Dr. K. Barry Delclos
NTP Designated Federal Official
Office of Liaison, Policy and Review
National Institute for Environmental Health Sciences
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Dear Dr. Delclos,

I am a first-year PhD student in the Interdisciplinary Toxicology Program at the University of Georgia, Athens. My undergraduate studies focused on Environmental Health Sciences, and has remained as a focal point as I have entered my PhD coursework. The research lab I work and learn in specializes in male reproductive toxicity. Therefore, much of my course and much of the lab work that I have conducted or read literature regarding environmental contaminants and their impacts on male reproductive system. The release of the draft NTP Research Report on the CLARITY-BPA Core Study: A Perinatal and Chronic Extended-Dose-Range Study of Bisphenol A in Rats peaked and its conclusions disturbed me as a learning and budding scientist, and lead me to have a few concerns. This response will refer to low-dose BPA as a dose of ≤ 50 mg/kg body weight/day, which is currently the accepted lowest adverse effect level (LOAEL) used by the United States Environmental Protection Agency.

One of the primary aspects of this study that stood out to me was the dose selection. The dose used in these experimental studies were at levels that were not environmentally relevant, where a copious number of studies conducted prior to this review, concluded adverse effects of BPA levels at much lower doses. While it is important to distinguish environmental and occupational exposures, these occupational exposures are not prevalent to the general population, yet in the most recent NHANES data, 98% of people in America had detectable levels of BPA in their urine. It is also important to remember that BPA is a known endocrine disrupting compound (EDC). Like most EDCs, BPA has been suggested to show a nonmonotonic dose-response curve, therefore one would expect to see a mixed bag of results at a wide range of doses such the concentrations used in this review. In the literature review conducted by Peretz et al 2014, many studies cited that low-dose exposure to BPA had a variety of effects. For example, in many rodent models, prenatal and neonatal exposures to low doses of BPA lead to the disruption of estrous cyclicity, and increased the testosterone production and incidence of ovarian cysts in females. Low-dose exposure to BPA was also reported to induce both benign and malignant lesions in the uterus and Wolffian duct in prenatally exposed mice. The review conducted in 2014 also reported that gestational exposure to low dose did not alter the birth weight of mice or rats, but suggested a dose-dependent association on offspring birth weight. There were also several studies cited in the prior review that mentioned that across various routes of exposure and different times of exposure, low dose BPA impaired sperm motility in both rats and mice. As demonstrated in just these few brief examples, BPA at levels below the LOAEL have been seen to show adverse effects in the animal models.

In regards to the release of the draft NTP Research Report on the CLARITY-BPA Core Study: A perinatal and Chronic Extended-Dose-Range Study of Bisphenol A (BPA) in rats, I have a few concerns. One of the first concerns that needs to be addressed is the fact that BPA is a known endocrine disrupting compound (EDC). Per literature the majority of EDCs have a nonmontonic dose-response. Therefore, one would not suspect to find a dose response shaped like a normal standardized bell-curve. This review did not make any conclusions about the effects of BPA on the endocrine system, which is troubling. Another issue that raises concern is how the doses were selected at a log scale and the lowest dose was based on the sensitivity of the instruments at a minimum of 5 parts per billion (ppb). However, the review mentions that

there are effects seen in the animal models at exposures lower than the sensitivity of the machine.

Another concern is that this draft only includes information being released by the core studies and not the research that was being conducted at Universities and Institutions. This draft did not address any of the epidemiological studies that have and are being conducted regarding BPA exposure. This report only addressed the information conducted on animal models and not the information regarding the research being conducted at Universities and a plethora of research institutions. These studies were limited to the interpretation of animal studies to the creation of a predictive model for human exposure to BPA. However there its especially tough to extrapolate information from animal models to the human, as developmental periods differ significantly. So, while some developmental periods may be similar in one animal model, other systems may develop at different critical times. As the literature, has shown that humans and animals develop at different time periods from embryo to adulthood, therefore the data obtained from animal studies must be taken with a grain of salt. Since these studies were limited to animals and not open to *in vitro* approaches, that could potentially expand upon the endpoints used in this draft. The endpoints used in this draft were vague and broad categories. Rather than address BPA and its effects as an EDC, the paper analyzed a wide range of endpoints but none that were specific enough to fully determine if BPA is a safe compound or not. Rather than focus on endpoints such as body weight, hematology, vaginal cytology in the female animals, and the examination of the thyroid, parathyroid, kidney and liver in the male animals, the review should cover more specific endpoints. There are countless of studies reviewed by Peretz et al in 2014 that highlight the variety of endpoints that were affected by BPA at low doses. For instance, the literature review conducted in 2014, analyzed the reproductive effects of BPA, and found that BPA could disrupt meiosis in mice and alter the gene expression in germ cells and early meiocytes in two other strains of mice.

Overall, I do not agree with the conclusion that BPA should be considered a safe compound. While there was much public outcry to remove BPA from plastics in the United States, I am on the side approaching BPA with caution. While my research interests focus on male reproductive toxicology, much of the literature I have read and analyzed suggests that BPA has adverse effects at doses much lower than were tested in this draft. I also disagree with the endpoints selected and reviewed in this draft. Before the conclusion of this draft I would like to see more conclusive information regarding BPA and its toxicity.

Thank you for your time,

Jacob Siracusa

Interdisciplinary Toxicology Program at UGA

Department of Environmental Health Sciences