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RE: Bisphenol A Interim Draft Expert Panel Report

In response to the NIEHS request for comment on the draft CERHR Report on the Reproductive and Developmental Toxicity of Bisphenol A, the following is intended to provide clarification and rebuttal to the comments on the published research on page 199-200 of the draft report. The publication is Ho et al, *Cancer Research* 2006, 66:5624-5632.

The revised report states "In bisphenol A-treated compared to vehicle control rats that received 17β-estradiol/testosterone exposure in adulthood, there was increased incidence and severity of prostatic intraepithelial neoplasia (100 vs. 40% incidence). *In humans, this is,* a precursor lesion to prostate cancer*, however in rodents it is a lesion of unknown significance.*" …. "The study authors concluded that developmental exposures of rats to bisphenol A increased susceptibility to *presumed* precancerous prostate lesions resulting from prostate epigenome alteration." ….. "It could be suggested that carrying the study further in terms of animal age might have produced more dramatic phenotypes *and clarified the relevance of PIN to prostate cancer in this model*." The italics in blue highlight the newly added changes in the revised report.

I strongly disagree that PIN lesions in the rodent are of unknown significance. In a consensus report sponsored by the NIH and published in *Cancer Research* 64:2270, 2005 entitled "Prostate Pathology of Genetically Engineered Mice: Definitions and Classification. The Consensus Report from the Bar Harbor Meeting of the Mouse Models of Human Cancer Consortium Prostate Pathology Committee", the issue of PIN lesions in the mouse model is discussed at great length. While the discussion focuses on genetically engineered mouse prostates specifically, it has applications to PIN lesions in rat models of hormonal carcinogenesis. In brief, this report states that there are **two types of mPIN lesions: ones which do not progress (and may have limited significance) and others that show invasion and/or progression in the animal model**. The later lesions are considered highly significant to

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prostate cancer and the human disease. Furthermore, this report cites alterations in apoptosis and proliferation within the PIN lesions as evidence of a relevant precancerous lesion with similarity to high-grade PIN lesions seen in humans which are considered precursor lesions to prostate cancer.

In the *Cancer Research* publication by Ho et al, the **hormonal treatment regime of T+E** used has been well documented to result in high-grade PIN lesions in the rat prostate after 16 weeks which **progresses to locally invasive prostate adenocarcinoma** with longer exposures. The readers are referred to a publication by Bosland et al, *Carcinogenesis* 1995; 16:1311-1317 "Induction at high incidence of ductal prostate adenocarcinomas in NBL/Cr and Sprague-Dawley Hsd:SD rats treated with a combination of testosterone and estradiol-17β or diethylstilbesterol". Thus it is clear that the high-grade PIN lesions observed in the rat model used by Ho et al meet the criteria established by the Bar Harbor Consensus Panel for PIN lesions that show invasion and/or progression in the animal model and have clear significance and relevance to human PIN, the precursor lesion to prostate cancer.

The manuscript by Ho et al, *Cancer Research*, 2006 furthermore documents **aberrant proliferation and apoptosis** in the high-grade PIN lesions of rats exposed neonatally to relatively low-doses of BPA followed by adult T+E exposure (Figure 2 of the publication). Thus this additional data meets the criteria of the Bar Harbor Consensus Panel that "Supportive objective studies using tissue markers can be used, such as proliferation and apoptosis assessment, which are known to be altered in human PIN". Finally, it is critical to point out that blinded pathological assessment was made for all the prostates examined in the Ho et al, Cancer Research 2006 publication as recommended by the Bar Harbor Consensus Panel for establishing the relevance of the rodent PIN lesions.

Based upon the above clarification, I request the ambiguous statements listed above in blue italics are removed from the BPA report.

Finally, based upon the above considerations, I request that the *Utility (Adequacy) for CEHRH Evaluation Process* statement in the revised BPA report which reads:

"This paper is suitable for the evaluation process in providing supplemental information. It is (sic) limited utility for the evaluation process."

be restored to the original statement in the original BPA report:

"This paper makes important contributions and is suitable for the evaluation process."

Respectfully submitted,

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