Subject: NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A
Date: Friday, January 25, 2008 6:07 PM
From: Cathy A Richter <crichter@usgs.gov>
To: "Shelby, Michael (NIH/NIEHS) [E]" <shelby@niehs.nih.gov>
Cc: Donald E Tillitt <dtillitt@usgs.gov>
Conversation: NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A

January 25, 2008

Dr. Michael D. Shelby
CERHR Director
National Institute of Environmental Health Sciences
PO Box 12233 - MD EC-32
79 T.W. Alexander Dr. - Bldg. 4401
Research Triangle Park, NC 27709
phone: 919-541-3455
email: shelby@niehs.nih.gov

Dear Dr. Shelby:

I am responding to the public comment period for the NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Bisphenol A, released November 26, 2007. The expert panel is charged with the demanding task of assessing adverse reproductive and developmental effects associated with human exposures to bisphenol A, and has obviously put a great deal of effort towards that goal. My main concern with the panel's report is that the exclusion of more than half the relevant, peer-reviewed literature is affecting the conclusions reached by the panel. For example, of 128 papers on in vivo developmental toxicity in mammals that were considered, 85 (66%) have been excluded. This has resulted in the loss of critical information. For example, a recent highly relevant paper showing development of preneoplastic and neoplastic mammary lesions in response to prenatal exposure to BPA (Murray, T. J., Maffini, M. V., Ucci, A. A., Sonnenschein, C. and Soto, A. M. (2007). Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. Reprod. Toxicol. 23, 383-390) was excluded for reasons that

seem vague and weak relative to the importance of this study. The public is not well served by ignoring so much of our current scientific understanding.

The most important criteria for inclusion of a study in the report should be that it has gone through peer-review. Peer review is the foundation of quality control in science. The panel cannot hope to duplicate the cumulative effort by independent reviewers and editors that led to publication of the current literature on biological effects of bisphenol A. Rejection of papers from consideration because of arbitrary cut-offs regarding sample size, dosing route and vehicle, and statistics (including litter effects) is unwise. In particular, the panel's insistence on large sample sizes is in direct conflict with NIH policy that animal studies use the smallest sample size that can provide the required statistical power. The dosing route is irrelevant for studies of effects of prenatal exposure, since fetuses receive BPA through the placenta regardless of the maternal dosing route. Recent work has further shown that oral and subcutaneous routes of exposure result in equivalent blood BPA concentrations in neonatal mice (Taylor, J. A., Welshons, W. V. and vom Saal, F. S. (in press). No effect of route of exposure (oral; subcutaneous injection) on plasma bisphenol A throughout 24 hr after administration in neonatal female mice. Reprod. Toxicol. Available online 17 January 2008). All of these issues are dependent on the experimental design of the study and are much better left to the in-depth analysis provided by the peer review process. Thus, the panel should be reluctant to exclude any peer-reviewed publication from consideration. This approach allows for the weight of evidence for or against particular effects to become apparent, and avoids any introduction of bias into the conclusions of the report.

Next to peer review in importance is controls. Missing or failed controls are, in my opinion, the only valid reasons to exclude a peer-reviewed publication from consideration. Proper controls are essential to interpretation of experiments. Negative controls are required in all experiments in order to show the state of the experimental system in the absence of any treatment. In experiments showing the absence of an effect, positive controls are required as well as negative controls in order to show that the experimental system is capable of producing the postulated effect. Experiments that do show an effect do not require positive controls for interpretation, although positive controls are always helpful for comparison. DES is an appropriate positive control for BPA, and for

nuclear estrogen receptor-mediated effects should be used at doses approximately 3 orders of magnitude greater than the doses of BPA tested. In the case of novel effects, that is, effects that are seen in response to BPA but not in response to well-characterized estrogenic compounds such as DES, positive controls are not possible. In these cases, we must use a weight-of-evidence approach. Replication of the putative effect in subsequent studies provides evidence in favor of the effect. A putative effect can be considered well-established after it is confirmed in independent laboratories.

Thank you very much for the opportunity to comment on this important work.

Sincerely,

Catherine A. Richter
Research Molecular Biologist
USGS, Columbia Environmental Research Center
4200 New Haven Rd.
Columbia, MO 65201
573-876-1841
fax 573-876-1896
CRichter@usgs.gov