

The mammary gland is a sensitive organ: lessons learned from UOG chemical mixtures

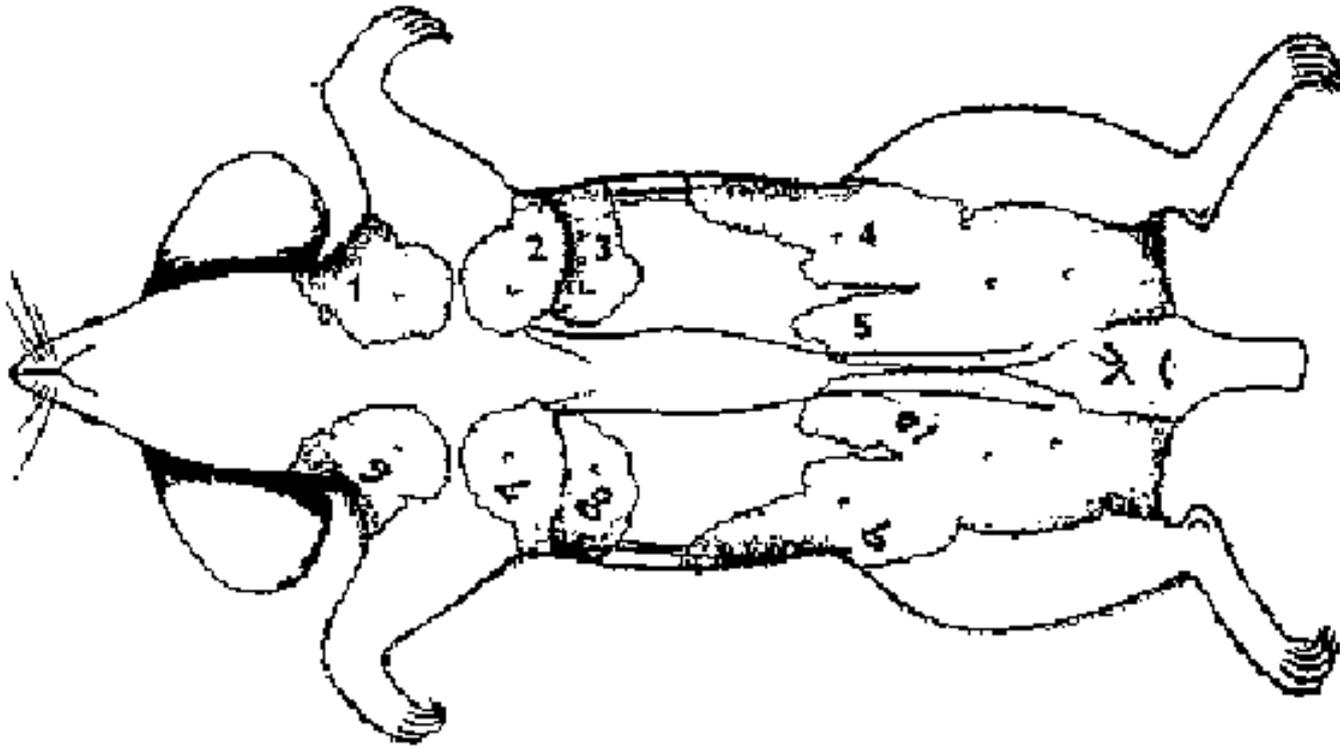
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Assistant Professor

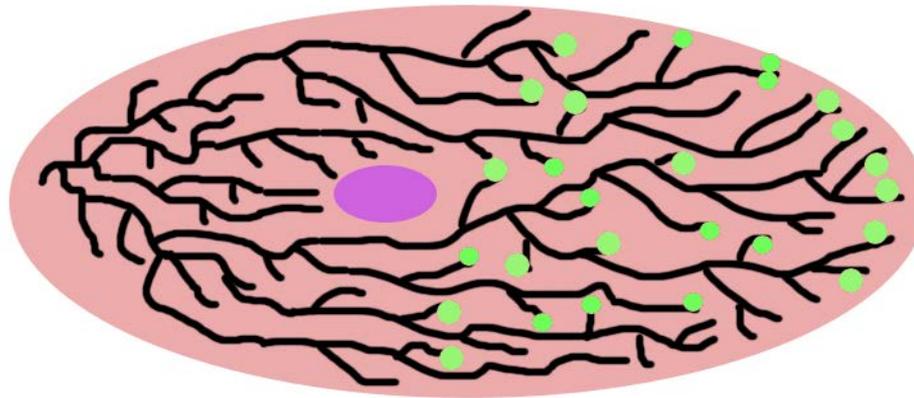
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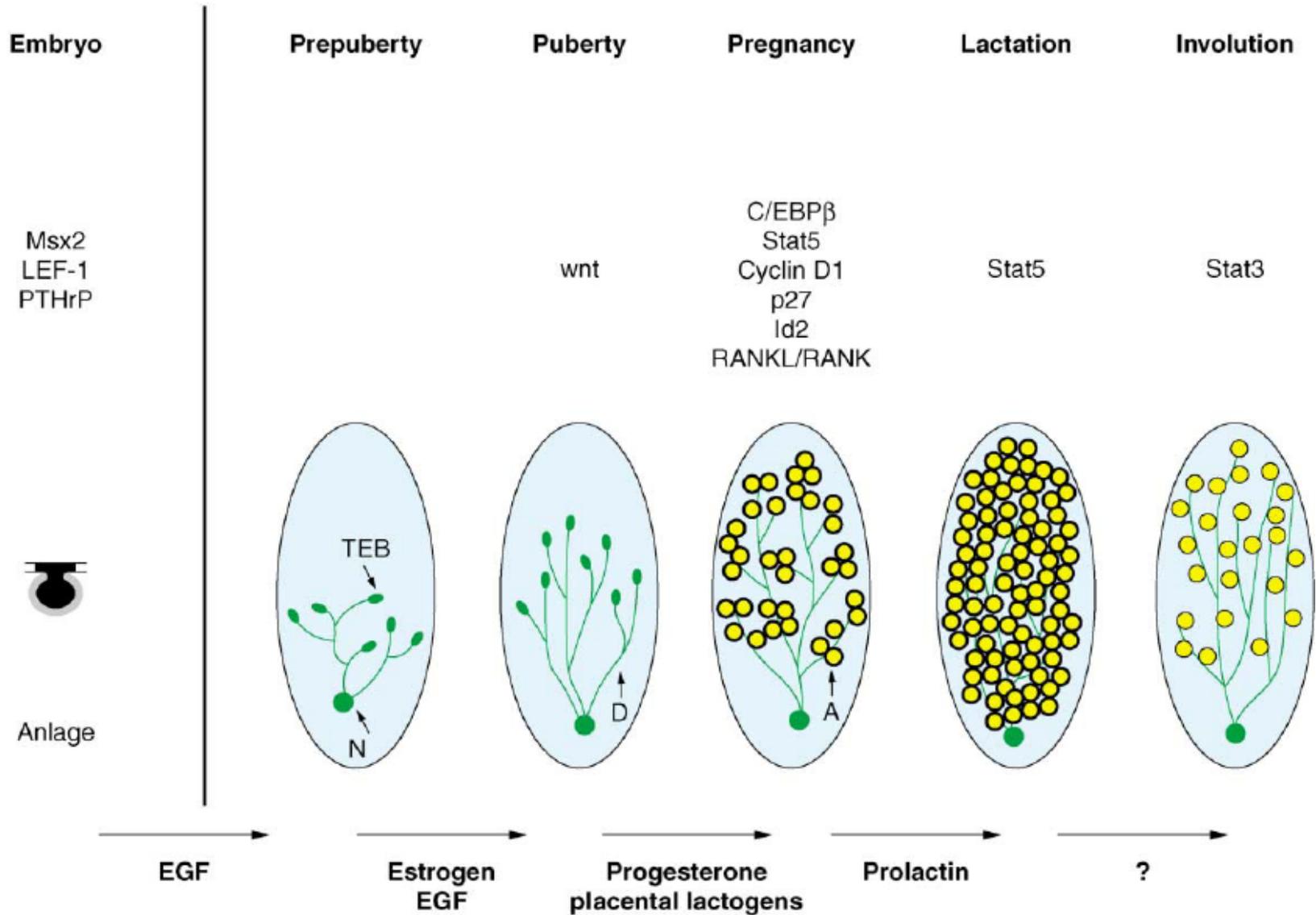
The mouse mammary gland



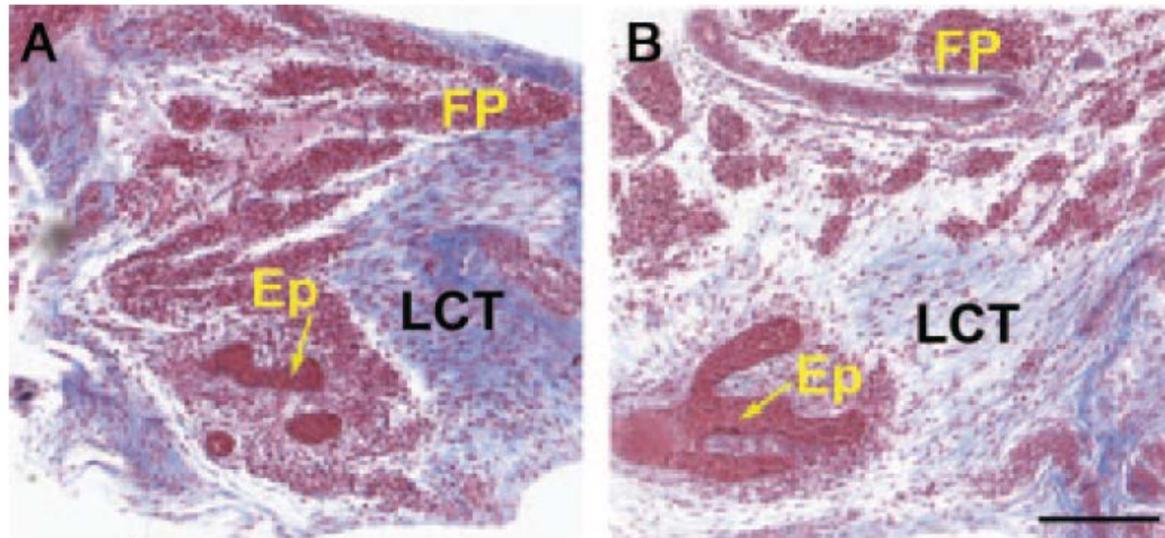
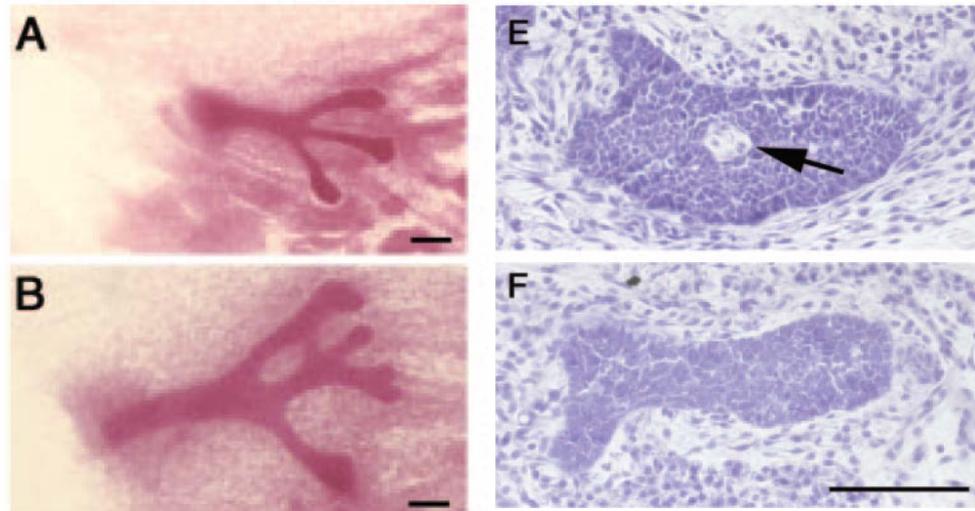
The mouse mammary gland



Identifying sensitive windows

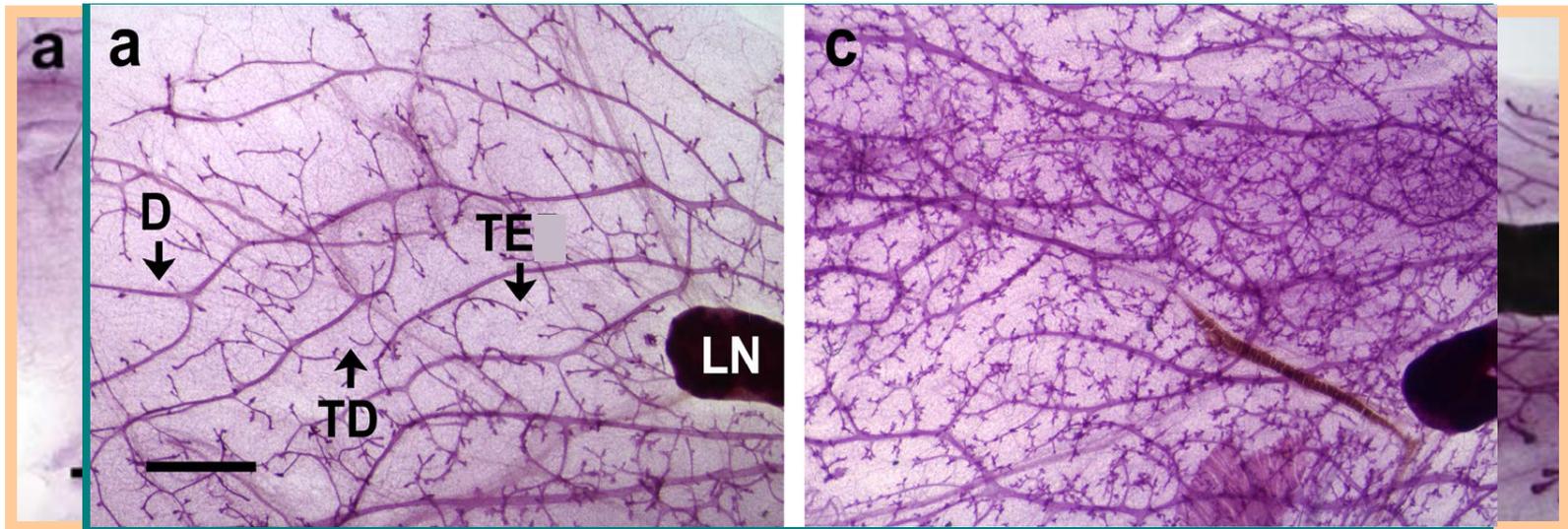


BPA alters the mammary gland during the period of exposure



Prenatal BPA exposure alters mammary gland development

Postnatal Day 30

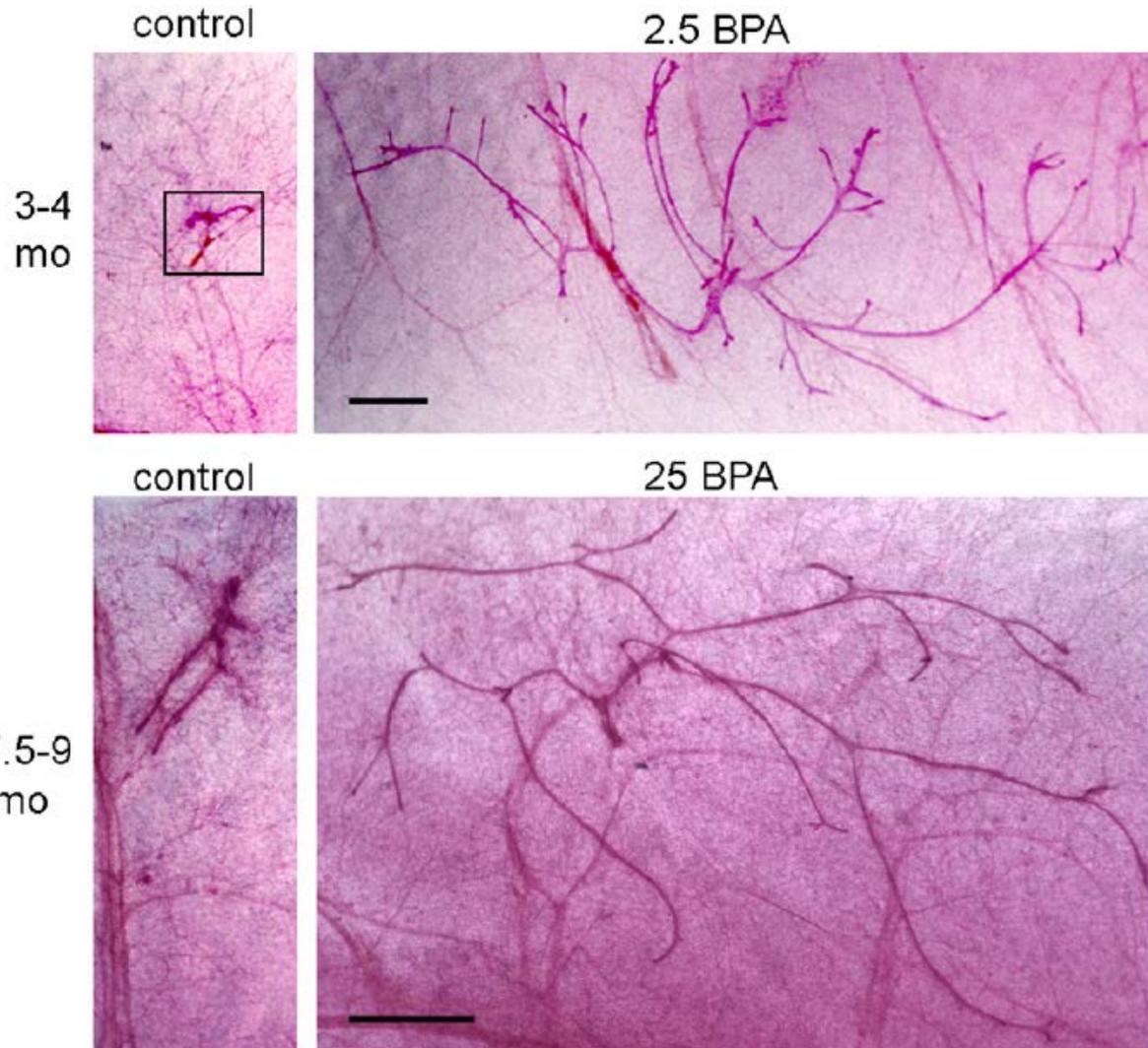


Control

BPA

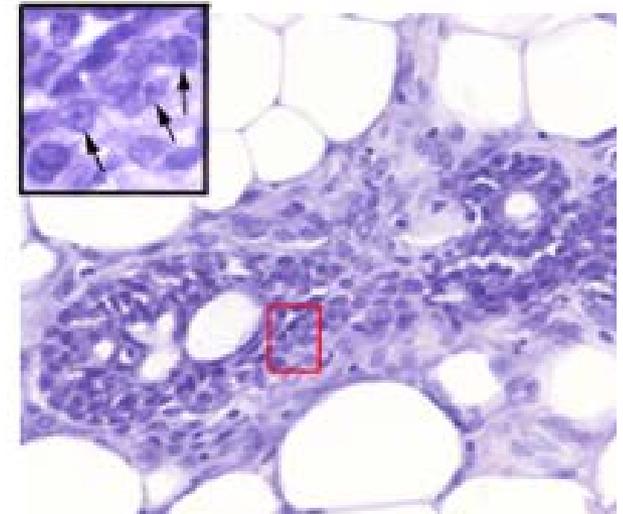
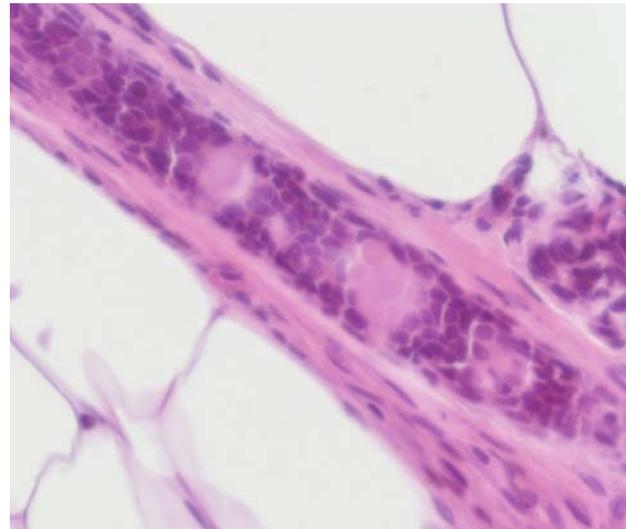
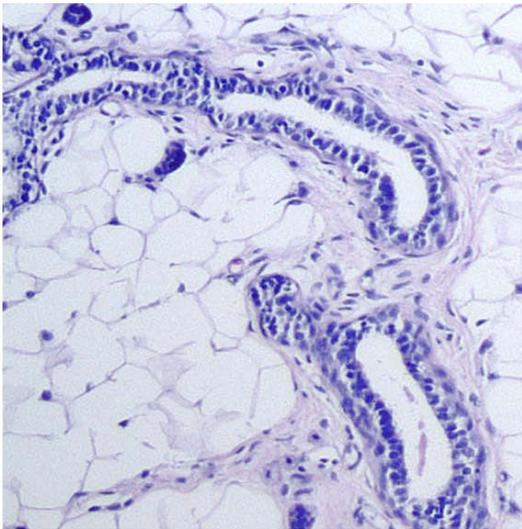
All of these effects manifested long after the period of exposure.

BPA also disrupts development of the male mammary gland



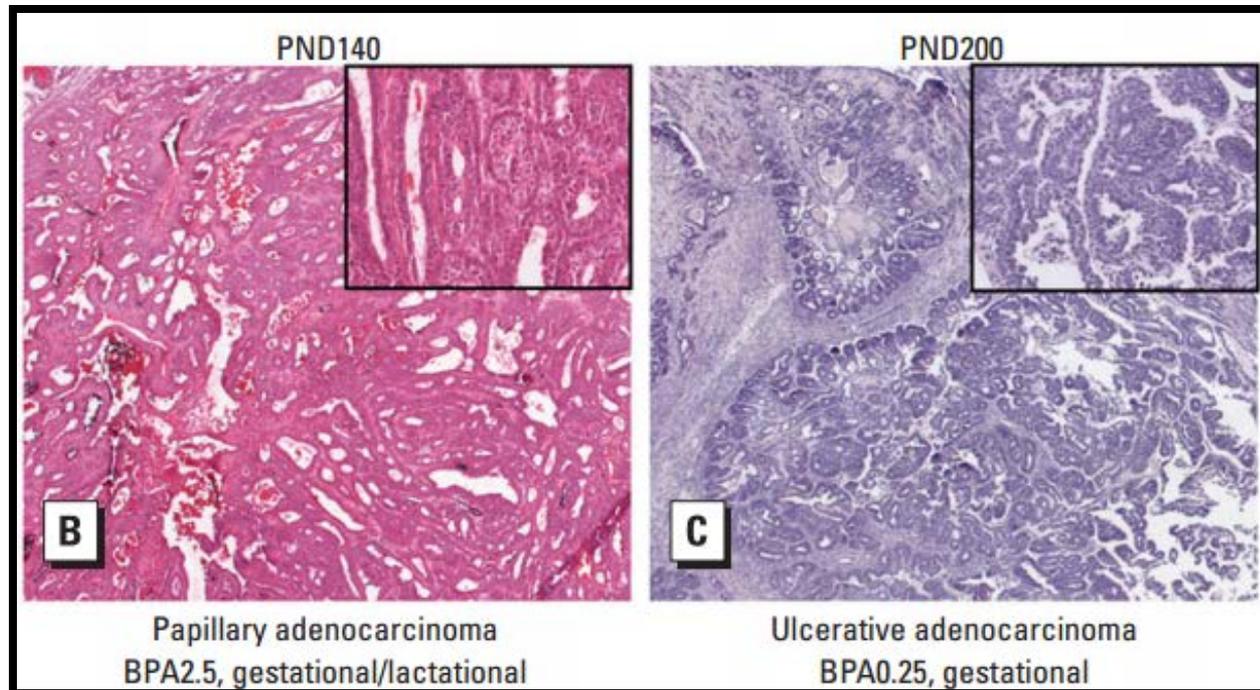
Perinatal exposure to BPA induces mammary gland lesions

- 1- mice developed pre-cancerous lesions
- 2- rats developed pre-cancerous lesions & carcinoma *in situ*

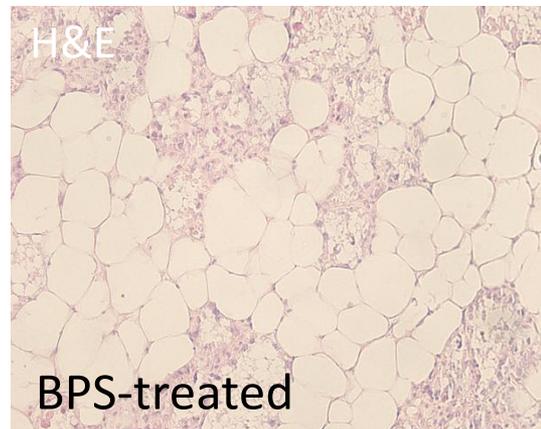
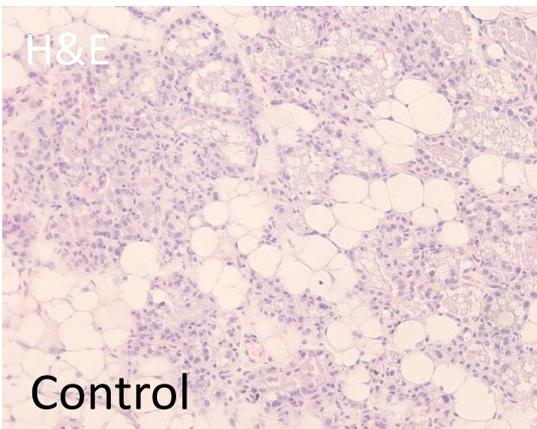
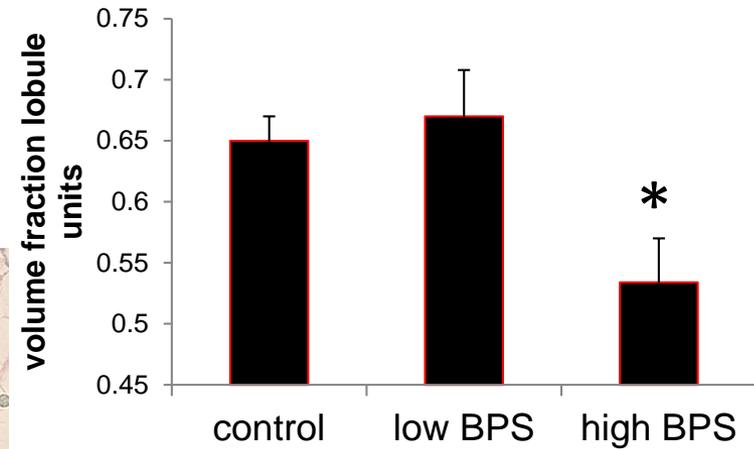
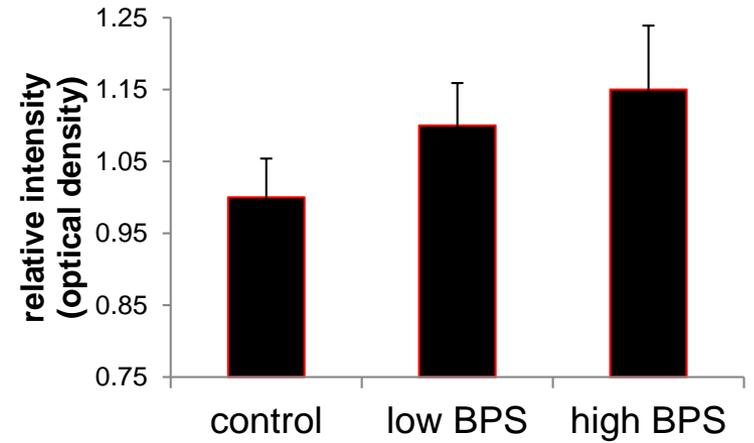


Murray et al. 2007, Vandenberg et al. 2008

BPA can induce frank carcinomas



BPS alters the lactating mammary gland

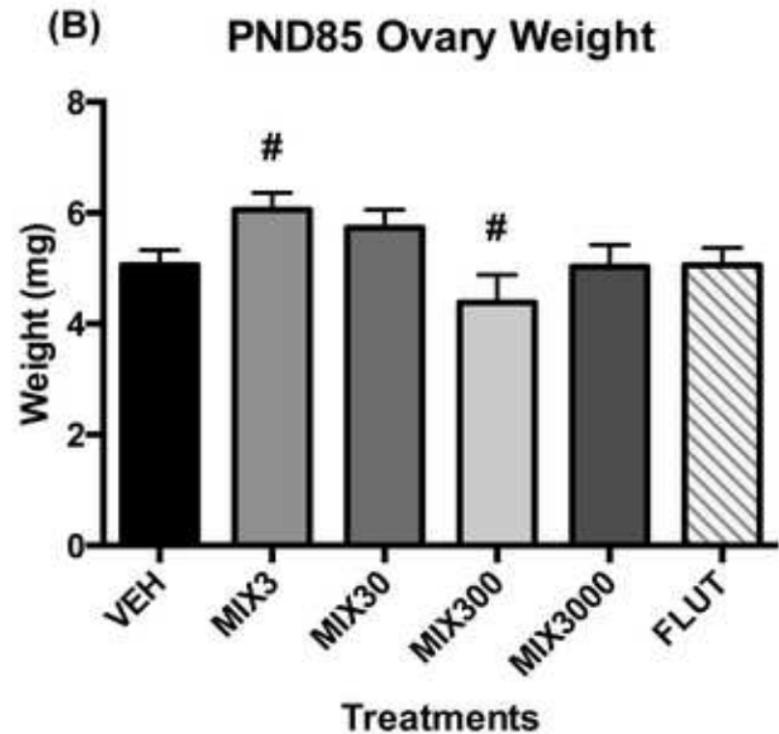
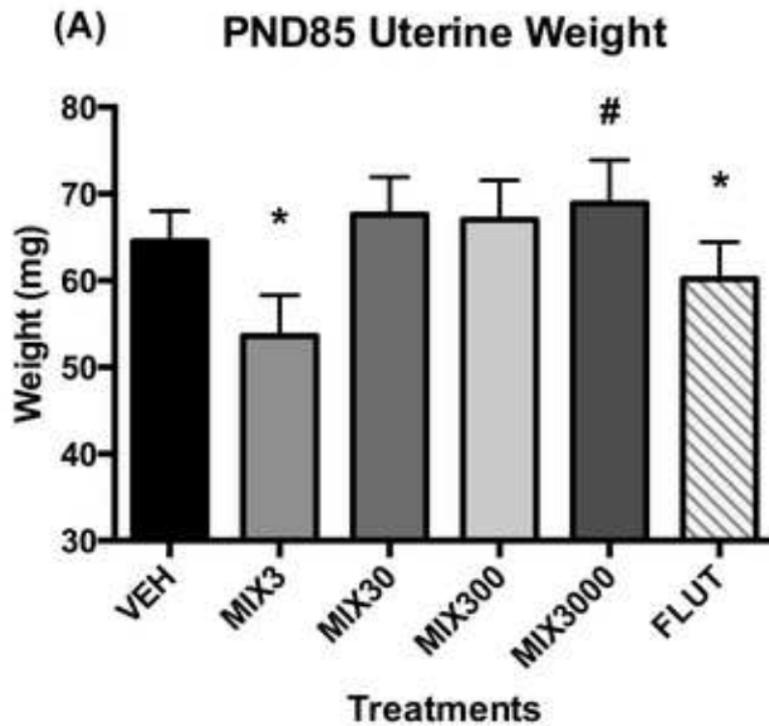


The mouse mammary gland: a sensitive tissue to probe chemical mixtures?

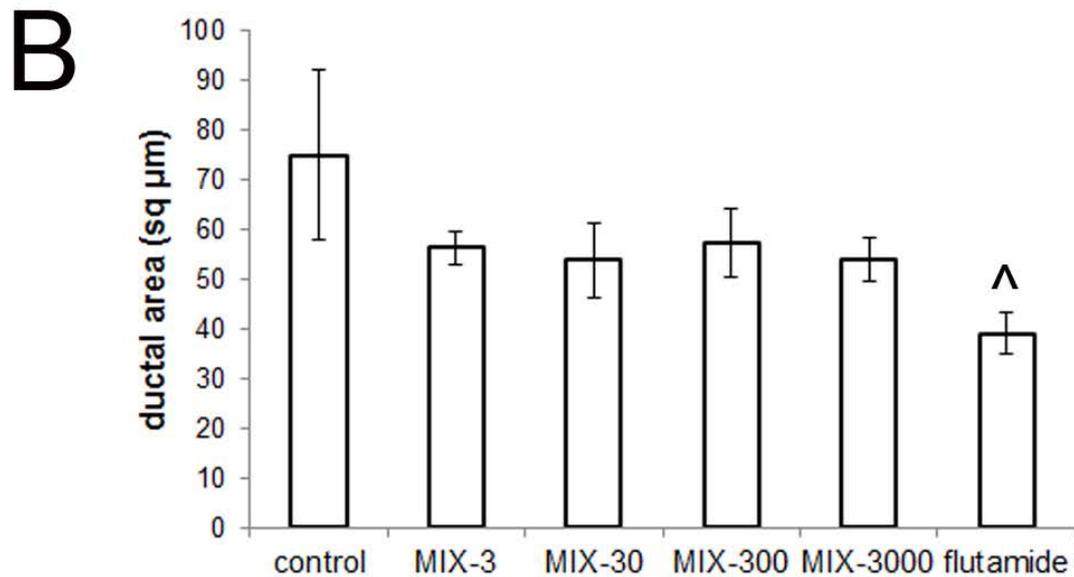
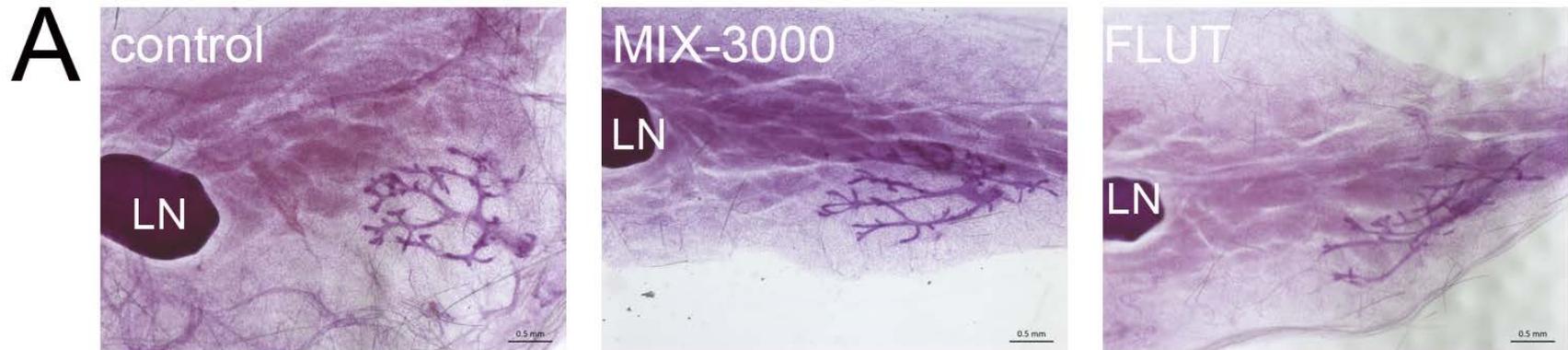
- Pregnant female mice exposed from pregnancy day 11 through parturition
- Mixture: 23 commonly used chemicals from unconventional oil/gas operations
- 3, 30, 300 and 3000 $\mu\text{g}/\text{kg}/\text{day}$
- Females evaluated at prepuberty (PND21) and early adulthood (PND85)

Chemical Name	Receptor Antagonist Activity				
	ER	AR	PR	TR	GR
1,2,4-Trimethylbenzene					
2-(2-Methoxyethoxy) ethanol	X	X			X
2-Ethylhexanol	X	X	X		X
2-Methyl-4-isothiazolin-3-one	X	X			X
Acrylamide		X			
Benzene	X	X			
Bronopol	X	X	X		X
Cumene	X	X	X		
Diethanolamine	X	X	X		
Ethoxylated nonylphenol	X	X	X	X	X
Ethoxylated octylphenol	X	X	X	X	X
Ethylbenzene	X	X			
Ethylene glycol	X	X	X	X	X
Ethylene glycol monobutyl ether	X	X		X	
Naphthalene	X	X	X	X	X
N,n-dimethylformamide	X	X	X		
Phenol	X	X	X		
Propylene glycol	X				
Sodium tetraborate decahydrate	X	X			
Styrene	X			X	X
Toluene	X	X			
Triethylene glycol	X	X			

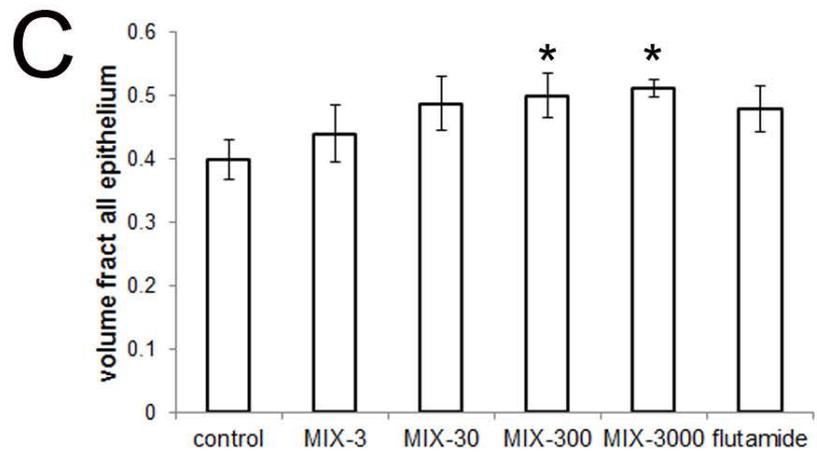
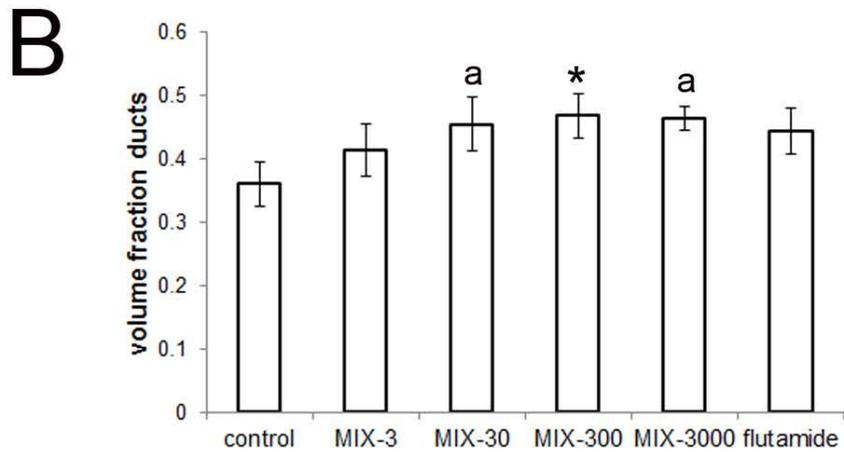
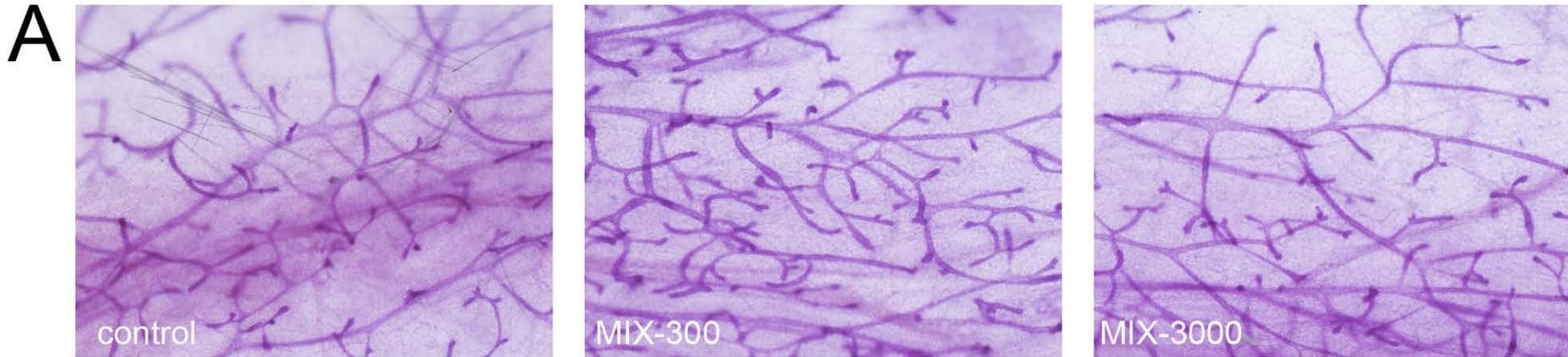
Fracking mixture affects endocrine endpoints in exposed females



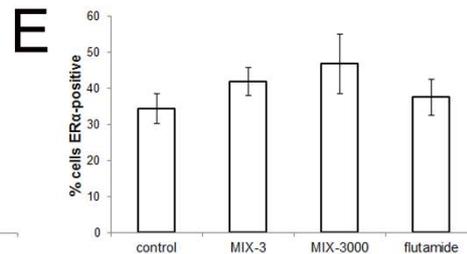
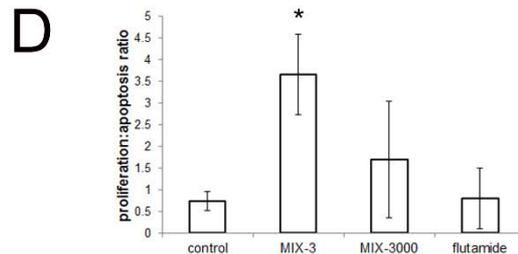
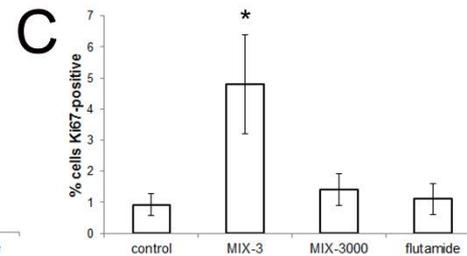
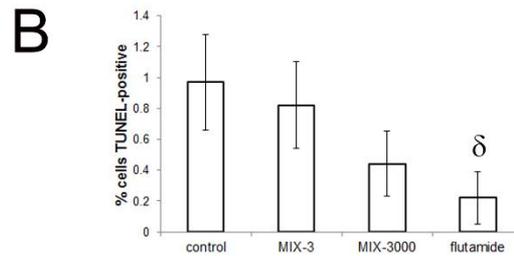
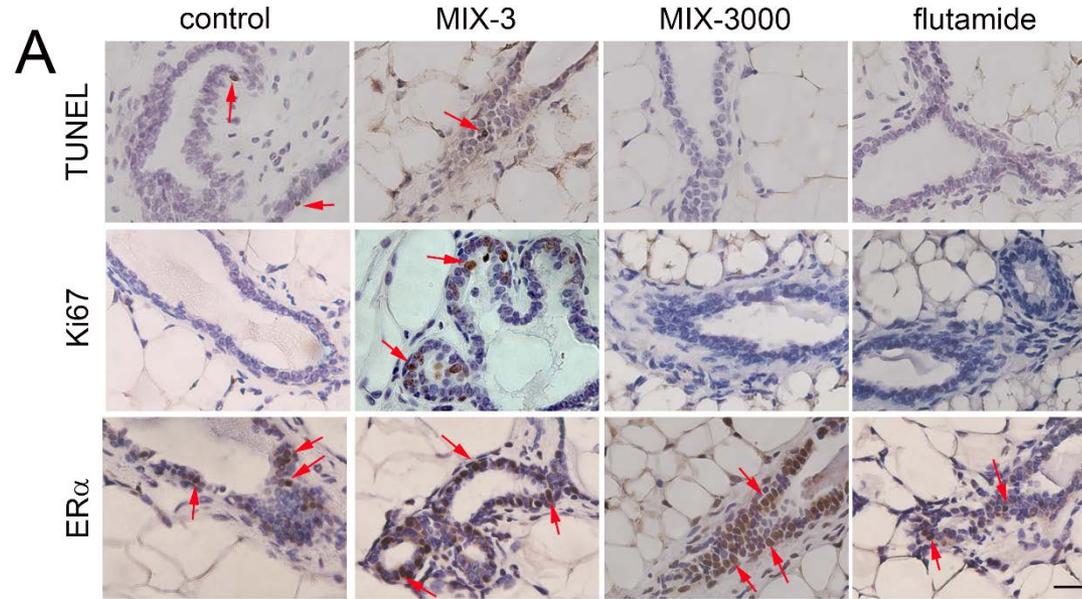
Mammary gland morphology is not affected by UOG mix at pre-puberty



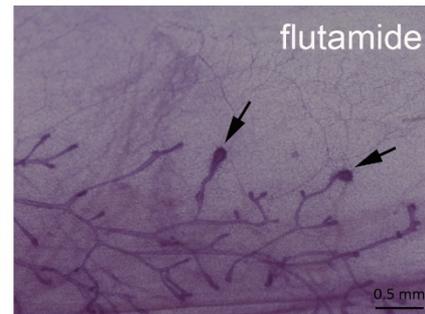
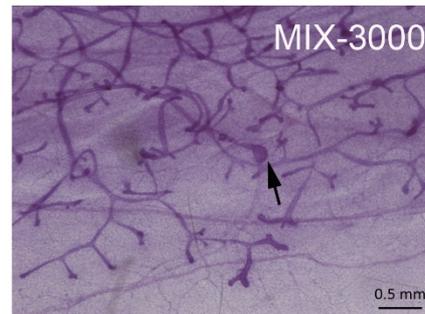
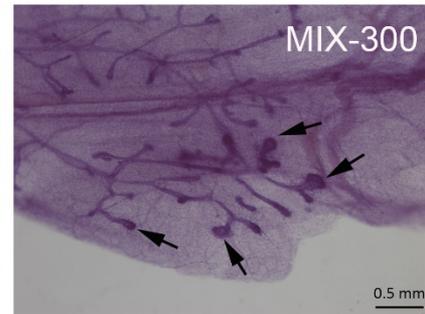
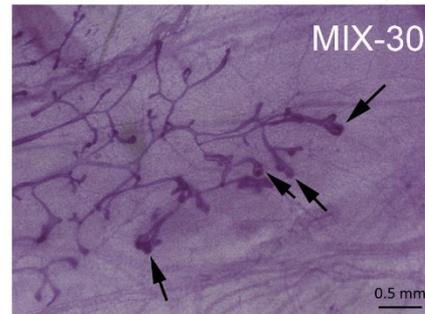
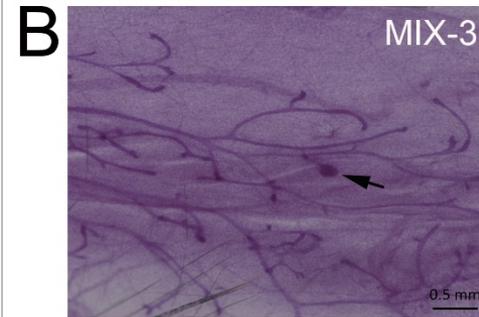
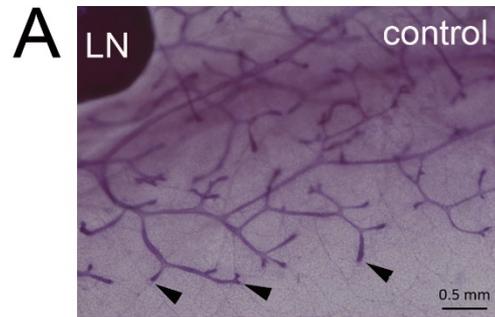
Density of epithelial ducts is significantly increased by UOG mix at PND85



UOG mixtures alter mammary epithelial cell proliferation



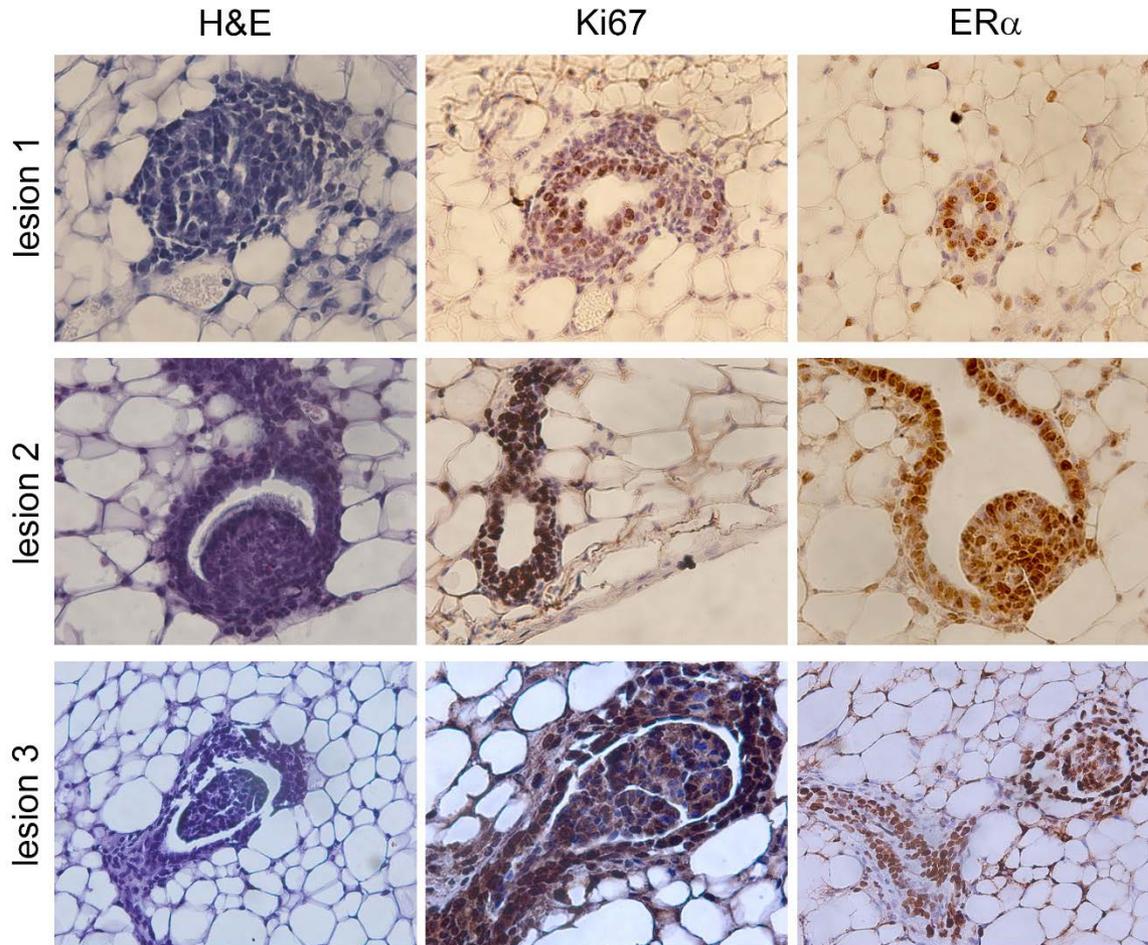
Abnormalities were observed in UOG mix whole mounts



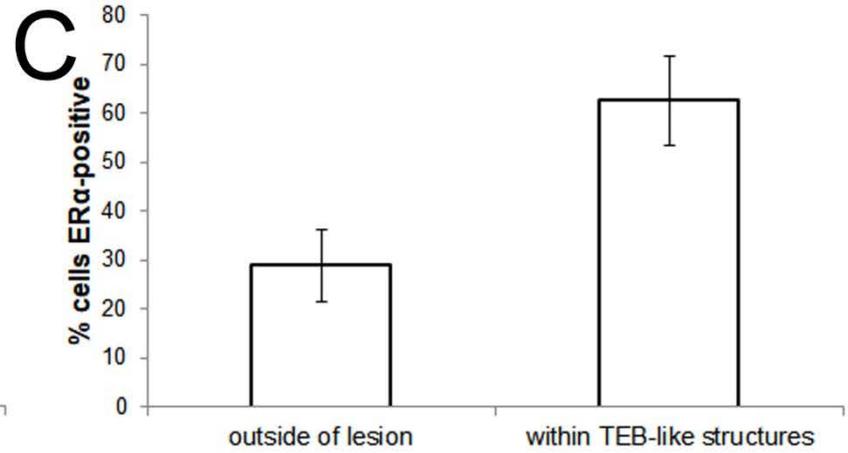
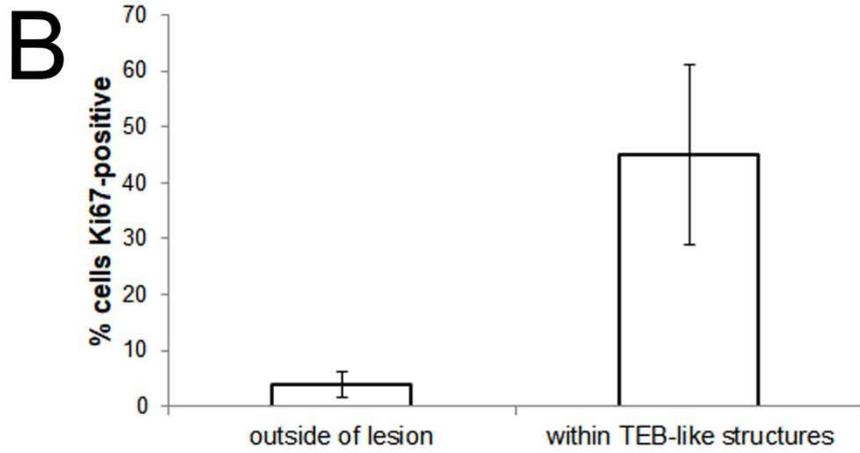
Abnormalities were observed in UOG mix whole mounts

	# with abnormal ends
Control	0/9
MIX-3	2/7
MIX-30	1/6
MIX-300	2/8
MIX-3000	2/5

Mammary lesions are highly proliferative intraductal hyperplasias



Mammary lesions are highly proliferative intraductal hyperplasias



Conclusions

- The mouse mammary gland may serve as a “canary in the coal mine” – a sensitive measure of the effects of endocrine disruptors
- There are a number of different developmental periods when this organ is sensitive to endocrine disruption
- Disruptions can lead to disease (e.g. cancer) or altered function (e.g. lactation)
- The mammary gland is sensitive to complex chemical mixtures such as compounds used in unconventional oil/gas operations

Future Directions

- What are the long-term effects of developmental UOG mixture exposures?
- Do UOG mixtures influence the mammary gland's sensitivity to chemical carcinogens? To hormones?
- Do exposures to UOG mixtures alter the function of the mammary gland (e.g., milk production, milk composition)?

Acknowledgements

Mary Catanese
Corinne Hill
Sarah Sapouckey
Charlotte LaPlante
Durga Kolla
Aastha Pokharel
Mary Morcos
Brian Martin
Danny McSweeney
Archana Gopal
Shawn Hallett
Michael Lemieux
Aastha Pokharel
D'Andre Quinerly
Deb Pimentel
Anupama Singh
Lauren Masse
Meg Bernier
Alfred Kimani
Alison Bowler

Susan Nagel
Chris Kassotis
Sasha Suvorov
Joe Jerry
Karen Dunphy
Sallie Schneider

Ana Soto
Beverly Rubin
Maricel Maffini
Perinaaz Wadia
Cheryl Schaeberle

