June 15, 2007

Dr. Michael D. Shelby
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Research Triangle Park, NC 27709

Sent as e-mail attachment to: Shelby@niehs.nih.gov

Re: Comments on the draft CERHR report of April 2007 on the reproductive and developmental toxicity of bisphenol A

Dear Dr. Shelby:

I am pleased to provide these comments on behalf of the Polycarbonate/BPA Global Group in regard to the draft CERHR report on the reproductive and developmental toxicity of bisphenol A. The Polycarbonate/BPA Global Group represents the leading global manufacturers of bisphenol A and polycarbonate plastic, who for many years have supported and conducted scientific research to understand whether bisphenol A has the potential to cause health or environmental effects and to support scientifically sound public policy.

We have also supported critical reviews by scientific experts of the many studies relevant to whether bisphenol A has the potential to cause health or environmental effects. When properly conducted, such reviews can be of high value to support public policy, guide future research and reduce controversy. Consequently, our comments are provided in the spirit of promoting a well-conducted and scientifically sound expert panel evaluation of the scientific evidence regarding the potential reproductive and developmental toxicity of bisphenol A.

At the outset, we recognize and appreciate the significant improvements that have been made by the expert panel in the interim draft report. The significance of these improvements is particularly noteworthy in light of the magnitude of the task and the less than ideal conditions under which the panel has conducted their work. In spite of the distractions, the panel has conducted their work in an exemplary fashion.

Our comments on the interim draft report fall into two broad areas:

## 1. Consistent Use of Evaluation Criteria Throughout the Report

In our earlier comments on the first draft report, we highlighted the need for clear criteria for review of individual studies and consistent application across all studies. This need has substantially been achieved in the interim draft report. The remaining aspects that still need attention are primarily in regard to internal consistency within the report (e.g., between the main parts of Sections 3 and 4 and their summary sections). For example, studies designated as inadequate should presumably not be carried forward into the summary tables and sections for development of conclusions.

Examples of inconsistencies left to clean up are listed in the attached Table 1. This is not intended to be a complete list and, in general, careful editing attention should be applied to ensure internal consistency in these Sections to support sound and defensible conclusions.

## 2. Metabolism, Pharmacokinetics and Human Exposure

Our earlier comments also highlighted the need for detailed knowledge of the metabolism and pharmacokinetics of bisphenol A as well as for information on human exposure. Regarding human exposure and, in particular, the use of biomonitoring as a means to directly assess human exposure, two additions to the report are especially noteworthy.

First, the additional discussion on pages 34-35 and 38 regarding the accuracy of various biomonitoring measurements is very helpful to highlight some of the analytical chemistry challenges for accurate determination of bisphenol A in biological samples. It is likely that some of the reported biomonitoring data on bisphenol A is invalid for the reasons discussed in these new paragraphs.

Second, it is noted in a number of places that the ELISA technique is likely to overestimate bisphenol A concentrations in biological samples. While this is true, it does not fully capture the limitations of the ELISA technique and suggests that the ELISA technique, while not accurate (i.e., overestimates actual concentrations), may still be sufficiently specific and precise to give a meaningful indication of bisphenol A concentrations in biological samples. In fact, not only are the values measured by the ELISA technique too high, it is not clear that they reflect the presence of bisphenol A at all.

A recent paper (Fukata et al. 2006; CERHR citation #2247) carefully compares LC/MS/MS, LC/ECD, and three commercially available ELISA kits for measurement of bisphenol A in 52 matched human urine and serum samples. The LC/MS/MS method, which positively identifies bisphenol A and bisphenol A monoglucuronide, correlates very well with the LC/ECD method. However, the three ELISA kits not only have poor correlation with the reliable LC-based methods, but they also have poor correlation with each other. From this set of data, it can be concluded that the ELISA kits not only produce inaccurately high values for bisphenol A, but they are not apparently measuring bisphenol A at all, in particular at the very low part per billion concentrations that might be present in biological samples.

The limitations of the ELISA technique become particularly important in regard to the few limited human studies that have been conducted on bisphenol A. Of particular note is the study of Sugiura-Ogasawara et al. (2005), which attempted to examine an association between miscarriage and bisphenol A exposure, using the ELISA technique to measure bisphenol A in blood samples. The many limitations of the study in general are well discussed in the interim draft report. In addition though, the reported bisphenol A values should not be treated simply as overestimates of bisphenol A concentrations, and thus as exposure misclassifications, but rather as invalid measurements that provide no reliable indication of bisphenol A exposure. While exposure misclassifications might still suggest that an association exists, invalid measurements cannot support any association. Considering the significant limitations of the ELISA technique, the reported association between serial miscarriage and bisphenol A exposure is not supported by the evidence and the study should be considered inadequate and of no utility for the evaluation.

Regarding future work, this study also does not support a follow-up study as may be suggested in the Section 4 Summary (page 391, line 40). In any case, before any follow-up study could be conducted, additional analytical method development to more accurately measure bisphenol A in human blood would be appropriate and necessary. In this regard, it should be noted that, in contrast to the ELISA values reported by Sugiura-Ogasawara, Fukata et al. found no detectable levels of bisphenol A or bisphenol A monoglucuronide in any of the 52 samples analyzed with reliable LC-based methods, even though the ELISA methods did suggest the presence of bisphenol A.

A few additional specific comments on metabolism, pharmacokinetics and human exposure are provided in the attached Table 2.

We appreciate the continued effort from all involved in this evaluation and look forward to a successful conclusion. 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 (703) 741-5588 or by e-mail at steve_hentges@americanchemistry.com.

Regards,

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

Attachments

**Table 1**

**Polycarbonate/BPA Global Group Comments on**
**CERHR Interim Draft Report of April 2007**
**Sections 3-4**

**June 15, 2007**

| Page | Lines | Comment |
|---|---|---|
| 143 | 48-49 | The Funabashi 2004 study should be designated inadequate due to uncertainty about the number of animals, duration of exposure and uncertain nature of effects. No changes are needed in the Summary part of Section 3 since this study is (appropriately) not mentioned in the Summary. |
| 147 | 7-8 | As per the study evaluation criteria at the beginning of Section 3, Ramos 2003 should be designated inadequate due to the use of DMSO and subcutaneous pumps as the route of exposure (see the Ramos 2001 evaluation for comparison). |
| 147 | 36-37 | The Naciff 2002 study is designated inadequate but is still included in Table 84 as a limited utility study. |
| 148 | 24-25 | The Naciff 2005 study is designated inadequate but is still included in Table 84 as a limited utility study. |
| 195 | 22-24 | The Fukumori 2003 study should be designated inadequate due to lack of information on the number of animals, statistics used and incomplete information on materials and methods. The study should then be deleted from Table 84. |

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| 212 | 10-21 | The Cagen 1999 study is more than marginally useful for the evaluation. The single dose of DES, which was intended to be a positive control, was three orders of magnitude below the LOEL for DES in other studies (McLachlan 1981; Newbold 1995). The claimed effect of low doses of orally administered DES on prostate weight has only been reported by one laboratory (vom Saal 1997), has not been replicated in any other laboratory, and could not be replicated in this study. In addition, orally administered DES is extensively glucuronidated via first pass metabolism (Metzler 1981) and DES-glucuronide has been shown to not have estrogenic activity (Waechter 2001). In light of all evidence, the lack of effects from the single dose of DES used in this study is not surprising and, in this study, DES effectively was a negative control that behaved as expected. Consequently, the BPA data from this study is fully useful for the evaluation. |
| 214 | 1-2 | For the same reasons discussed immediately above for the Cagen 1999 study, the BPA data from the Ashby 1999 study is useful for the evaluation and should not be discounted. |
| 217 | 4-5 | Considering the weaknesses identified, for example the use of only a single dose, the Gupta 2000 study should be designated as limited utility. |
| 218 | 32-33 | Considering the weaknesses identified, for example the use of only a single dose, the Timms 2005 study should be designated as limited utility. |
| 220 | 2-3 | The Palanza 2002 study should be designated as limited utility at best. The study used only one dose and no adverse developmental or reproductive effects were measured. |
| 220<br>222<br>224 | 30-31<br>7-8<br>8-9 | The three Nishizawa studies should be designated as inadequate for the evaluation. These are gene expression studies and no adverse developmental or reproductive effects were measured. |
| 236 | 9-11 | Due to the use of subcutaneous exposure, the Honma 2002 study should be designated as inadequate for the evaluation. |

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| 248 | 37-38 | Due to the weaknesses described, the Ryan 2006 study is of limited utility. |
| 281 | 35-46 | The Takagi and Negishi 2003 studies are designated inadequate and should be deleted from the Summary section. |
| 282 | 13-51 | The Iwasaki 2003, Park 2005 (two studies), Nikaido 2004, Takagi, Kubo 2003 and Rubin 2001 studies are designated inadequate and should be deleted from the Summary section. |
| 284 | 37-51 | The Ramos 2001 and Kato 2006 studies are designated inadequate and should be deleted from the Summary section. |
| 285 | 6-30 | The Sharpe 2003, Kato 2006, Toyama 2004, Durando 2007, Murray 2007 and Khurana 2000 studies are designated inadequate and should be deleted from the Summary section. |
| 285<br>286 | 32-49<br>1-31 | The Nakahashi 2001, Aikawa 2004, Park 2005, Toyoma 2004, Markey 2003, Iwasaki 2003, Nikaido 2004, Markey 2001 and Munoz-do-Toro 2005 studies are designated as inadequate and should be deleted from the Summary section. |
| 286<br>287 | 36-51<br>1-25 | The Takagi , Kubo 2003, Facciolo 2005, Patisaul 2006, Carr 2003, Fujimoto 2006, Negishi 2003, Farabollini 1999, Farabollini 2002, Dessi-Fulgheri 2002, Adriani 2003, and Porrini 2005 studies are designated inadequate and should be deleted from the Summary section.<br><br>The Ema 2001 study, which is designated as adequate and included in Table 84 of the Summary section as a High Utility study, should be included in Section 3.4.2.3 of the Summary section on nervous system development and in Table 88. The Ema 2001 study includes neurodevelopmental endpoint data. |
| 287 | 27-50 | The Kawai 2003, Miyatake 2006, Rubin 2006, Zoeller 2005 and Kobayashi 2005 studies are designated as inadequate and should be deleted from the Summary section. |
| 288 | 1-10 | The Yoshino 2004 study is designated as inadequate and should be deleted from the Summary section. |

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| 290 | --- | The High Utility ranking for the Akingbemi 2004 study (experiment 1, PND 21-35) in Table 84 is inconsistent with the limitations of this study listed on pages 166-167. Due to the limitations, the study has limited utility at best. |
| 296 | --- | Experiment 2 (GD 12 – PND 21) of the Akingbemi 2004 study was designated inadequate and should be deleted from Table 85. |
| 296 | --- | The High Utility ranking for the Akingbemi 2004 study (experiment 3, PND 21-90) in Table 85 is inconsistent with the limitations of this study listed on pages 166-167. Due to the limitations, the study has limited utility at best. |
| 312 | --- | The utility of the Della Seta 2006 and Negishi 2004 studies are limited by the use of only a single dose group. Both should be moved to the Limited Utility section of Table 88. |
| 323<br>326 | 4-30<br>14-48 | Reviews of what presumably are different studies (Funabashi 2001 and Funabashi 2004) are both attributed to study #382. |
| 326 | 38-39 | The Della Seta 2005 study should be ranked inadequate due to the use of only a single dose group and the unusually low pregnancy rate in the control group. Although the authors report that bisphenol A affected duration of licking-grooming of pups, the range of this behavior in normal controls was not discussed. The experimental data do not support the authors' conclusion that bisphenol A causes adverse effects on maternal behavior. |
| 344<br>345 | 20-23<br>6-8 | The utility ranking for the two Chitra 2003 studies (#362 and #2225) are inconsistent. Both should be designated inadequate because of their similar study designs and inconsistencies between the two studies (e.g., prostate weight). Neither study should be discussed in the Summary section. |
| 392 | 8-10 | Based on limitations listed above, the Della Seta 2005 study should be designated as inadequate and removed from the Summary section. |
| 393<br>394 | 1-51<br>1-43 | Numerous studies ranked inadequate for the evaluation process should be removed from the Summary section. |

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| 392 | 17-25 | The Chitra 2003 study (#2225) was designated inadequate and should be removed from the Summary section. As discussed above, the second Chitra 2003 study (#362) should also be designated inadequate and removed from the Summary section. Additional studies that were ranked adequate (e.g., Kim 2002) and measured male reproductive parameters (e.g., organ weights) should in included in the weight of evidence evaluation. |
| 396-404 | --- | The Takahashi and Oishi 2003 study is inconsistently included in the tables as High Utility or Limited Utility. A more consistent treatment would be High Utility for the oral exposure experiments and Limited Utility for the non-oral experiments.<br><br>The Yamasaki 2002 study is included in the tables as High Utility but discussion of this study is completely missing in the preceding Summary section text. |
| 398 | --- | The Ashby 2003, Kim 2002 and Takahashi and Oishi 2001 studies are correctly included in the High Utility section of Table 105, but discussion of these studies is completely missing in the preceding Summary section text. |
| 402 | --- | As discussed above for Tables 84 and 85, the three Akingbemi 2004 experiments should not be in the High Utility section of Table 107. Experiments 1 and 3 have limited utility at best and experiment 2 is designated inadequate and should be deleted from Table 107. |

**Table 2**

**Polycarbonate/BPA Global Group Comments on**
**CERHR Interim Draft Report of April 2007**
**Section 1-2**

**June 15, 2007**

| Page | Lines | Comment |
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| 28 | 5 | Add Völkel, 2002 (CERHR citation #589) in addition to Tsukioka, 2003 (CERHR citation #582). |
| 29 | 7-8 | This sentence is inaptly phrased and suggests that extensive metabolism results in systemic circulation of parent compound. In fact, due to extensive metabolism, no parent compound was detectable in blood following ingestion of bisphenol A at levels well above typical human exposures (Völkel, 2002). The sentence might be better rephrased as "Because of extensive first-pass metabolism, little or no parent compound is systemically circulated, as discussed in more detail in Section 2." |
| 30 | --- | The units in Table 12 should be in micrograms/kg/day (µg/kg/day), not g/kg/day as frequently indicated. |
| 39 | 4-5 | Considering the challenges for accurate bisphenol A analysis at trace levels in biological samples, the inconsistency in reported data, and the well-conducted human toxicokinetic studies, the weight of evidence does not support the conclusion that "Bisphenol A is absorbed in humans…" as parent compound. Rather, the evidence more strongly indicates that bisphenol A is absorbed as bisphenol A monoglucuronide and not parent compound. |
| 65 | 1-10 | The addition of the data from Tominaga, 2006 adds valuable perspective on the significant and important differences in bisphenol A pharmacokinetics between primates and rodents. As part of the overall weight of evidence evaluation of studies in Sections 3 and 4, this data leads to the logical corollary that rodent toxicology studies likely overestimate the risk to humans. |