BY ELECTRONIC MAIL

January 25, 2012

Michael Babich, Ph.D.
Directorate for Health Sciences
Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

Re: CHAP discussion of the xenograft research by Drs. Kim Boekelheide and Richard Sharpe at the November 2-4, 2011 meeting

Dear Mike:

The Phthalate Esters Panel (PE Panel) of the American Chemistry Council appreciates the willingness of the members of the Chronic Hazard Advisory Panel (CHAP) on phthalates to consider the xenograft data generated at Brown University and the University of Edinburgh. The November 2 presentations from Drs. Boekelheide and Sharpe gave the CHAP members much to consider as they prepare their report to the Commission. Among the more striking aspects of the research is the consistency of the results from the two labs, despite the fact that the techniques used were quite different. Both investigators believe that the data strongly suggest species differences in response to gestational exposure to phthalate esters.

The CHAP members asked a number of questions of Drs. Boekelheide and Sharpe about the significance of their work to the interpretation of the *in vivo* animal data. Part of that consideration includes whether the doses of monobutyl phthalate (MBP) received by the fetal human testis tissue in the rat host were sufficiently high. Regrettably, that discussion occurred after Drs. Boekelheide and Sharpe had departed. As this is a critical issue in considering these data, we encourage the CHAP to explore it directly with Drs. Boekelheide and Sharpe, as well as with Dr. Rebecca Clewell who has done extensive work on the toxicokinetics of phthalate metabolites. Regardless of the differences in the relative proportion of monoester to diester between rats and humans, the absolute concentration of monoester is the prime question.

Regarding the question of whether MBP levels in the experiments were high enough to test for Leydig cell (LC) effects, Drs. Boekelheide and Sharpe provided several relevant points in their presentations and subsequent discussion. First, the absence of LC effects in the xenografted fetal human tissue is consistent with results of in *vitro* experiments using fetal human tissue, with in *vivo* experiments in marmosets, and with all other studies of non-human primates or human cells in culture. You may recall that Dr. Sharpe indicated that the marmoset

is an "extremely good model for the human in terms of testis development." Secondly, when asked about the adequacy of the dose, Dr. Boekelheide observed that the induction of multi-nucleated gonocytes (MNGs) in all of the species tested (including human) indicates that a biologically significant exposure to MBP did occur. In the case of the fetal human tissue, Dr. Boekelheide reported that the Brown researchers observed MNG induction at the lowest dose administered to the rat host (100 mg/kg/day). Dr. Boekelheide also noted that the lowest effect level for MNG induction in the rat experiments is "essentially identical" to that for the LC effects.

As a consequence, the default assumption that the rat data for male developmental effects are relevant to human exposure should, in Dr. Sharpe's words, "be looked at with a little more suspicion."

The CHAP members also expressed concern that the results presented had not been published. Since that time, the Panel is aware of the availability of an article from Dr. Sharpe's laboratory that includes the data from his presentation.[1] You may want to contact both Drs. Boekelheide and Sharpe about the status of other relevant publications. Please do not hesitate to contact me at steve_risotto@americanchemistry.com or (202) 249-6727 if you would like to discuss this issue further.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

[1] Mitchell RT *et al.* Do Phthalates Affect Steroidogenesis by the Human Fetal Testis? Exposure of Human Fetal Testis Xenografts to Di-n-Butyl Phthalate. *J Clinical Endrocrinology and Metabolism,* January 11, 2012, doi: 10.1210/jc.2011-2411.