May 21, 2008

Dr. Barbara Shane
Executive Secretary for the NTP Board of Scientific Counselors

NTP Office of Liaison, Policy, and Review
NIEHS, P.O. Box 12233, MD A3-01
Research Triangle Park, NC 27709

Dear Dr. Shane:

As a developmental biologist working with endocrine active substances at NIEHS for over 30 years, I am submitting a public comment on the NTP Draft on Bisphenol A dated April 14, 2008. This is my opinion and not necessarily that of the NIEHS/NTP. First, overall I am pleased with the revised draft that has taken into consideration the comments received by investigators who have expertise in the BPA field. However, my current concern focuses on the exclusion of the study by Newbold et al., Reproductive Toxicology 24(2):253-258, 2007 in forming the NTP's conclusion of potential risks to human from BPA exposure. The study from my lab, which underwent internal NIEHS review and peer-review at the journal level, documents the long-term adverse effects of neonatal BPA exposure in an experimental animal model. These adverse effects include a statistically significant increase in ovarian cysts and cystic endometrial hyperplasia (CEH) of the uterus, plus the occurrence of more serious uterine pathologies including adenomyosis, leiomyomas (fibroids), atypical hyperplasia, and stromal polyps. Although the later uterine lesions are not statistically different from controls, similar alterations in the female reproductive tract following exposure to environmental estrogens like low doses of diethylstilbestrol (DES) have been previously published. Further, paraovarian cysts, progressive proliferative lesion of the oviduct, and cystic mesonephric (Wolffian) duct remnants in the uterus were found in all BPA groups but not controls. These lesions have been well studied and all are associated with exposure to estrogenic substances during development. Thus, our findings with BPA are consistent with what we know of exposure to other environmental estrogens although many of the lesions are not statistically different from controls. While the NTP acknowledges the long term effects of developmental BPA exposure on the mammary gland (increased susceptibility to develop mammary gland tumors later in life) and the prostate (predisposition to develop hormonally-induced preneoplastic lesions later in life), the long term effects of BPA on the female reproductive tract have been under considered. This may result in an underestimation of the potential risk of BPA exposure, and known estrogen target tissues to be overlooked. I ask the NTP to reexamine the Newbold study and to revise the current draft to state that there is supporting scientific evidence for long term effects of BPA on the prostate, mammary gland **and uterus and ovary**.

As stated in the draft, my study was undervalued because "the literature is not sufficiently developed (page 28)". This reason seems vague and inadequate relative to the importance of the data. It does not consider the fact that the animal model used in the study is one of the most well documented animal models for human health risks. The developmentally-exposed mouse model has been successful used by numerous laboratories to replicate and

predict the adverse effects of the prototype environmental estrogen DES on similarly exposed humans, both males and females. Further, over the last 3 decades, these adverse effects have been shown in numerous experimental animal models including rats, hamsters, guinea pigs, and monkeys. More recent biochemical and molecular studies have identified the mechanisms that are responsible for the adverse changes caused by exposure to estrogenic substances during critical stages of development. In addition, this animal model has been successfully used to study effects of other environmental estrogens. Since BPA and DES share many biochemical mechanisms, data reported in my BPA study, and especially the comparison of low dose DES effects, should certainly provide information worthy of consideration.

Other BPA studies have not reported similar ovarian and uterine effects because 1) either the exposure started after the critical developmental period or 2) the animals were too young for the tumors to have developed.

Taken together, the effects on all the estrogen target tissues (prostate, mammary gland, uterus, and ovary) should be used to conclude "that there is concern BPA is a harmful reproductive toxicant and potential carcinogen when exposure occurs during the developmental period".

Respectfully submitted,

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