



Brain and Behavior



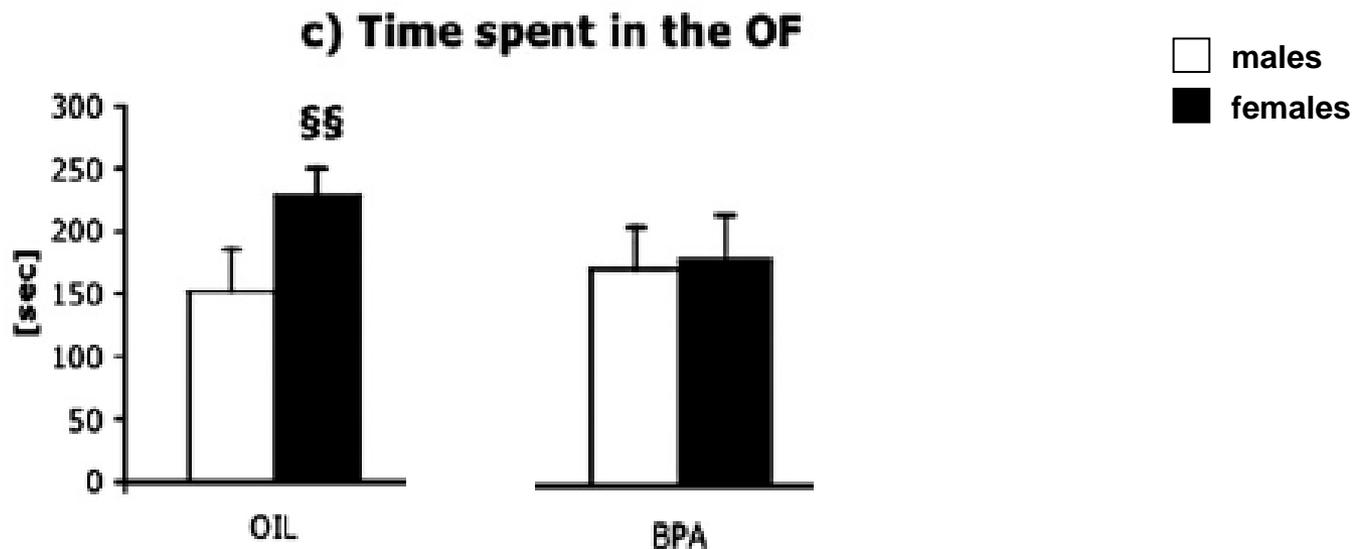
Brain and Behavior – “Low” Dose Effects

- 3 oral studies reporting effects at 10 $\mu\text{g}/\text{kg}/\text{day}$ (Palanza *et al.* 1999, Laviola *et al.* 2005, Gioiosa *et al.* 2007) and other studies reporting effects at $< 1 \text{ mg}/\text{kg}/\text{day}$ (Ceccarelli *et al.* 2007, Ryan *et al.* 2006, Della Seta *et al.* 2006, Negishi *et al.* 2004)
 - Maternal behavior, novelty-seeking, exploration, reward response, anxiety, cognition, and emotional behavior
- Collectively the literature suggest a loss or reduction of sexual dimorphisms in non-reproductive behaviors and in certain regions of the brain
 - Certain behavioral responses and effects at the cellular and molecular levels also suggest an effect on the dopaminergic system



Loss of Sexual Dimorphism (Gioiosa *et al.* 2007)

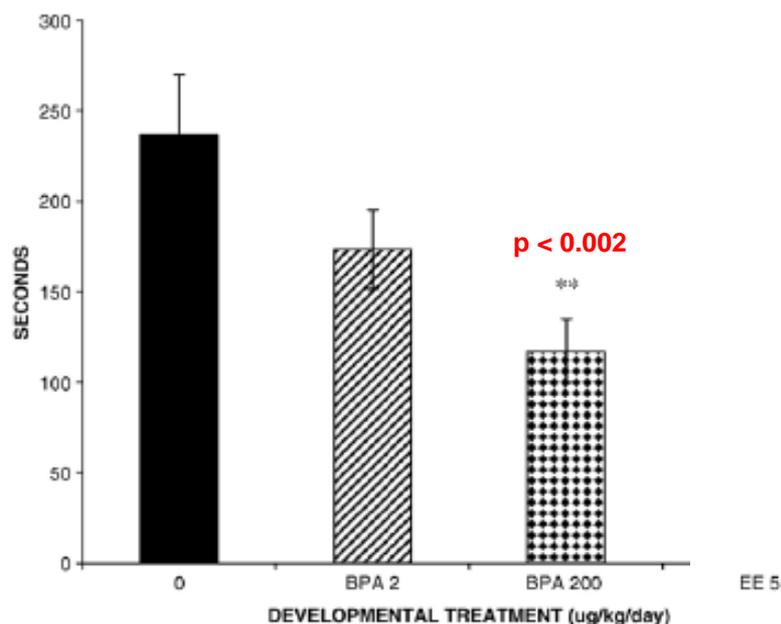
- CD-1 mice
- 10 $\mu\text{g}/\text{kg}/\text{day}$ BPA (oral to dam GD11 - PND8; 15-16 litters/group)
- Open field test
- Loss of sexual dimorphism in exploratory behavior





Anxiety Behavior in Females (Ryan *et al.* 2006)

- C57/Bl-6 female mice
- 2 and 200 $\mu\text{g}/\text{kg}/\text{day}$ BPA (oral to dam GD3 – PND21; 14-16 litters/group)
- Light/Dark chamber
- Increased anxiety behavior at 200 $\mu\text{g}/\text{kg}/\text{day}$ BPA



Light/Dark Chamber: Time spent in light chamber



Brain and Behavior – Reproducibility

- Difficult to evaluate reproducibility of specific effects
- Effects would not have been detected in guideline compliant multigenerational studies
 - Behavior not assessed (Tyl *et al.* 2002 & 2008)
 - Rat multigenerational study by Ema *et al.* 2001 did include neurobehavioral endpoints
 - No behavioral effects of BPA reported
 - Did not cover endpoints affected in academic studies



Brain and Behavior – Data Limitations

- Adverse consequences of effects unclear
- Relevance for human health also uncertain

Note:

- Key studies were considered of “high utility” by the CERHR Expert Panel
 - New study by Gioiosa *et al.* (2007) had characteristics of a “high utility” study



Weight of Evidence for Brain and Behavior

- **Effects reported in several well-conducted “low” dose studies**
- **Endpoints not included in guideline studies**

-
- **Uncertain adversity**
 - **Uncertain human relevance**

Clear evidence of adverse effects

Some evidence of adverse effects

Limited evidence of adverse effects

Insufficient evidence for a conclusion

Limited evidence of no adverse effects

Some evidence of no adverse effects

Clear evidence of no adverse effects



CERHR Expert Panel

- The NTP concurs with the CERHR Expert Panel conclusion of “some concern” for neural and behavioral effects in exposed pregnant women and fetuses, infants, and children
 - Conclusion strengthened by new data

Serious concern for adverse effects

Concern for adverse effects

Some concern for adverse effects

Minimal concern for adverse effects

Negligible concern for adverse effects



Questions and Discussion