



Prenatal exposure to an environmentally relevant phthalate mixture accelerates reproductive aging in multiple generations of female mice

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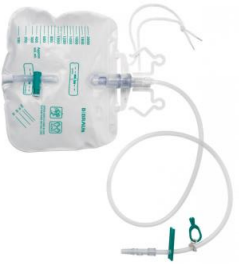
Introduction

- Background
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- Experimental Design
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- Acknowledgements



Phthalates

- Phthalates are ubiquitously used in many consumer products including medical bag and IV tubing, PVC pipes, children's toys, food storage containers, and personal care products
- Daily exposure via ingestion, inhalation, and dermal contact



Phthalates are Known Endocrine Disrupting Chemicals

- Males
 - Decreased sperm quality
 - Delayed preputial separation
 - Reduced anogenital distance
- Females
 - Accelerated primordial follicle recruitment
 - Disrupted estrous cyclicity
 - Inhibited ovarian steroidogenesis



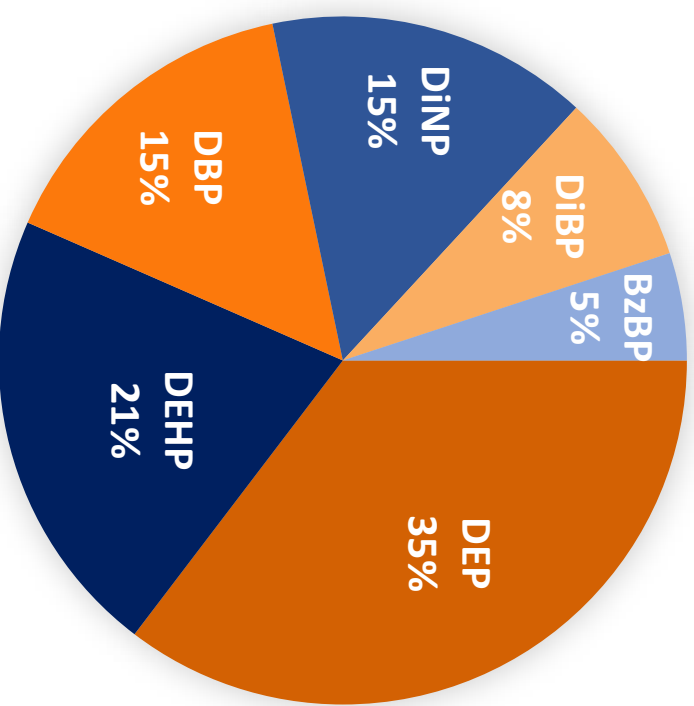
Single Phthalate vs. Phthalate Mixture

- Many studies focus on single phthalate exposure
- Humans are exposed to mixtures of chemicals, including phthalates



Phthalate Mixture

- DEP: Diethyl Phthalate
- DEHP: Di(2-ethylhexyl) Phthalate
- DBP: Dibutyl Phthalate
- DiNP: Diisononyl Phthalate
- DiBP: Diisobutyl Phthalate
- BZBP: Benzylbutyl Phthalate

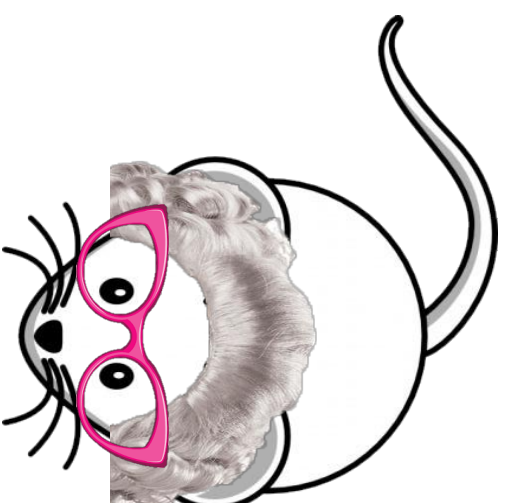


Based on levels detected in the iKids study

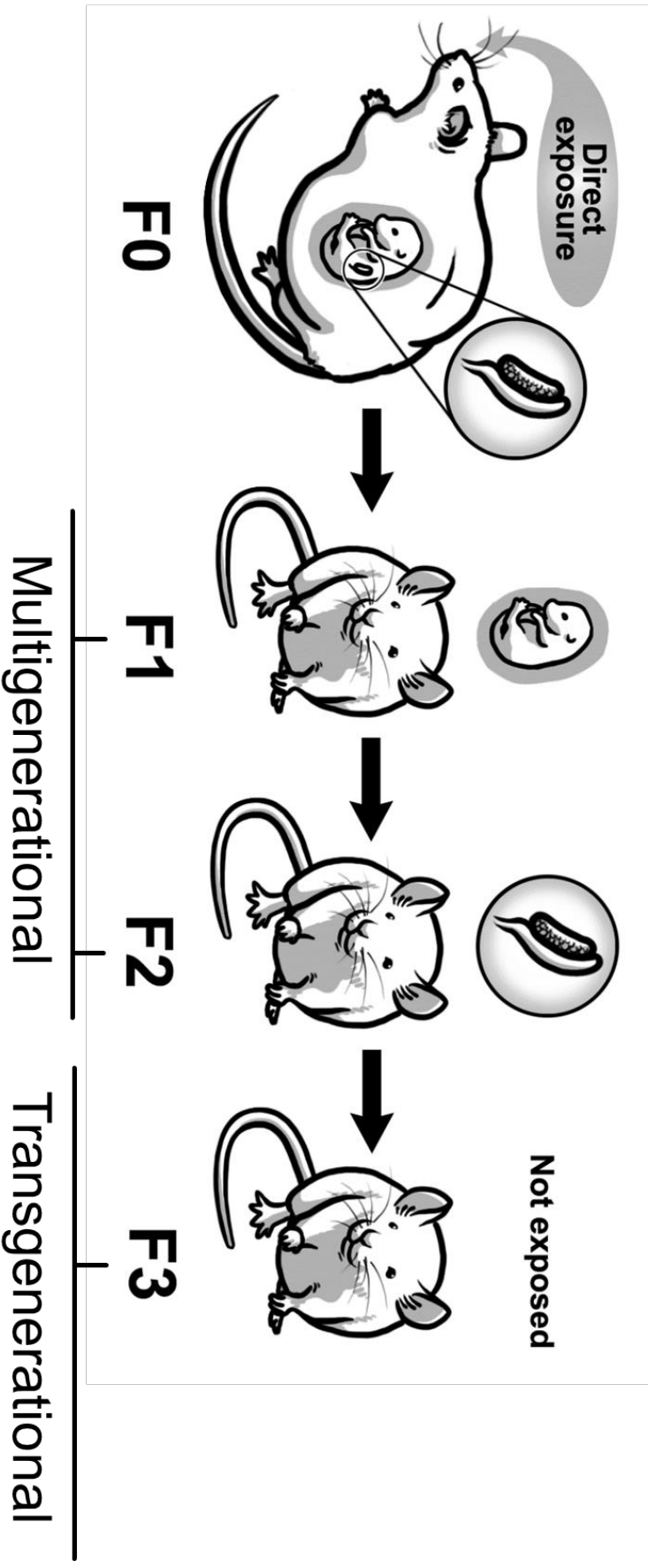


Reproductive Aging in Females

- Normal reproductive aging
 - Depletion of the follicle pool
 - Dysregulation of the hypothalamic-pituitary-gonadal (HPG) axis
 - Acyclicity
 - Decreased fertility
- Ovarian aging
 - Increased inflammation
 - Increased fibrosis
 - Increased reactive oxygen species
 - Increased cysts (rodents)



Transgenerational Exposure



Modified photo courtesy of Katie Chiang

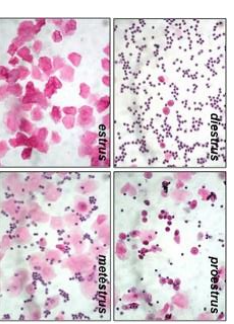
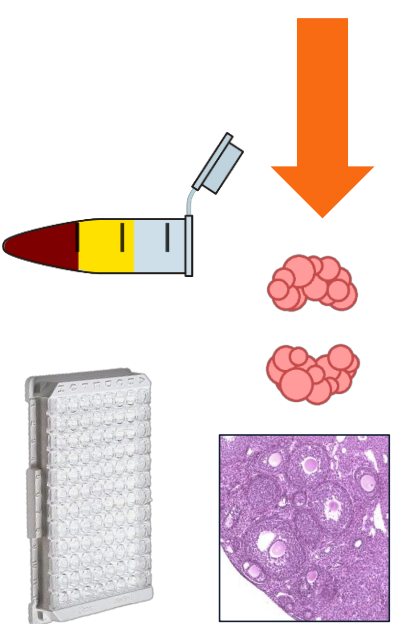
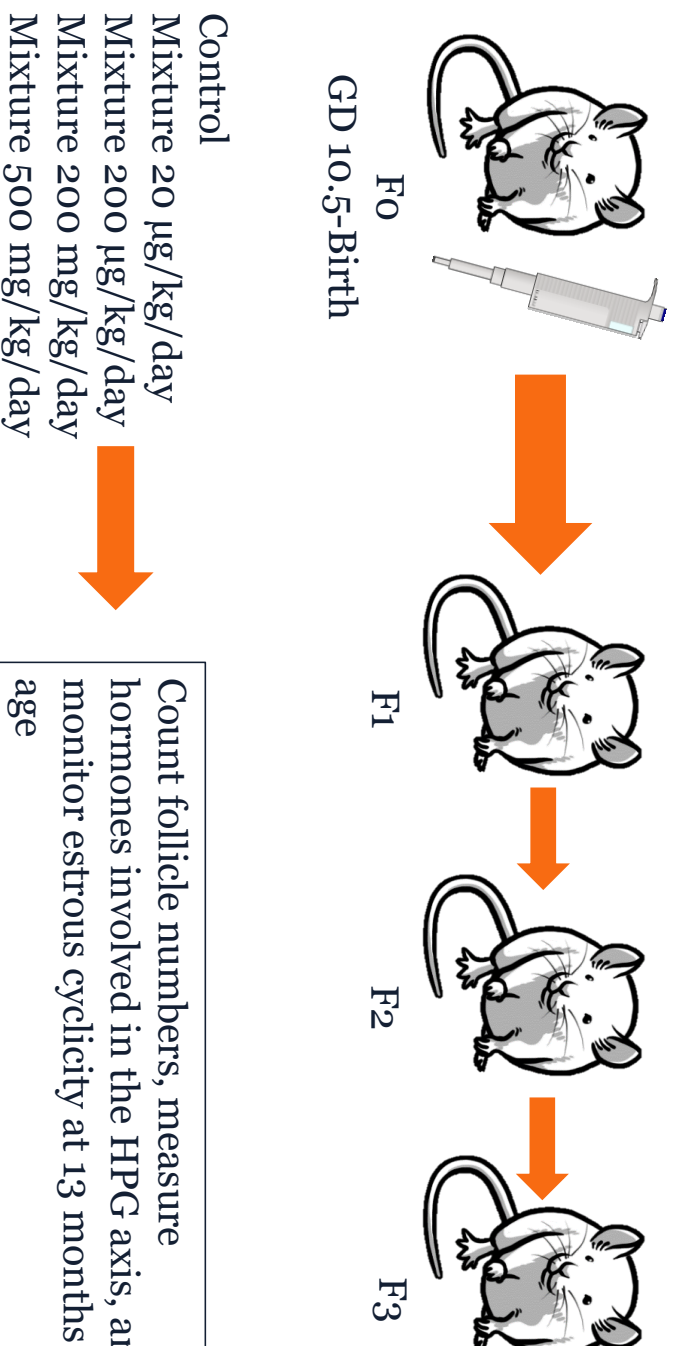


Hypothesis

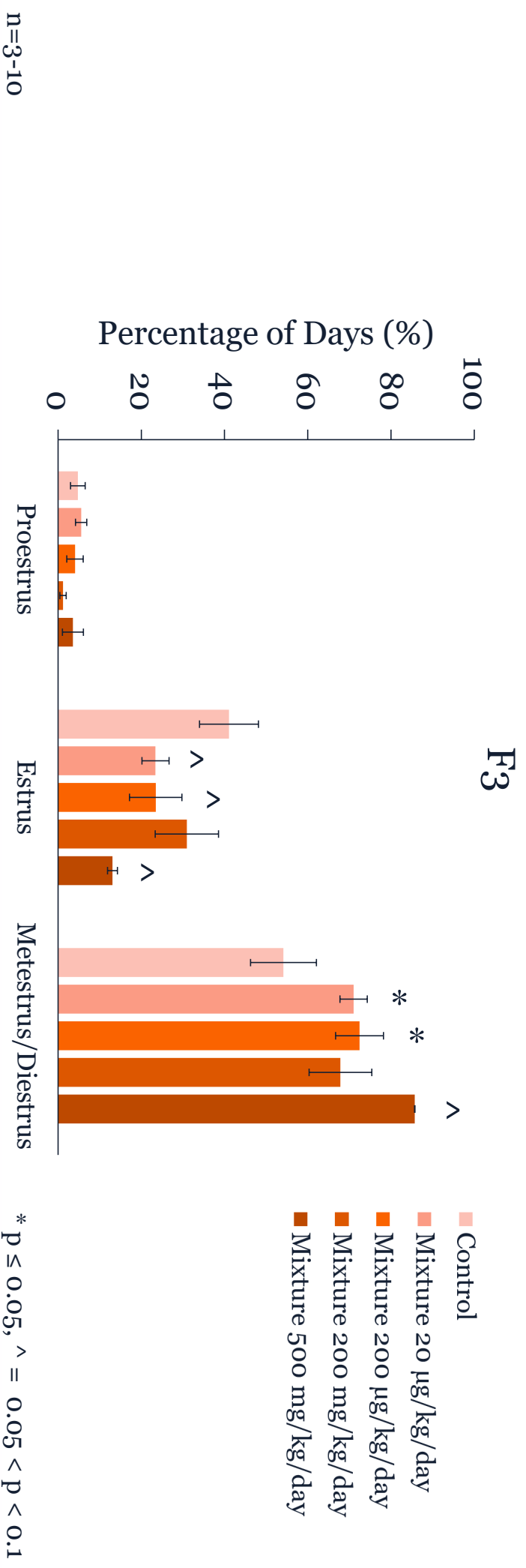
Prenatal exposure to a mixture of phthalates accelerates reproductive aging in multiple generations of female mice.



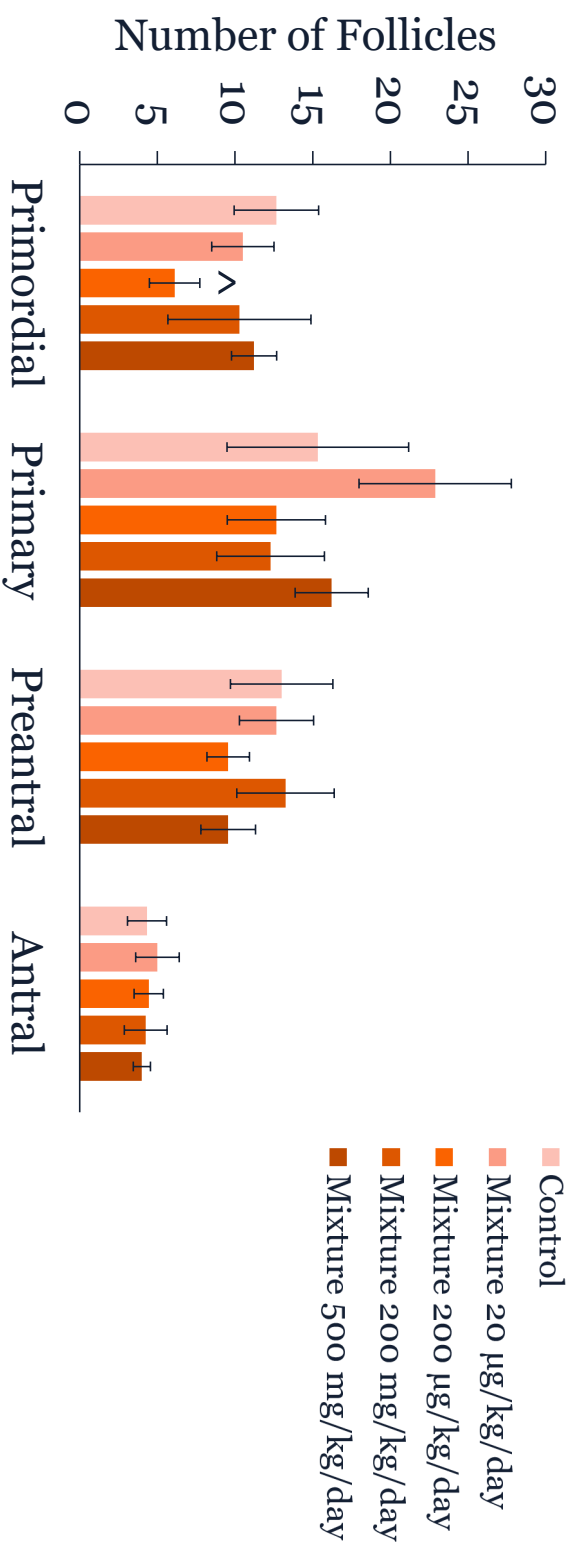
Experimental Design



Phthalate Mixture Caused Irregular Cyclicality in the F3 Generation



Phthalate Mixture May Not Affect Follicle Numbers in the F1 Generation



n=6-9

[^] = 0.05 < p < 0.1



Phthalate Mixture May Increase the Occurrence of Cysts in the F1 Generation

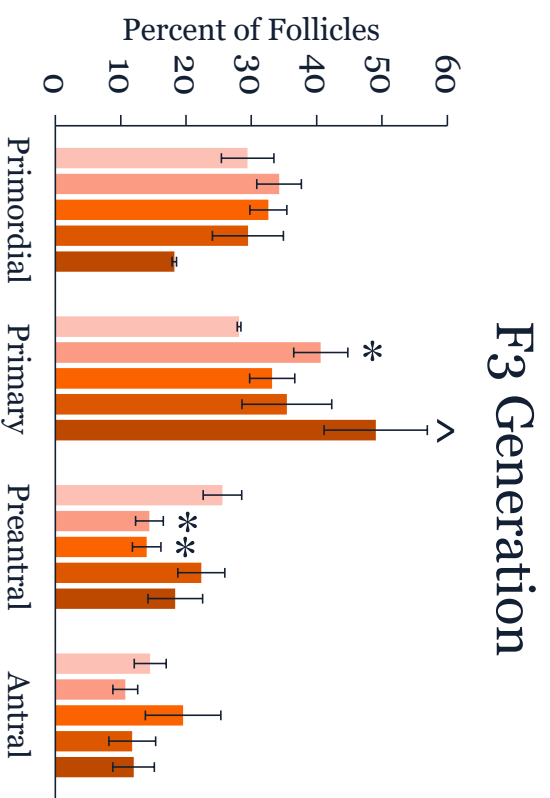
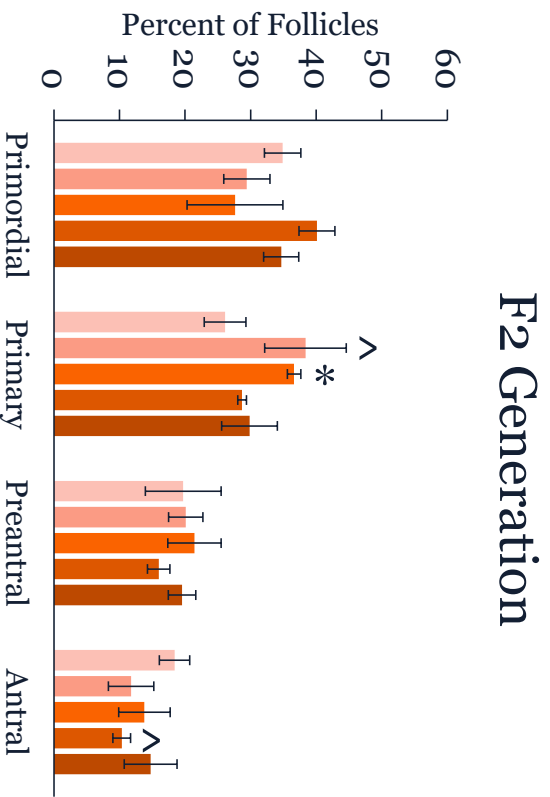


Cystic ovary from mouse prenatally exposed to the phthalate mixture in the F1 generation at 13 months of age.

Treatment	Percent Ovaries with Cysts
Control	33.3
20 µg/kg/day	55.6
200 µg/kg/day	77.8
200 mg/kg/day	62.5
500 mg/kg/day	55.6



Phthalate Mixture Altered Folliculogenesis in the F2 and F3 Generations



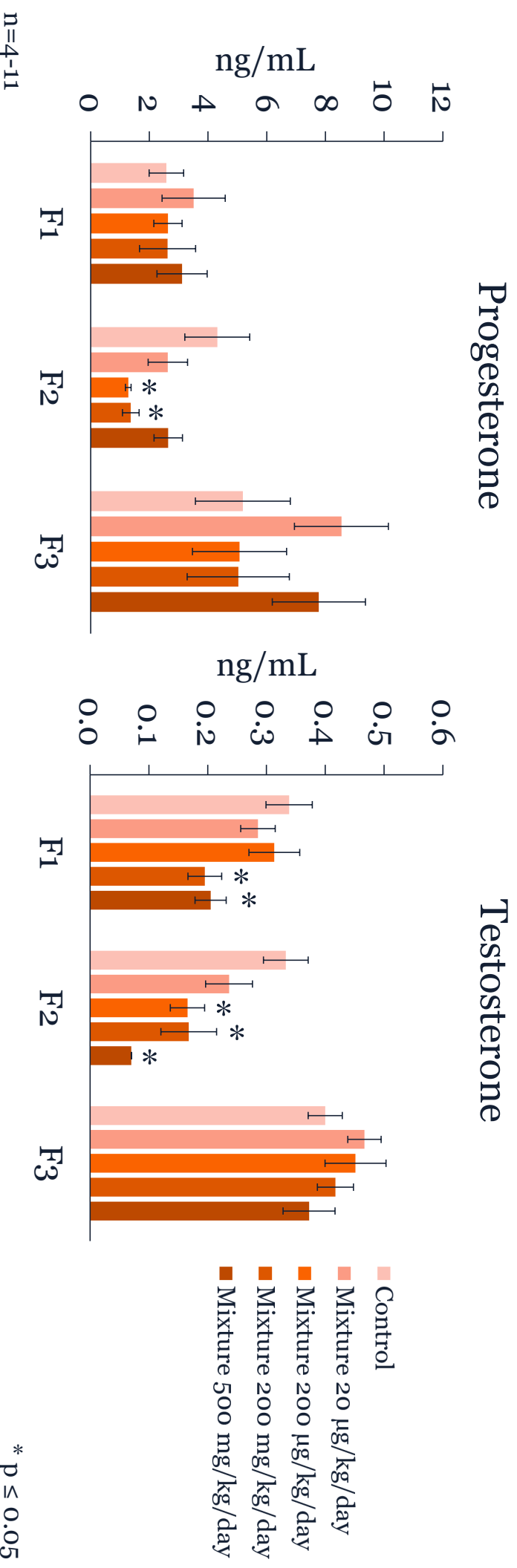
- Control
- Mixture 20 µg/kg/day
- Mixture 200 µg/kg/day
- Mixture 200 mg/kg/day
- Mixture 500 mg/kg/day

* p ≤ 0.05, ^ = 0.05 < p < 0.1

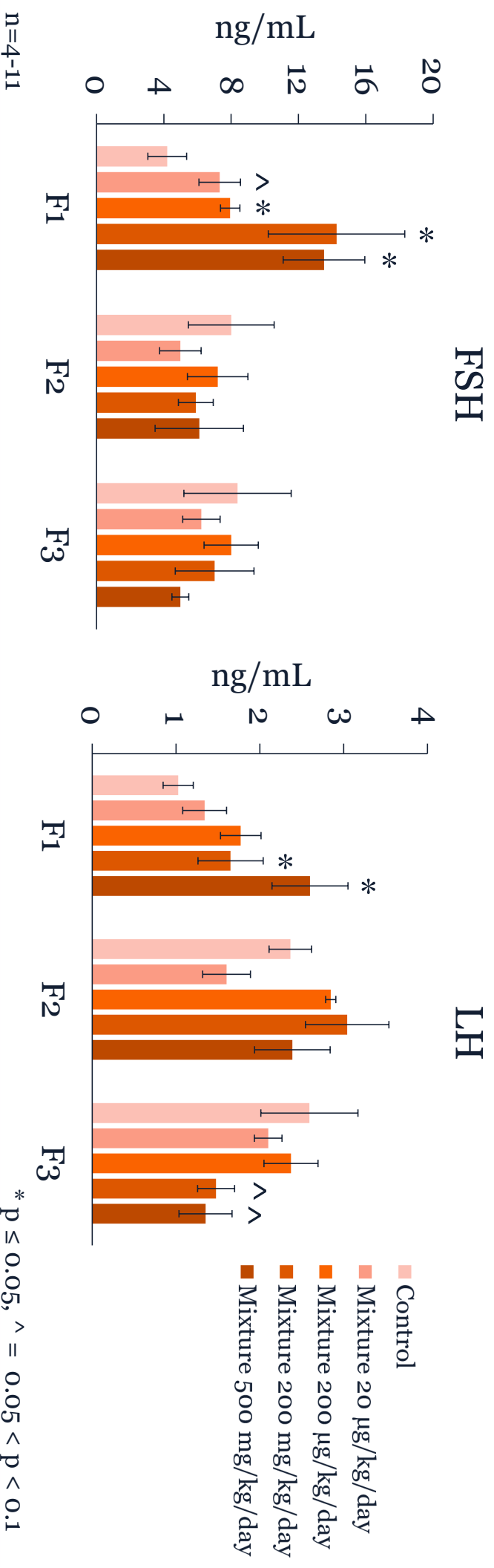
n=3-4



Phthalate Mixture Decreased Sex Steroids in the F1 and F2 Generations

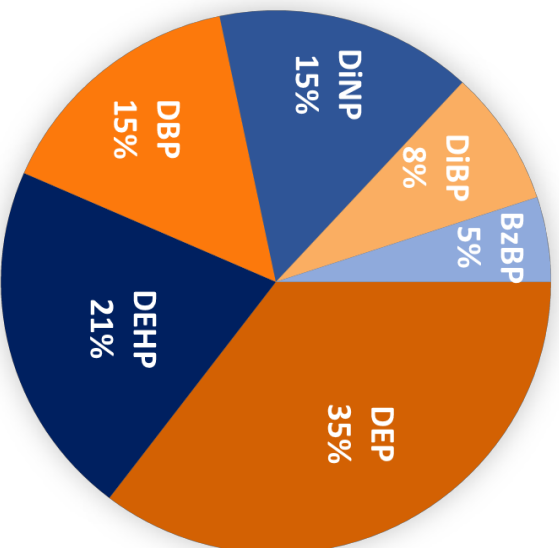


Phthalate Mixture Altered Gonadotropins in the F1 and F3 Generations

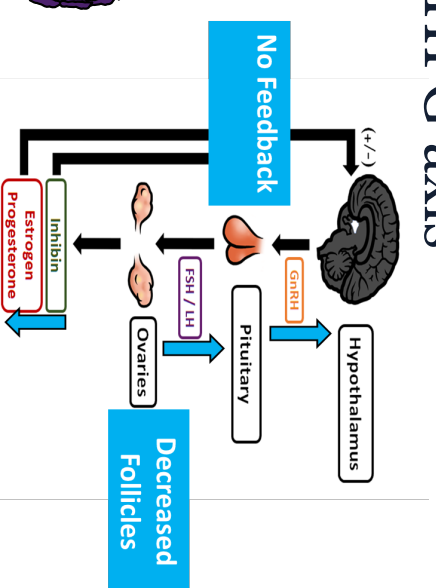
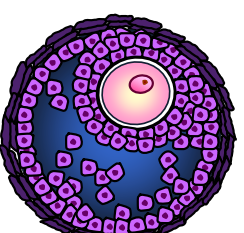


Overall

Summary



- Phthalate mixture accelerates some biomarkers of reproductive aging:
- Increased time spent in metestrus/diestrus
- Altered follicle pool
- Dysregulation of the HPG axis



Conclusion

Prenatal exposure to an environmentally relevant phthalate mixture accelerates some biomarkers of reproductive aging in a multi- and transgenerational manner in female mice.



Future Directions

Determine if phthalates:

- Accelerate the aging of the ovary by increasing fibrosis, reactive oxygen species, and inflammation
- Accelerate the decline in reproductive capacity by causing acyclicity and decreasing fertility quicker than controls



Acknowledgments

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