

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

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- Framing of study was not clear in draft report
- Endpoints that were not analyzed
- Dismissal of 'low dose effects'
- Possible effects of stress may alter response to BPA
- Lack of exposure data
- Inappropriate use of historical controls

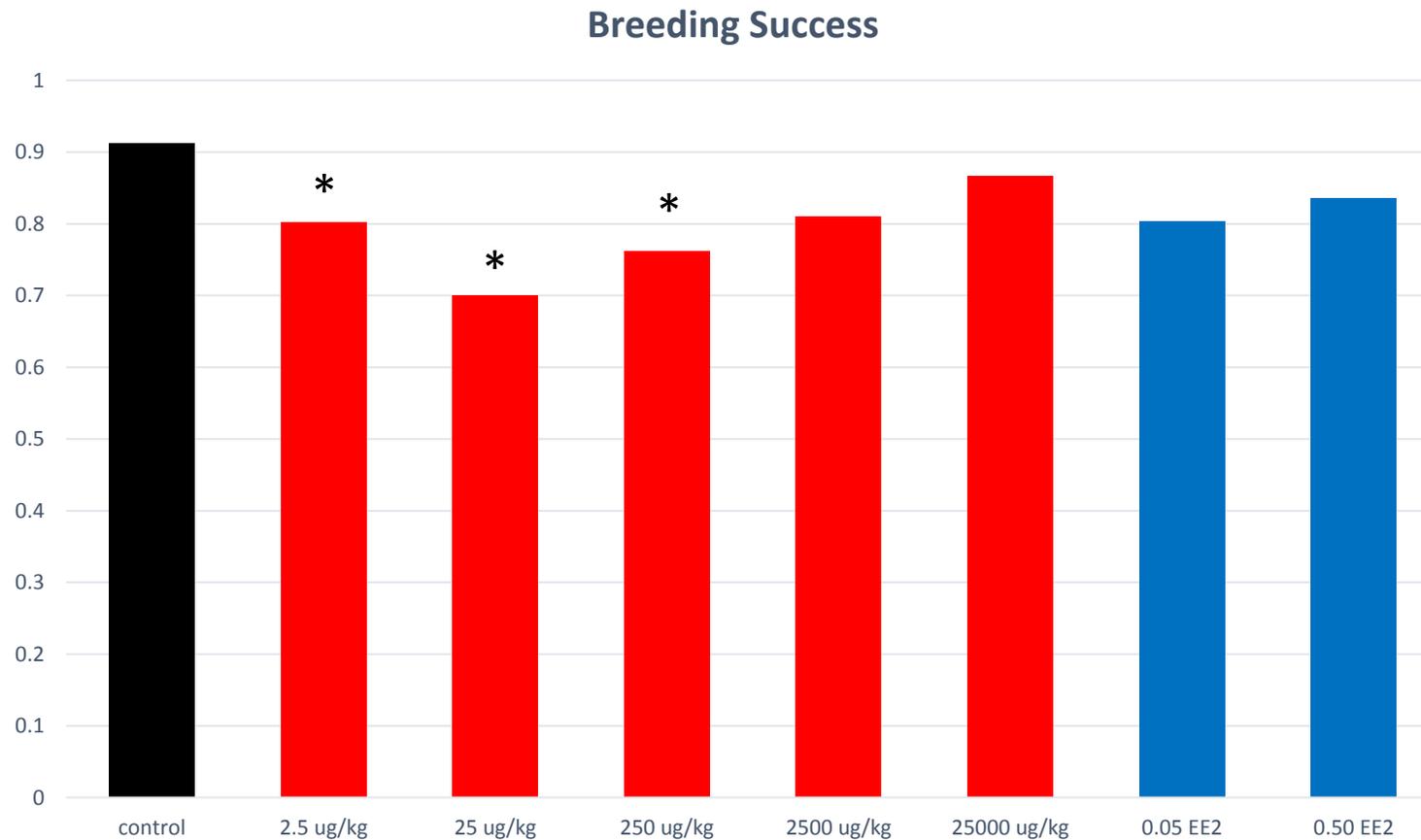
1. Framing of the study (Schug et al. 2013)

- The NTP, NIEHS, and U.S. FDA “developed a consortium-based research program to link more effectively academic and guideline-compliant research.”
- “By drawing upon the strengths of academic and regulatory expertise and research approaches, CLARITY-BPA represents a potential new model for filling knowledge gaps, enhancing quality control, informing chemical risk assessment, and identifying new methods or endpoints for regulatory hazard assessments.”
- “Thus, a chronic toxicity study examining a wide dose range using a relevant long-term oral dosing protocol that includes developmental exposure and new endpoints not typically assessed in guideline studies was considered to be of value by NTP and NIEHS. In addition, FDA’s ongoing review of BPA offered an opportunity to test a new, collaborative research model based on enhancing the links between academic and guideline-compliant research.”

1. Framing of the study (Schug et al. 2013)

- “By drawing on the strengths and rigor of a guideline-compliant study conducted in accordance with GLP and the expertise of the extramural scientists, the CLARITY-BPA consortium is designed to enhance risk assessment by resolving scientific uncertainties about BPA’s health effects to better inform regulatory decision-making.”

2. Endpoints that were not analyzed in the report

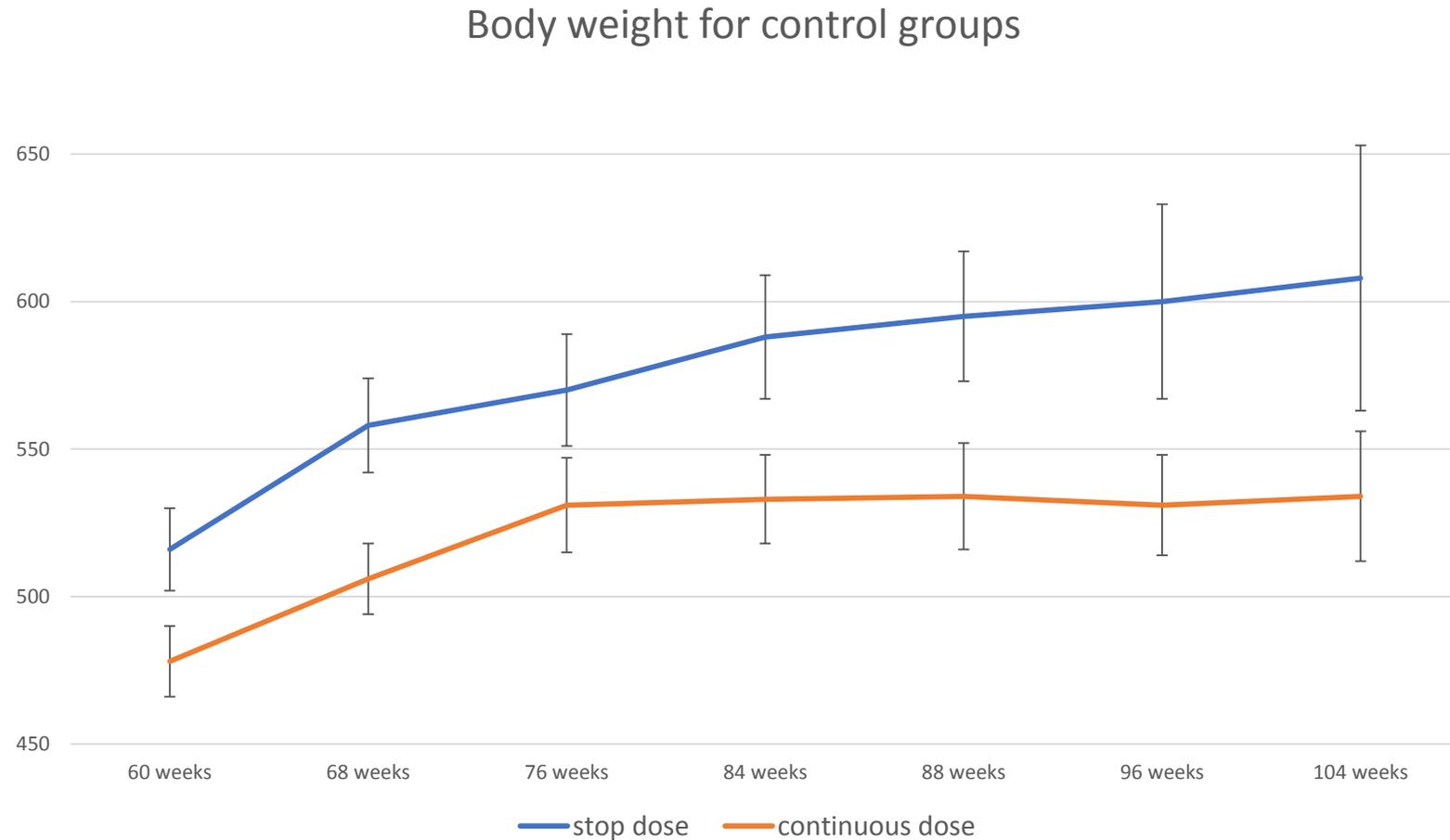


* $p < 0.05$, Chi Square test

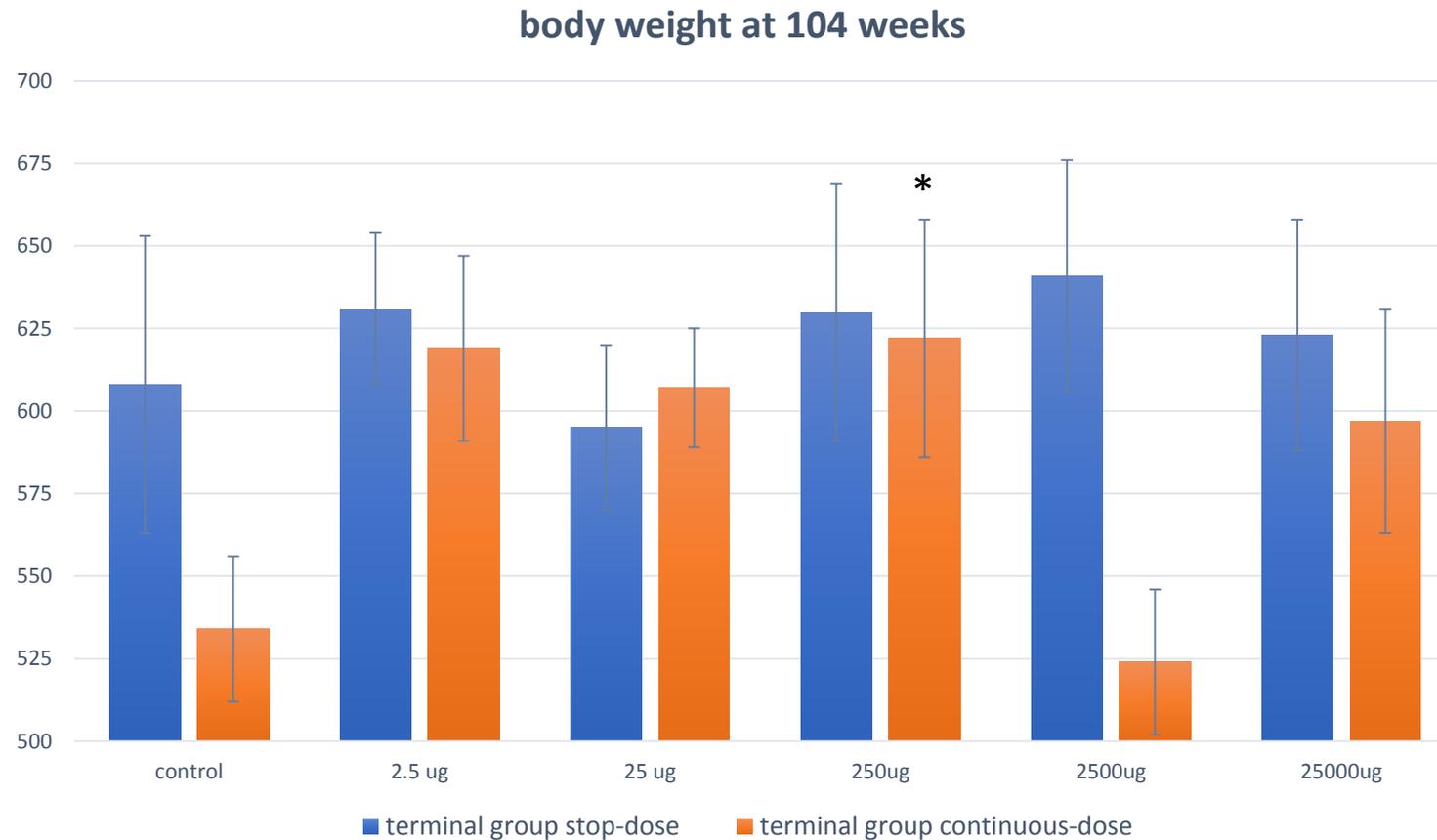
3. Effects observed at low doses

- Increased body weight (females) at 250 $\mu\text{g}/\text{kg}/\text{day}$
- Mammary adenocarcinoma (females) at 2.5 $\mu\text{g}/\text{kg}/\text{day}$
- Mammary ductal dilation (males) at 2.5 $\mu\text{g}/\text{kg}/\text{day}$
- Hyperplasia of the vagina at 25 $\mu\text{g}/\text{kg}/\text{day}$
- Kidney cysts and nephropathy (females) at 2.5 $\mu\text{g}/\text{kg}/\text{day}$
- Kidney cysts and hyperplasia (males) at 25 and 250 $\mu\text{g}/\text{kg}/\text{day}$
- Prostatic inflammation at 2.5 $\mu\text{g}/\text{kg}/\text{day}$

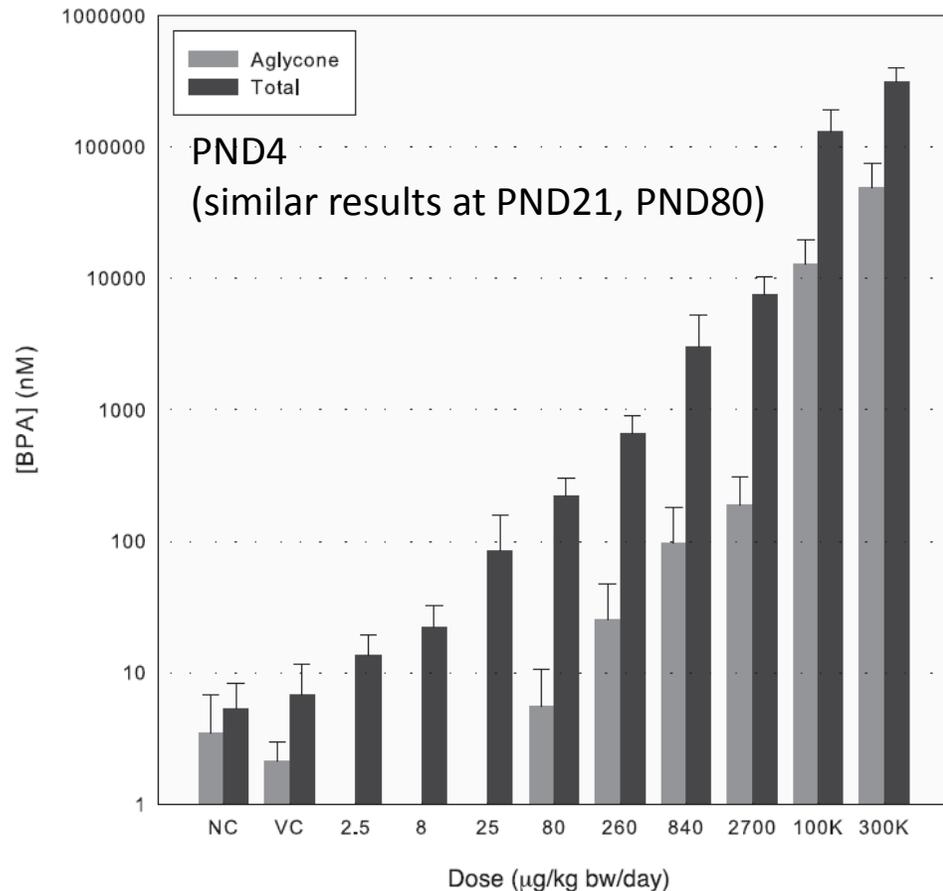
4. Possible effects of stress: alter response to BPA?



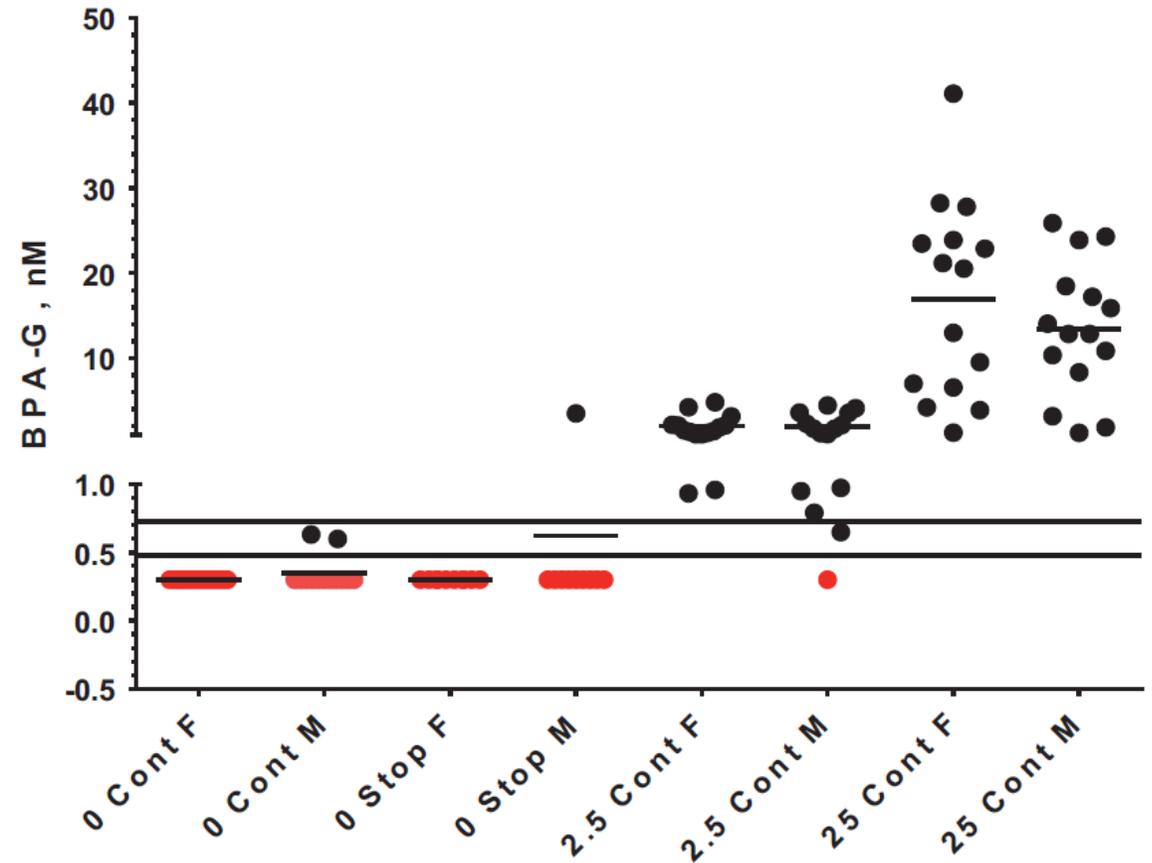
4. Possible effects of stress: alter response to BPA?



5. Lack of exposure data



Chuchwell et al. 2014



Heindel et al. 2015

Schug et al. 2013: “The core study will also provide animals and tissues developed under conditions of analytical standardization often not included in academic research (e.g., internal dosimetry and analytical quantification and certification of dose, diet, and background of BPA and other sources of potential endocrine activity).”

6. Proposed use of historical controls is problematic

- “There was a statistically significant increase in the incidence of female mammary gland adenocarcinoma (22% versus 6%, $p = 0.016$) or the combination of adenoma and adenocarcinoma (24% versus 8%, $p = 0.018$) in the 2.5 μg BPA/kg bw/day dose group... Limited historical control data for this strain of rat in experiments conducted at NCTR using the same diet show a background rate of 12-17% for adenocarcinoma or adenoma in the female mammary gland”

6. Proposed use of historical controls is problematic

- Keenan et al. 2009 provides guidance on the use of historical controls: “The concurrent control group is the most relevant comparator for determining treatment-related effects in a study.”
- To utilize historical controls, they should be made available for all endpoints.
- To utilize historical controls, information about background contamination of the chemical in question should be provided.