Comments on the Draft NTP Brief on Bisphenol A (CAS NO. 80-05-7)

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by

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On page 28 of the *Draft NTP Brief on Bisphenol A (CAS NO. 80-05-7)*, the authors briefly describe results from Newbold *et. al.* (*1*) and conclude that "Replication of these findings and further study of the linkage of early and late occurring events will be important in establishing a better understanding of any long-term consequences of exposures of the developing organism to bisphenol A." Thus, it seems that a fundamental problem with Newbold *et. al.*'s (*1*) study design study was not identified. Newbold *et. al.* (*1*) stated the following about their experimental design: "At delivery, pups from all litters were pooled, then separated by sex, and randomly standardized to 8 female pups per dam." Therefore, their design failed to control for the "litter effect", *i.e.*, the tendency of littermates to respond similarly to one another relative to non-litter mates (*2-5*).

The importance of controlling for litter effects in developmental studies is well-documented. For a recent published discussion on this problem see: (*6-8*). A failure to control for litter effects increases the potential for false positive results (*9*). Multiple sources are

available from various agencies that specify the importance of controlling for the litter effect. For instance, the Organization for Economic Co-operation and Development state the following in their developmental neurotoxicity (DNT) study guidance (*10*): "The statistical unit of measure should be the litter (or dam) and not the pup." Further, Holson *et. al*. (*5*) stated: "Treating multiple offspring from the same litter as independent subjects is a fundamental violation of assumptions that can severely inflate alpha levels [references omitted]. The current DNT practice sometimes recognizes this principle in young preweaning animals, but not always in adults, on the false assumption that litter effects do not extend beyond infancy or weaning. This is, however, a mistaken assumption." Though Newbold *et. al*. (*1*) did not evaluate DNT endpoints, litter effects are not limited to the developing nervous system, and Newbold *et. al.'s* (*1*) failure to control for the litter effect may have influenced the endpoints measured and reported as being affected by bisphenol A.

Despite the important role that the NTP Brief is destined to play in future policy-making at the national level, the above experimental design flaw was not identified during NTP's peer review process. This is troubling because the NTP is a well-recognized, well-respected entity, and the conclusions drawn in the Brief, once finalized, will very likely be taken at face value without further inspection of the works cited therein. A failure to critically review studies cited in a document of this magnitude raises concerns over the quality of the process used to produce the NTP Brief, and the conclusions drawn.

Disclaimer

The author declares he has no competing financial interests.

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