ENVIRONMENTAL WORKING GROUP

June 20, 2007

Dr. Michael D. Shelby
Director
Center for the Evaluation of Risks to Human Reproduction
National Institute of Environmental Health Services
Department of Health and Human Services
P.O. Box 12233
MD EC-32
Research Triangle Park, NC 27709

Re: Comments on the Interim Draft NTP-CERHR Report on the Reproductive and Developmental Toxicity of Bisphenol A

Dear Dr. Shelby:

As you know, in March of 2007, the National Institutes of Health, citing potential conflicts of interest, fired the contractor you hired to prepare the Bisphenol A (BPA) review document for the panel evaluating the chemical for your center, the federal Center for the Evaluation of Risks to Human Reproduction (CERHR). Environmental and public health advocates supported that decision by NIH but expressed serious concerns about the integrity and objectivity of the BPA review document itself and endorsed for a process that would allow for an objective review of the science with significant revision to the document. In response, NIH pledged to review the entire document to ensure that it accurately represented the state of the science on the reproductive toxicity of BPA.

Presumably, the new interim draft report your expert panel has released should reflect the results of the review that NIH pledged to conduct. But we find no public record of such a review having been conducted. Instead, we understand that what may have been a closed-door session in North Carolina was convened, not of independent experts, but of members of the expert panel already vested in the draft document. And instead of the open and transparent process needed to ensure a quality BPA review, this meeting was announced only 72 hours in advance, severely limiting opportunities for public comment, if the public was indeed allowed to attend.

And our thorough evaluation of the interim draft document produced through this process shows that significant and systematic revisions have been made to the BPA review document that magnify the scientifically unsupportable bias towards industry-funded studies that was inherent in the previous draft prepared by your now-fired subcontractor. Our findings raise questions about the ability of this expert panel to produce unbiased conclusions. If this BPA review document is to stand as a scientifically valid assessment of the risks that BPA poses to human reproduction and development, it must undergo the review promised by NIH, and this review much be thorough, open, transparent, and independent.

Environmental Working Group has analyzed the latest version of the BPA review document and come to the following conclusions.

1. The current document is less objective, more biased, and based on an even more inconsistent and arbitrarily applied set of criteria than the document prepared by the fired contractor, Sciences International.

2. The arbitrary and inconsistent application of scientific criteria used in evaluating the quality of studies of BPA toxicity leaves the panel with an unbalanced and incomplete science base to determine BPA's reproductive risks to humans.

3. An objective and fair review of the science of BPA's reproductive toxicity is not possible based on this review document. The NIH must follow through on the commitment it made and place the evaluation of the science of BPA's reproductive toxicity in unbiased hands, which in this case means halting the current review and starting over.

The following describe some of the most serious inconsistencies and arbitrary criticisms from the panel:

Inconsistent and arbitrary findings on studies using DMSO: In some studies, the panel critiques the use of dimethyl sulfoxide (DMSO) as a vehicle for BPA administration. In other studies, the panel finds no fault with the use of DMSO. This inconsistency appears to be arbitrary. In addition, of all the BPA administration vehicles used in the dozens of studies reviewed by the panel, the panel targets only DMSO as being of concern in its potential to influence study findings, and only in select studies, even though other administration vehicles should raise similar concerns.

In the draft, the panel states "Dimethyl sulfoxide (DMSO) has significant biological activities of its own and its use as a vehicle for in vivo studies raises significant concern about the relevance of those results for the human oral exposure situation. Those studies which used DMSO to solubilize BPA and injected or implanted that mixture were deemed of little or no utility because of this double limitation (injection + DMSO)."

The following points illustrate how this critique by the panel was used arbitrarily to justify elimination of some very high quality studies that found BPA toxicity at low doses:

1) Several studies from the Soto lab at Tufts University were disregarded, purportedly due to the panel's concern about the potential confounding effects that might arise from the use of DMSO as a vehicle to deliver BPA to test animals. Other studies using DMSO were treated differently. For example, on page 194 of the document, there is a study from Fukumori et al (translated to English by the American Plastics Council, suggesting that it is industry funded) in which BPA is injected into rats with DMSO as the vehicle; this study was

found to be "suitable for inclusion" by the panel. There is no critique about the use of DMSO as a vehicle in this study.

2) What makes the exclusion of Soto's studies more suspect is that many of them have negative controls that consist of DMSO alone. If these low doses of DMSO had some sort of biological effect on the endpoints that are being investigated in these studies, the negative controls would show these effects; however, no effects were seen in the control animals. Only the animals that were administered BPA and DMSO had relevant changes in the endpoints that were being examined, but the studies were still thrown out by the panel.

3) While the panel isolates DMSO as a vehicle that may have biological properties, they do not comment on the use of oil as a vehicle. Other types of oil, especially corn oil, have been found to be contaminated with estrogens; this is summarized in a recent commentary in Environmental Health Perspectives (Schettler 2003). Corn oil is used as a vehicle in many studies that are included in the draft and the panel does not bring this potential source of contamination up at all.

Inconsistent and arbitrary critique on the route of administration: In this case, the panel criticizes one form of administration of BPA to test animals, while ignoring, with no explanation or scientific justification, the well-known issues with other methods of dosing animals.

The panel criticizes subcutaneous dosing of BPA in studies while ignoring the inherent weaknesses of other forms of administration, especially oral gavage. They focus on the merits of BPA administration via food or gavage, stating "the panel carefully considered the value of studies where Bisphenol A was administered anywhere other than to the mouth or stomach of the experimental animal," and concluded that all of these studies should receive minimal consideration. Several studies using subcutaneous dosing found reproductive effects at very low levels of exposure but were considered inadequate by the panel.

While the panel is quick to point out the weaknesses in subcutaneous and intravenous administration, they fail to note that oral gavage is also a traumatizing process and may have its own effects on an animal's reaction to a compound. In 2006, scientists found that animals that were administered estradiol (an estrogenic compound) via gavage had completely different responses than when they were exposed via implanted capsules (Garza-Meilandt et al, Behavioral Neuroscience, 2006 August: 120(4): 905-16, Estradiol's effects on learning and neuronal morphology vary with route of administration). If the panel is intent on drawing conclusions on study relevance based on routes of administration, they should assess the limitations of all routes, including gavage.

This inconsistency could inject a dramatic and biologically inaccurate bias into the panel's deliberations. It is generally accepted that human exposure to BPA tends to occur in small, steady doses, best replicated by subcutaneous pump, as opposed to

boluses of high doses that occur via gavage. By systematically excluding these studies, the panel introduces a bias into the process that is not supported by the science.

Inconsistent conclusions on the use and response of positive controls: The panel recognizes the inherent value of positive controls, stating at the beginning of section 3.0 Developmental Toxicity "A positive control is valuable to show that an experimental model is capable of responding to a certain stimulus. This is of even more value when there is no response to a main exposure under study". However, when faced with several industry funded studies in which the positive controls fail to show the expected response, indicating a failed experiment, the panel downplays the significance.

Several industry funded studies included in this evaluation show minimal or no response to the positive control. In the evaluation of the study by Cagen (Cagen, 1999 pg 156), the panel notes "the lack of much effect with diethylstilbestrol treatment is a weakness" but goes on to state "this study is adequate for the evaluation process". This is repeated in another evaluation of a study by Cagen (Cagen, 1999 pg 211) where it is stated "lack of response of the positive control DES group is problematic..." but the study is still deemed "marginally useful for the evaluation". Another study by Ashby et al (Ashby, 1999, pg 212) was also accepted as "marginally useful for the evaluation process due to absence of response of the positive control group and small sample sizes".

It is unclear why the panel would consider these studies adequate in any way, marginal or otherwise, when the positive control fails.

The panel also states that they are unclear why the dose of DES (0.2 ug/kg/day) used as a positive control would work since "only 1 study has shown effects at this dose" (pg 212) and again on pg 213 "the lack of effect of the positive control is a weakness, but it is unclear why this dose (0.2 ug/kg/day) of diethylstilbestrol was expected to give a positive response".

Yet, the panel must be aware that a number of examples in the literature show that the same or smaller dose of DES administered prenatally to mice has produced changes in the reproductive system of male and female offspring (Gupta, Timms et al, Nikaido et al, and Honma et al), so the panel is incorrect in stating that the dose of DES that is used as a positive control is too low to be effective. Instead of recognizing that the studies in which the positive controls fail to elicit the expected response may have flaws in study design, the panel simply criticizes the dose of the positive control, despite evidence in the literature that this dose is adequate.

Inconsistent treatment of studies that do not use positive controls: In the beginning of section 3.0 Developmental Toxicity, the panel outlines the importance of positive controls, "A positive control is valuable to show that an experimental model is capable of responding to a certain stimulus. This is of even more value when there is no response to a main exposure under study". In fact, they go on to criticize several

studies throughout the draft for not including positive controls (Zoeller et al. pg 169, Negishi et al. pg 178, Golubkova et al. pg 322). All of these studies were considered "inadequate", partly because they did not include positive controls.

In contrast, two industry funded studies that were included in the evaluation from Ema et al. (pg 364) and Tyl et al. (pg 366) didn't include positive controls; yet, they were highly praised by the panel with the following statements "this thorough multiple generation rat study is highly valuable for human risk assessment of low dose exposure for bisphenol A…and this study is adequate and useful for the evaluation process" for the Ema study and "this study is highly valuable for human risk assessment for oral exposure to bishpenol A…this study is adequate and useful for the evaluation process" for the Tyl study. Nowhere in the evaluation of these studies is there any comment on the lack of use of positive controls.

Inconsistent conclusions on diet: The panel was inconsistent in expressing concerns about phytoestrogen content of feed by bringing it up as a relevant issue in assessments of some studies while pointedly ignoring it in other studies. The panel takes care to criticize certain studies based on the high phytoestrogen content of the diet that was fed to lab animals, noting in a study by Nagel "the Purina 5001 chow has high and variable levels of soy phytoestrogens" (pg 210). However, on the next page, the panel evaluates an industry funded study conducted by Cagen in which animals were given certified rodent chow 5002, which is also considered to have high phytoestrogen content (Thigpen et al. 2004); however, there is no mention of the high phytoestrogen diet in the evaluation of this industry funded study.

In a study by Ashby (also industry funded), the pregnant animals are fed a diet that contains 18.5% soy, but there is no mention by the panel of how this may affect the outcome.

Replication of prior studies: In general, when a lab attempts to replicate a prior study, it is prudent to follow the prior study protocol as closely as possible in order to duplicate the conditions in the original study. The panel notes that two industry funded studies (from Cagen et al and Ashby et al, pg 210-212) "attempted to duplicate the findings reported by vom Saal et al and Nagel et al"; however, the panel notes in both cases that there are differences from the original studies with respect to the strain of animal that was used and the type of feed, as well as other environmental conditions. It has been well established in the literature that these factors can completely change the outcome in studies that investigate endocrine disruption. If these studies were truly designed as replicate studies, they would necessarily have used the same animal strain and the same feed, two critical components of study design that can influence findings. The panel never brings up this issue.

Summary:

These examples illustrate how the CERHR panel has applied arbitrary and inconsistent standards throughout this evaluation of the developmental and reproductive toxicities

of BPA. They bring up, in many cases, valid concerns regarding the use of appropriate vehicles, type of feed, and need for positive controls but express concerns inconsistently and in every case described above, in a manner that appears to be systematically biased towards industry-funded science.

The results of this lack of consistency are revealed in a general analysis of section 3.0 of the two drafts of this document. In the first draft (prepared by Sciences International), almost 90% of industry-funded studies and 70% of non-industry funded studies were found to be adequate. In the next draft (prepared by the CERHR panel), 70% of industry-funded studies and only 30% of non-industry funded studies were found to be adequate. The panel quadrupled the number of studies considered "inadequate" compared to the previous draft, but in doing so, they rejected independent studies (academic or government) at three times the rate of industry funded studies. This illustrates that the inconsistent application of standards across all evaluated studies throughout this draft appears to systematically reject independent studies and favor industry funded studies being categorized as " adequate" for the panel's final evaluation.

As you know from our testimony at the March 2007 expert panel meeting, our own tests of 100 name-brand canned foods confirmed widespread exposures of the public with this ubiquitous reproductive and developmental toxin (EWG 2007). The need for an objective evaluation of the literature concerning BPA is absolutely vital, since the findings of this panel may influence decisions that affect the public health of millions.

Sincerely,

Anila Jacob, M.D., M.P.H.
Senior Scientist
Environmental Working Group

References

Environmental Working Group (EWG). 2007. A Survey of Bisphenol A in Canned Foods. Available at http://ewg.org/reports/bisphenola.

Garza-Meilandt A, Cantu RE, Claiborne BJ. 2006. Estradiol's effects on learning and neuronal morphology vary with route of administration. Behavioral Neuroscience 120(4): 905-916.

Gupta C. 2000. Reproductive malformation of the male offspring following maternal exposure to estrogenic chemicals. Proc Soc Exp Biol Med 224(2): 61-8.

Honma S, Suzuki A, Buchanan DL, Katsu Y, Watanabe H, Iguchi T. 2002. Low dose effect of in utero exposure to bisphenol A and diethylstilbestrol on female mouse reproduction. Reproductive Toxicology16(2): 117-22.

Nikaido Y, Yoshizawa K, Danbara N, Tsujita-Kyutoku M, Yuri T, Uehara N, Tsubura A. 2004. Effects of maternal xenoestrogen exposure on development of the reproductive tract and mammary gland CD-1 mouse offspring. Reproductive Toxicology 18(6): 803-11.

Schettler T. 2003. Corn and corn-derived products: sources of endocrine disruptors. Correspondence in Environmental Health Perspectives 111(13).

Thigpen JE, Setchell KD, Saunders HE, Haseman JK, Grant MG, Forsythe DB. 2004. Selecting the appropriate rodent diet for endocrine disruptor research and testing studies. ILAR Journal 45(4): 401-416.

Timms BG, Howdeshell KL, Barton L, Bradley S, Richter CA, vom Saal FS. 2005. Estrogenic chemicals in plastic and oral contraceptives disrupt development of the fetal mouse prostate and urethra. Proc Natl Acad Sci USA 102(19):7014-9.