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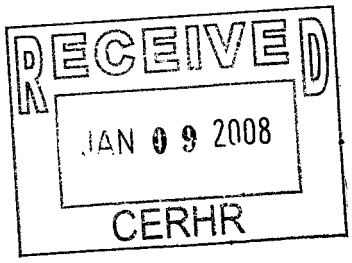

January 3, 2008

Dr. Michael Shelby
CERHR Director
National Institute for Environmental Health Sciences
PO Box 12233 – MD EC 32
79 T.W. Alexander Drive, Bldg 4401
Research Triangle Park, NC 27709

Dear Dr. Shelby:

I am submitting public comments for the final draft of the CERHR report to the NTP on the Reproductive and Developmental Toxicity of Bisphenol A. I am pleased that my public comments regarding the second draft were taken into consideration when rewriting the final draft. My current comments focus on one point in particular that impacted the adequacy or inadequacy of study design and thus the final conclusions reached regarding BPA toxicity, i.e. **Mode of BPA administration**:

The committee was charged with looking at all the evidence regarding BPA exposures in humans and animals. *By selectively eliminating data collected from non-oral routes of administration, the committee has introduced a significant bias to the process.* Study designs are set based on the questions being asked as well as the endpoint in question. In classical toxicology studies, the mode of compound administration requires using route of exposure expected for that compound in the human population. This is because toxicology studies are specifically designed for evaluating toxicity in human populations. It is critical to note, however, that <u>there are marked cons to oral administration</u> as listed below:

1. Administration through feed or water source will result in variable accumulation within each individual subject. While this may mimic human exposures, it is problematic for a controlled scientific study since variable exposures will lead to variable responses. Large variation in responses will lead to high error bars resulting in non-significant data when statistically analyzed. Thus there is a higher probability of *underestimating* exposure consequences and producing <u>false negatives</u>.

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2. An alternate oral route method is through gavage which assures consistent exposure between subjects. There are problems associated with this exposure route. First, gavage can produce stress which elevates circulating prolactin and glucocorticoid hormone levels. Even without obvious external stress, handling alone will elicit these responses which can interfere with hormone-sensitive reproductive end organs.
3. More importantly, daily gavage results in bolus exposure to a potential toxicant which does NOT mimic the typical exposure that humans experience for BPA. Low-level exposure through out the day is predicted based upon a short half life for BPA and consistent detectable levels in 93% of the human population. Despite this experimental exposure that is "significantly different from that experienced by humans" (pg 122), the committee has accepted gavage studies as adequate and of high utility for their evaluation.

The BPA committee systematically eliminated studies (classified them as inadequate) if given through non-oral administration. *Non-oral exposures* are frequently used in *valid scientific studies* conducted by endocrinologists and other scientists due to multiple "pros" critical to the endpoint analysis which is frequently mode-of-action based. While first pass metabolism does not occur with non-oral routes, the pros of non-oral routes must be weighed and not systematically discarded as the committee has done *a priori*:

1. Injection of BPA results in accurate and consistent exposures to all subjects. Further, if applied subcutaneously and in oil-vehicle with slow-release kinetics, this can *better mimic human exposure patterns* as compared to bolus exposure with gavage. A down side that must be considered is that a stress hormone response will occur.
2. Use of pellets or minipumps will also result in consistent exposure levels in all subjects and will not produce stress. The marked advantage of this approach is that slow-release will *better model human exposure patterns*.
3. While first-pass metabolism will not occur with non-oral routes, the data can be *highly relevant* if one considers the final circulating level of free BPA which is what is biologically relevant.
    a. The fetus and neonate in both humans and rodents have no or lower liver metabolism of BPA since the UGT2B isoform is either not expressed or is expressed at low levels. Table 32 on pg 58 of the final BPA report shows a maximum BPA serum concentration of 48.3 mg/L in male rats at postnatal day 4 and 0.024 mg/L in adult male rats following gavage of 10 mg/kg BW – a fold difference of 2000 due to minimal first-pass metabolism in the neonatal rat. Thus in neonatal exposure studies of BPA, the subcutaneous injection exposures may deliver similar free BPA levels as with oral exposures or BPA levels with minimal differences. This information was reported by the committee in the final report. *Despite this knowledge, the committee continued to classify all neonatal exposures that used non-oral routes as inadequate for the evaluation process.*
    b. While not available to the CERHR committee during the course of their literature review, a recent study by Taylor et al (*Repro Tox*, in press) documented nearly identical serum levels of unconjugated BPA over a 24 hr period in neonatal day 3 female mice when exposed to a single oral dose or

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subcutaneous injection in oil at both low and high doses of BPA. Thus these new findings clearly show that studies in neonatal rodents employing sc injections as the route of exposure are equally (or perhaps more) valid than oral exposures.

c. While serum levels of free BPA will differ based on mode of exposure, the *final circulating unconjugated BPA level is what must be considered.* For neonatal exposures, a low-dose (10 μg/kg BW) sc BPA injection will result in circulating levels very similar to those following oral exposures. Thus even considering lack of first pass metabolism, the final circulating levels of BPA following sc injection would be similar to 10-50 μg/ kg BW (or higher) given orally, depending on the postnatal day. This is still a low-dose exposure (as currently defined by the EPA) and should NOT be of limited utility since it does not significantly differ from levels experienced by humans.

By accepting all oral studies despite problems and situations that do NOT mimic human exposure, and categorizing as inadequate and/or of limited utility all studies using non-oral routes of administration which have many pros (such as better mimic of slow constant exposures) and in which biologically relevant unconjugated BPA levels can be or have been measured and/or calculated, **the committee evaluators have clearly introduced preconceived bias into the evaluation process**. On page 122 of the report, the Committee states that their intent was to limit the impact of studies which are "*significantly different from that experienced by humans*". Thus all non-oral exposures, including developmental studies, were relegated to the inadequate and/or of limited value category while gavage, bolus exposures were included as adequate and of high utility despite exposures differing significantly from that experienced by humans. Furthermore, high-dose oral exposures, such as that given in the 1982 NTP study were included as informative in the present report (Pg 108-109) despite delivering BPA levels that were significantly different from human exposures. At the same time, non-oral exposures to BPA at low-doses that resulted in circulating BPA levels *lower than the 1982 NTP study* were categorized as inadequate. Thus we must conclude that the categorization scheme used by the NTP BPA Panel is specious and NOT scientifically or factually based.

Given the new report (Taylor et al, *Reprod Tox*, in press, 2008) which documents that neonatal exposures to BPA via sc injections produce equivalent unconjugated serum BPA levels as oral exposures, *we request that the NTP reclassify neonatal studies that have used non-oral exposure routes which were regarded as inadequate solely do to this study design.* These studies should now be classified as *adequate for the evaluation process* and their findings should be used to weight the evidence that BPA may be a harmful reproductive toxicant or potential carcinogen when delivered during the developmental period.

Respectfully submitted,

[Redacted]

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