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RE: Peer Review of the Draft NTP Research Report on the CLARITY-BPA Core Study

A concern with the study is the lack of F2 generations used. The exposures only started with the F0 dams after it was confirmed that they had been impregnated or at least showed that mating had occurred. The concern from this is that any developmental impacts on the reproductive system that would impact future generations would not show up. The exposure came at a point when the female reproductive system should be fully developed in the F0 rats. Studying reproductive health of BPA would be more accurate if the BPA exposure of the parents started at birth or even prenatally. The study would be more complete if the impact on an F2 generation was measured.

An additional concern is that it seems like the study did not include a measurement of BPA or BPA metabolites in the urine or blood. These were mentioned (page 31, line 5), but no figures or charts showed this information. It would be useful to know if there is any differentiation adsorption and excretion of BPA, its metabolites, or EE2. The orders of magnitude in changes to the dosing of BPA is enough to potentially impact the ADME of the BPA. The highest doses of BPA may lead to a saturation of the enzymes that would normally break down BPA, which would lead to a higher burden on the body. The main purpose of the study was to determine if there were any measurable impacts to the health of the rats, but the lack of BPA measurements makes it less translatable to humans.

A strength of the study is that it did not focus only on estrogenic activity. Estrogen mimicking compounds do not always act as a replacement for estrogen. They may also block estrogen activity. Beyond that, these compounds may have countering impacts based on the location of the receptor. In one organ it may be a promoter, while in another organ it may be an inhibitor. No impacts on the male sperm development were seen in this study. This helps to support that BPA mainly works in estrogenic activities. The males did have additional lymphocyte infiltration in the epididymis at 25000 ug BPA/kg bw/day. This infiltration was also seen with the .5 EE2 group. This outcome may indicate some impact on the male reproductive system, but it could easily be due to an alternative effect from the BPA. Changes in the immune system would lead to system wide changes that could be seen from BPA. The NCTR study with BPA showed that male rats had an increase in mammary gland hyperplasia when exposed to EE2, but this was not seen in the current study. The authors explained that this lack of mammary gland hyperplasia is due to the age of the rats for their exposures (page 72, lines 3-4).

Some of the significant findings in the study do lead to concern with the female reproductive organs. The uterus had cystic endometrial hyperplasia at the two highest doses. The corpea lutea showed depletion and interstitial cell hypertrophy could be seen with the 25000 ug BPA/kg BW/day in the continuous-dose rats. There were several other significant findings in the female reproductive system. Although they may not have had too much of an impact on the rats, it would still be prudent to determine if these particular findings would lead to changes in the F2 generation. If increases in lesions

and carcinogenesis can be seen in those offspring, then it would become a more relevant endpoint for the study.

Thank you for the consideration of this feedback. I look forward to the conclusions and Grantee Study findings.

Davis Reardon