert panel highlighted significant research needs. The expert panel stated "*Additional data are needed to clarify bisphenol A exposures and internal dosimetry in the general population, newborns, and occupationally-exposed individuals… These data would provide insight into the roles of metabolism and exposure route on internal dose*."[5] Likewise, NTP stated "*Additional research is needed to understand the metabolism of bisphenol A in both laboratory animals and humans*" and "*Thus, the understanding of bisphenol A metabolism during development in the rat is still incomplete. In addition, it is difficult to translate the rat findings to humans…*"[11]

To address these important research needs, FDA has now completed and published a series of four in-depth studies that examine the metabolism and pharmacokinetics of BPA in both rodents and primates.[12,13,14,15] While these studies will not be reviewed here in detail, they

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[10] NTP Brief on Bisphenol A, September 2008, page 6.

[11] NTP Brief on Bisphenol A, September 2008, page 13.

[12] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. Toxicology and Applied Pharmacology. 247(2):158-165. Available at http://dx.doi.org/10.1016/j.taap.2010.06.008.

[13] Doerge, D. R., Vanlandingham, M., Twaddle, N. C., and Delclos, K. B. 2010. Lactational transfer of bisphenol A in Sprague-Dawley rats. Toxicology Letters. 199(3):372-376. Available at http://dx.doi.org/10.1016/j.toxlet.2010.09.022.

[14] Doerge, D. R., Twaddle, N. C., Vanlandingham, M., Brown, R. P., and Fisher, J. W. 2011. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague-Dawley rats. Toxicology and Applied Pharmacology. In Press. Available at http://dx.doi.org/10.1016/j.taap.2011.07.009,

collectively demonstrate that BPA is efficiently metabolized to biologically inactive metabolites, which are then quickly eliminated from the body. Notably, a study in rats demonstrated that the developing fetus also has the ability to metabolize BPA, although very little BPA reaches the fetus due to the efficient metabolism of BPA by the mother. Also, the ability of neonatal monkeys only a few days after birth to metabolize BPA is essentially equivalent to that of adult monkeys. As a result of efficient metabolism, estrogenic effects from BPA are unlikely due to the very low levels of un-metabolized BPA in the body after oral exposure.

Although both rodents and primates have the ability to metabolize and eliminate BPA from the body, there are important differences between them. For example, primates clear BPA from the body faster than rodents and, in contrast to rodents, the ability of primates to metabolize BPA is not dependent on age. Because of these differences, the FDA authors concluded "*These observations imply that any toxicological effect observed in rats from early postnatal exposures to BPA could over-predict those possible in primates of the same age, based on significantly higher internal exposures and overall immaturity at birth*."[15] This conclusion is of particular importance for consideration of BPA for listing as a reproductive toxicant under Proposition 65 since essentially all of the relevant toxicity data is from studies on rodents. Due to differences in developmental timing between rodents and primates, an early postnatal exposure in a rodent might be equivalent to a late prenatal exposure in a primate.

As a prelude to the metabolism/pharmacokinetic studies, FDA developed a sensitive analytical method for measurement of BPA (both parent and conjugated forms) in biological specimens.[16] Although the method development itself is not directly relevant to the potential toxicity of BPA, in the course of developing the method FDA gained considerable experience with the confounding issue of laboratory contamination during sample analysis. This is an important issue since a number of small-scale studies have reported the presence of un-metabolized BPA in human blood, which would appear to conflict with extensive data demonstrating that BPA is efficiently metabolized. Based on direct experience with laboratory contamination, the FDA authors commented on the apparent discrepancy by stating "*The*

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[15] Doerge, D. R., Twaddle, N. C., Woodling, K. A., and Fisher, J. W. 2010. Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys. Toxicology and Applied Pharmacology. 248(1):1-11. Available at http://dx.doi.org/10.1016/j.taap.2010.07.009.

[16] Twaddle, N. C., Churchwell, M. I., Vanlandingham, M., and Doerge, D. R. 2010. Quantification of deuterated bisphenol A in serum, tissues, and excreta from adult Sprague-Dawley rats using liquid chromatography with tandem mass spectrometry. Rapid Communications in Mass Spectrometry. 24(20):3011-3020. Available at http://dx.doi.org/10.1002/rcm.4733.

simplest explanation for this discordance is sample contamination leading to false positive determinations of aglycone BPA in human blood, which otherwise would contain levels undetectable by any current analytical methodology."

This issue was more directly addressed in a human volunteer study conducted by the Pacific Northwest National Laboratory with participation from the FDA and CDC laboratories.[17] In this study, a group of 20 volunteers were provided with a diet enriched in canned foods, which resulted in an atypically high intake of BPA. Blood and urine samples were collected at frequent intervals throughout the clinical study and analyzed for un-metabolized BPA (blood) and metabolized BPA (blood and urine). Consistent with previous human and animal studies, including those detailed above, this study confirms that BPA is efficiently metabolized and rapidly excreted in urine. Illustrating the efficiency of human metabolism, no un-metabolized BPA was detected in the blood of any participant at any time point in the study, even with a very sensitive analytical method and atypically high exposure levels. Only the biologically inactive metabolite of BPA was transiently found at low levels before it was eliminated from the body. Based on their results, the authors note that reported high levels of un-metabolized BPA in blood are unlikely to be valid, and that sample contamination has likely been the cause of high levels of BPA reported in small-scale studies.

As noted above, the results of this study, along with the recent studies in rodents and primates, strongly indicate that, because of the efficient way that BPA is processed in the body, it is very unlikely that BPA could cause human health effects. In particular, these studies indicate that the biological plausibility of human health effects has not been clearly shown. To the contrary, these and other studies indicate that human health effects are biologically implausible.

Notably, the findings from the initial FDA studies have already been incorporated into an updated assessment from the Japanese National Institute of Advanced Industrial Science and Technology (July 2011), which confirmed that BPA is not a human health hazard. Based substantially on the FDA findings, this assessment also reduced the "uncertainty factor" for BPA, which indicates that the science supporting the safety of BPA is stronger and with less uncertainty.

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[17] Teeguarden, J. G., Calafat, A. M., Ye, X., Doerge, D. R., Churchwell, M. I., Gunawan, R., and Graham, M. 2011. Twenty-four hour human urine and serum profiles of bisphenol A during high-dietary exposure. Toxicological Sciences. 123(1):48-57. Available at http://dx.doi.org/10.1093/toxsci/kfr160.

It is clear from all the foregoing recent studies, along with the prior available scientific literature, that there is not a basis upon which OEHHA can conclude that BPA is a reproductive toxicant under the criteria of section 25306, subsection (g). Accordingly, we respectfully submit that OEHHA should find, under section 25306, subsection (h), that BPA does not satisfy the definition of "as causing reproductive toxicity" and should not be listed under the authoritative body mechanism.

Please do not hesitate to contact me if I can be of further assistance to clarify any comments or if additional information is needed. I can be reached at (202) 249-6624 or by e-mail at steve_hentges@americanchemistry.com.

Respectfully submitted,

Steven G. Hentges, Ph.D.
Executive Director
Polycarbonate/BPA Global Group
American Chemistry Council
700 2nd Street, NE
Washington, DC 20002

cc: Cynthia Oshita (OEHHA)
Stanley W. Landfair (McKenna Long & Aldridge)
F. Jay Murray, Ph.D.