Low dose effects of cadmium on puberty onset

Mary Beth Martin

Georgetown University

Lombardi Comprehensive Cancer Center

Estrogen like effects of cadmium

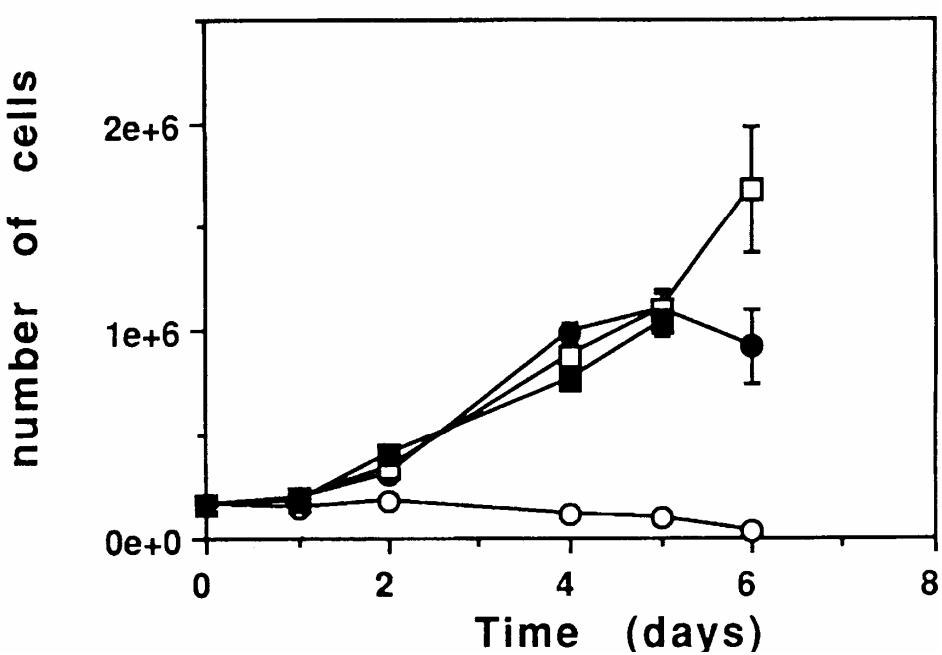
In the human breast cancer cells (MCF-7 cells):

- decreases the expression of ER-α
- increases the expression of PR, pS2, and cathepsin D
- induces cell growth

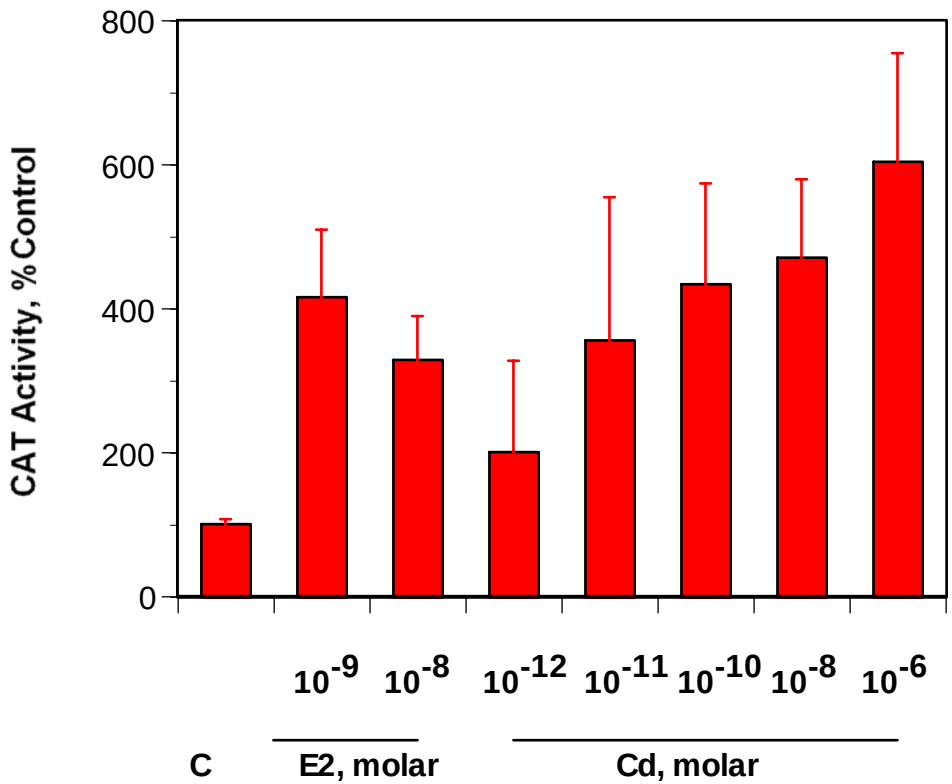
In transient transfection assays:

- activates ER-α

Effect of cadmium on the growth of MCF-7 cells



Effects of cadmium on ER-α activation

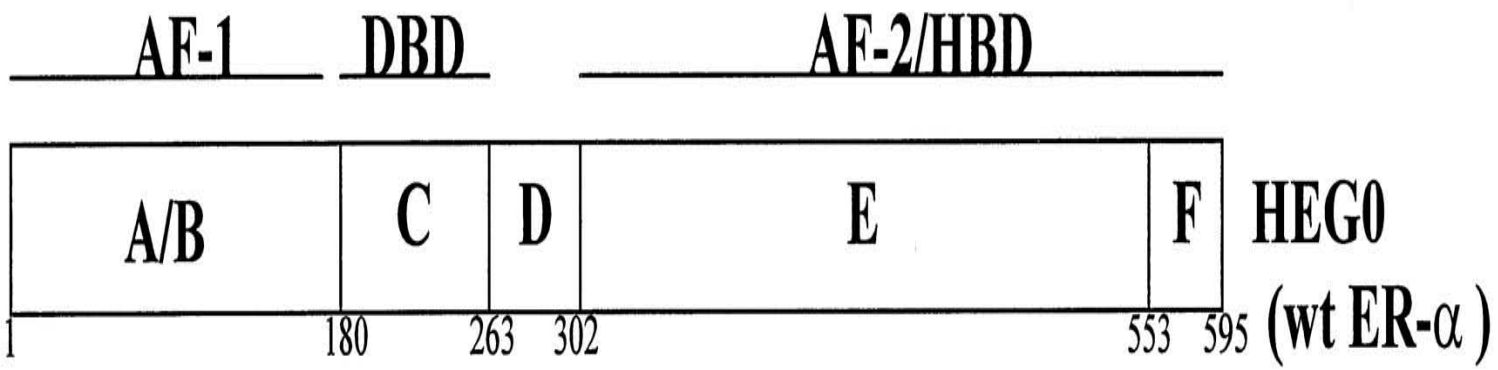


Goals

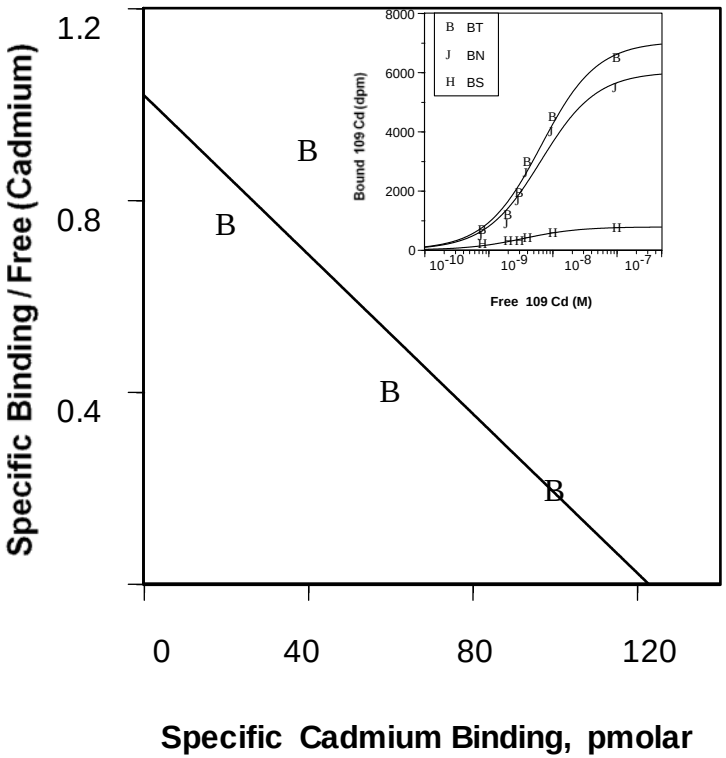
- Determine the mechanism by which cadmium activates estrogen receptor-α
- Determine whether environmentally doses of cadmium have estrogen like activity in animal models

Potential Mechanisms of Activation

- Activates the protein kinase c signal transduction pathway
- Replaces zinc in the DNA Binding Domain
- Interacts with the Hormone Binding Domain
    - Cadmium binds to ER-α
    - Cadmium blocks estradiol binding
    - Cadmium activates through the HBD
    - Identify the interaction site



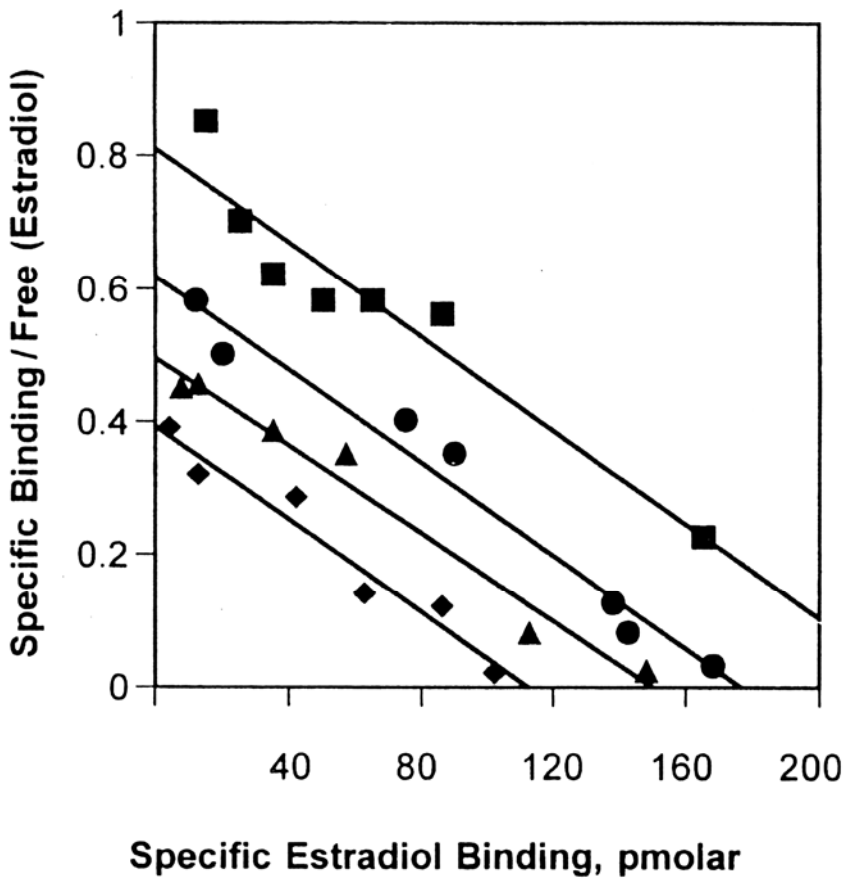
Binding of ^{109}Cd to rER-α



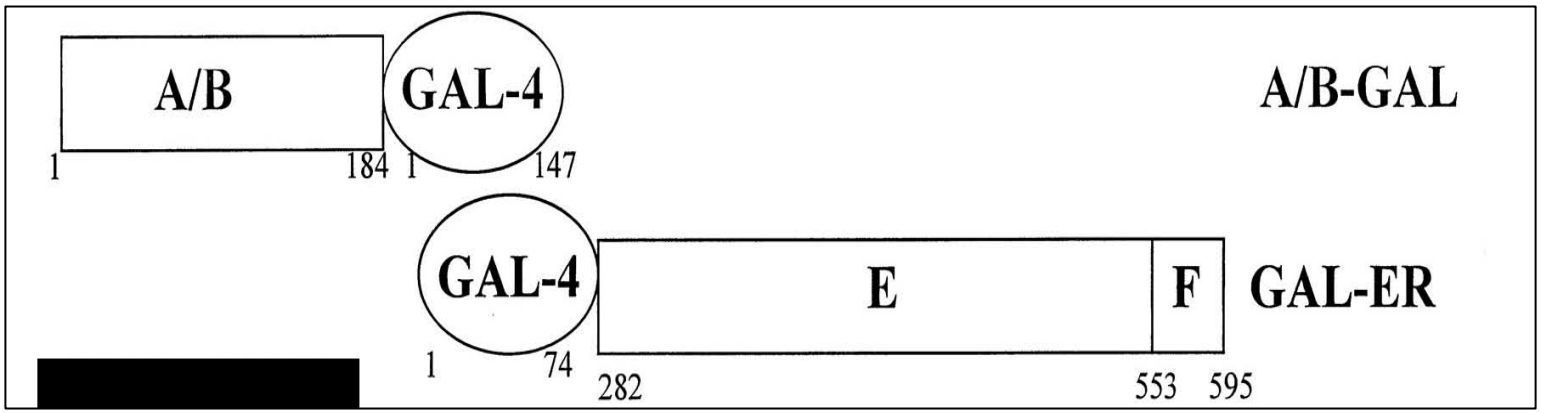
- $K_d = 5 \times 10^{-10}$ M

Effect of Cd on estradiol binding

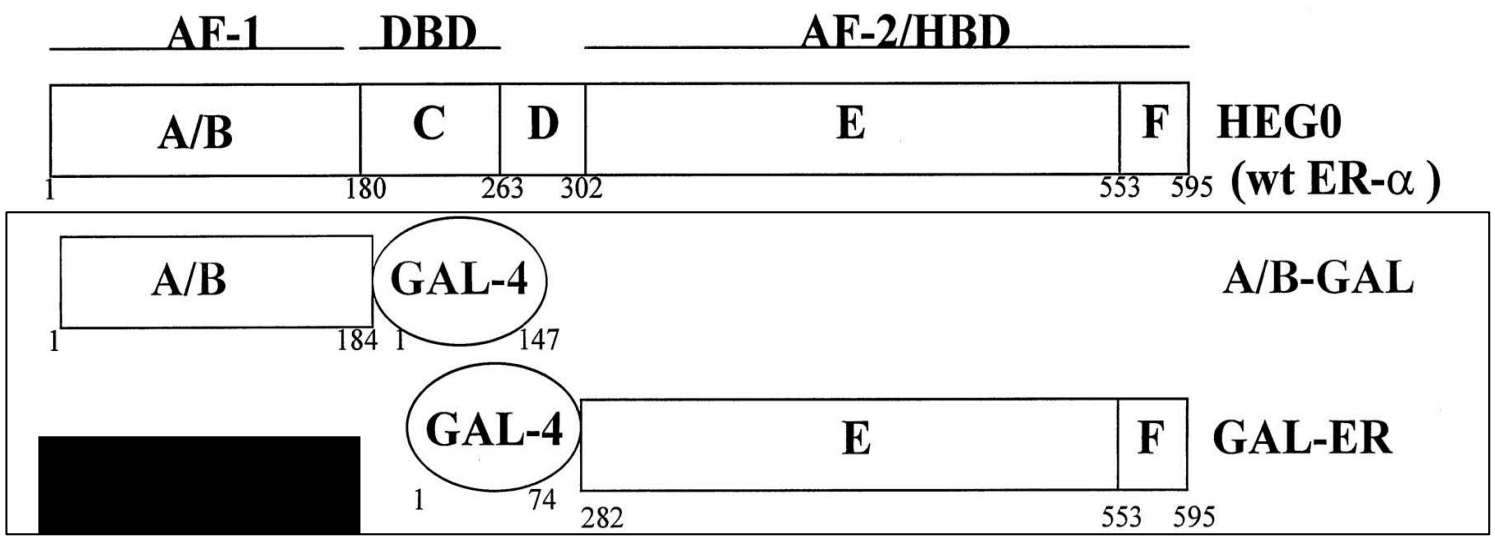
$K_i = 3 \times 10^{-10}$ M



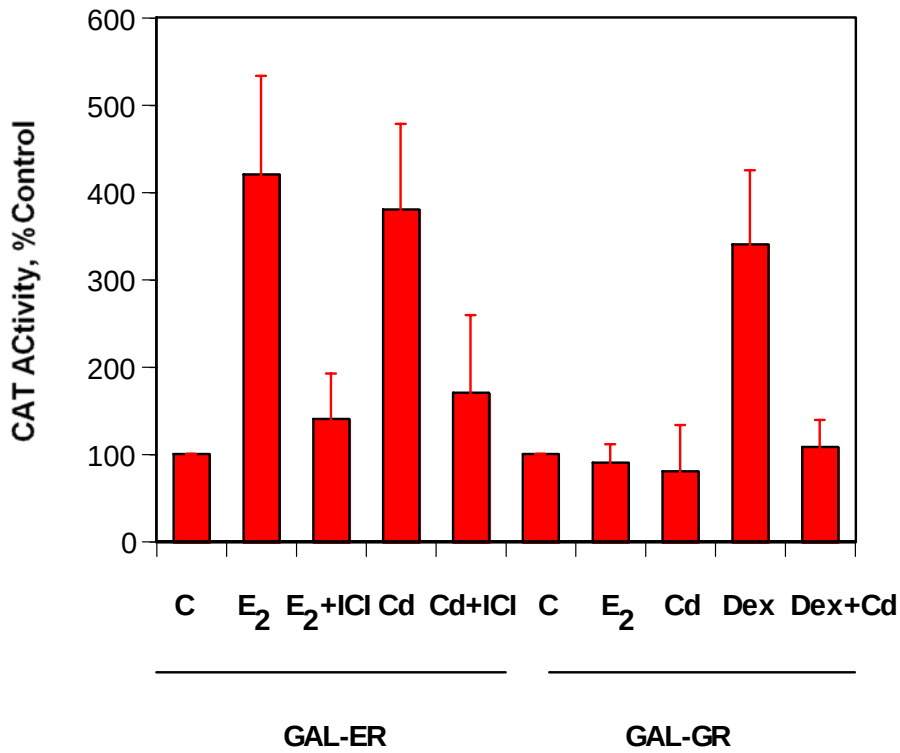
Cadmium activates ER-α through the HBD



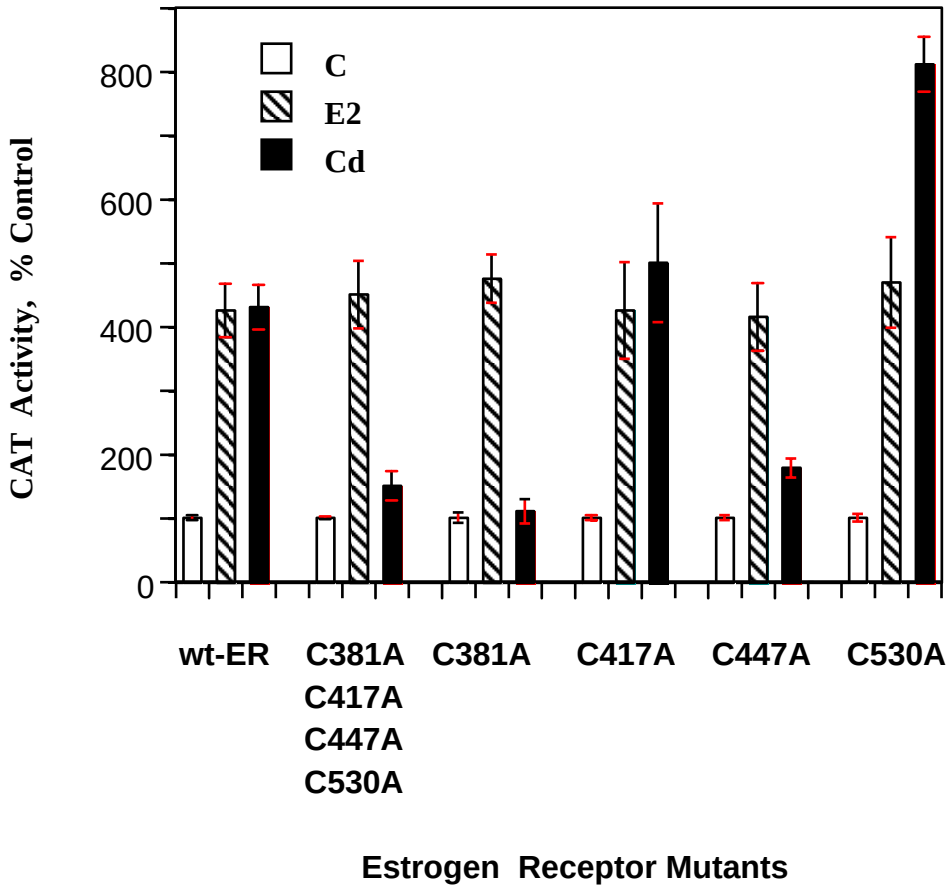
Cadmium activates through the HBD



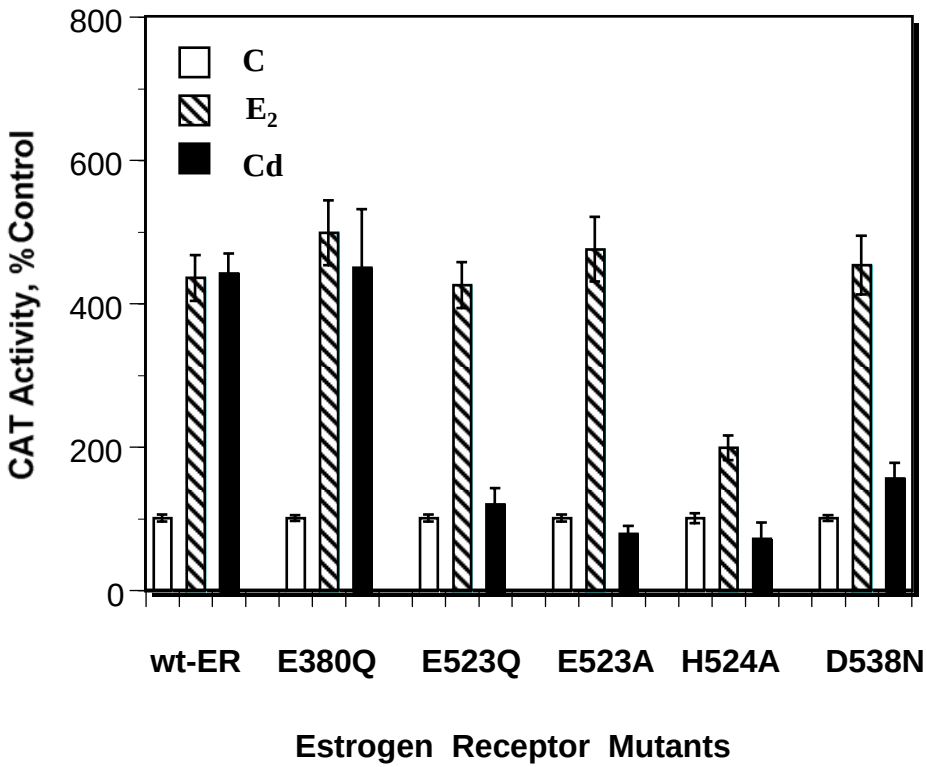
Effects of cadmium on Gal-ERα



Effect of cadmium on ER-α mutants



Effect of cadmium on ER-α mutants



Cadmium binding to ER-α mutants

	Binding (x 10^{-9} M)	
	^{109}Cd	$[^{3}H]E_2$
Wt- ER	0.45	nt
C381A	5	nt
C447A	3	nt
E523Q	0	50
H524A	0	140
D538N	0	37

Summary

Cadmium activates ER-α through a high affinity interaction with the Hormone Binding Domain

Determine whether environmentally doses of cadmium have estrogen like activity

Cadmium Exposure

WHO Provisional Tolerable Weekly Intake (PTWI) =

7 ug/kg body weight per week

Dietary Exposure:

0.2 to 0.5 ug/kg body weight per day

Cigarette Smoke:

2 to 4 ug per pack per day

Estrogen like effects of cadmium

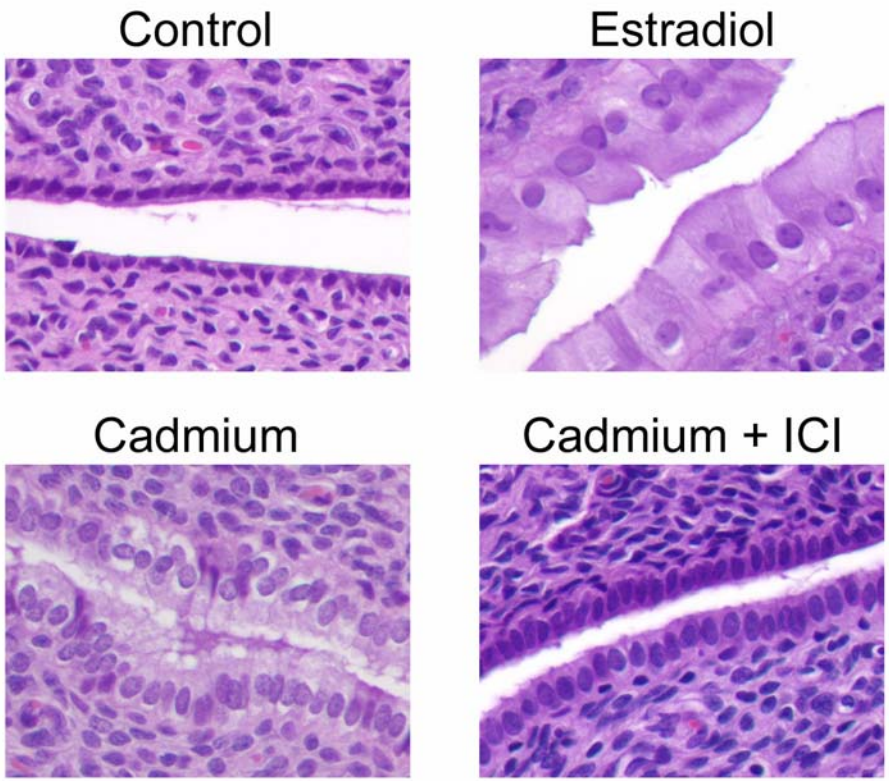
Female Sprague-Dawley:

- ovariectomized on postnatal day 28
- recover for 3 weeks
- treated with a single i.p. dose of cadmium 5 ug/kg body weight

Effects of cadmium on uterine wet weight

	Uterine wet weight, gm	fold increase	body weight, grams
Control	0.075		187
	(+/-0.0069, n=17)		(n=9)
Cadmium	0.141*	1.9	189
	(+/-0.0111, n=21)		(n=12)
ICI-182,780	0.048	0.64	182
	(+/-0.0027, n=13)		(n=10)
Cadmium	0.046	0.61	182
+ ICI-182,780	(+/-0.0035, n=11)		(n=8)
Estradiol	0.284**	3.8	172
	(+/-0.0168, n=22)		(n=10)

Effects of Cadmium in the Uterus

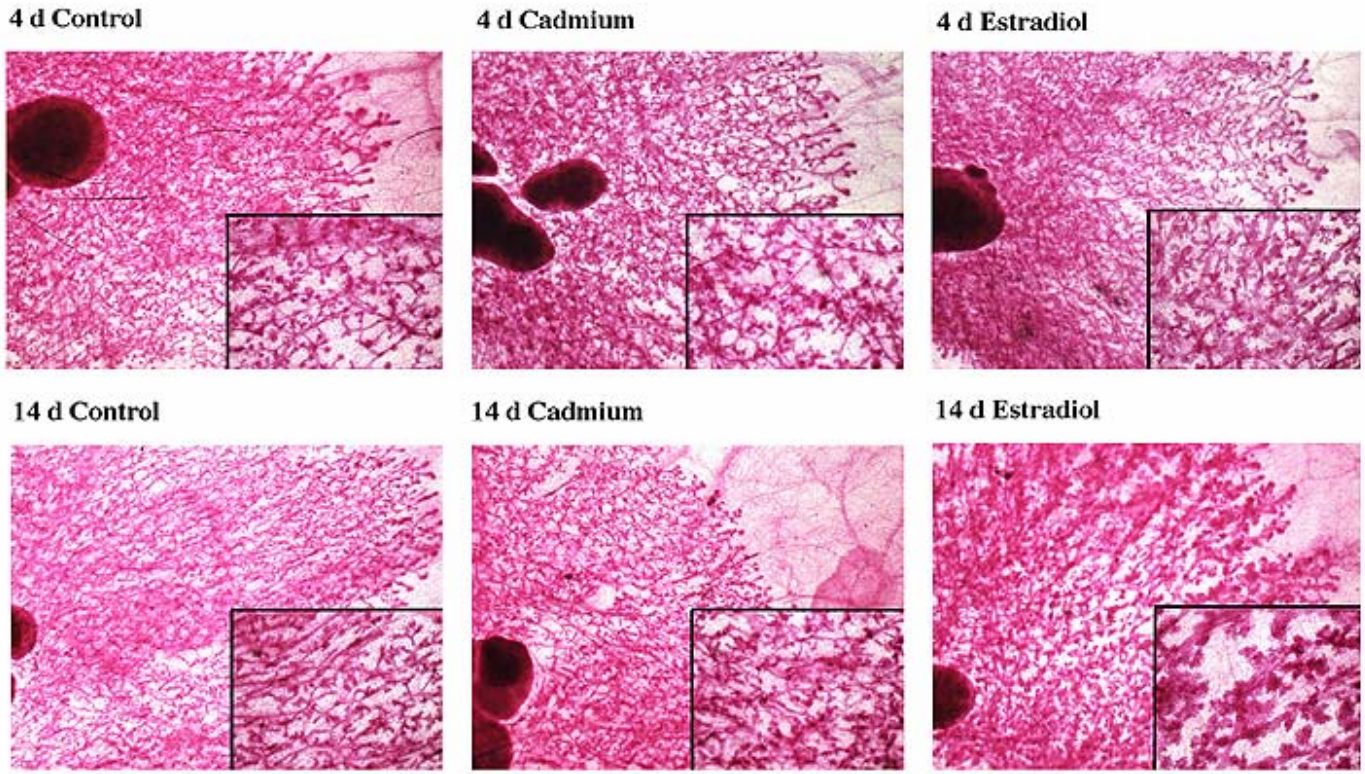


Effects of cadmium on mammary gland density

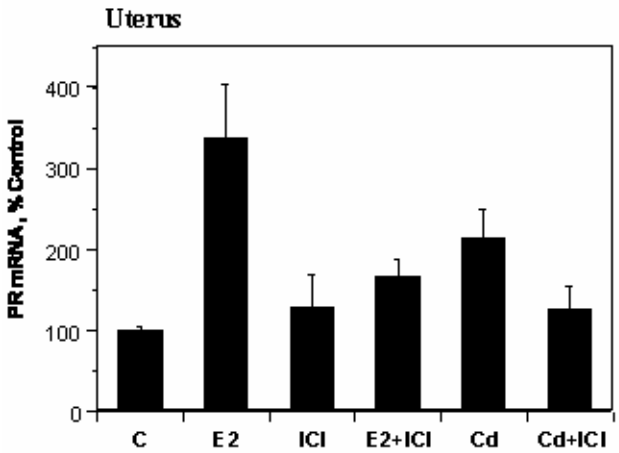
	Day 4	Day 14
Control	**54.3** (+/- 2.5, n =17)	**75.4** (+/-1.9, n = 9)
Cadmium	**82.8*** (+/- 4.0, n = 20)	**99.8*** (+/- 2.9, n = 14)
ICI-182,780	**69.7** (+/- 3.7, n = 8)	**72.7** (+/- 2.2, n = 8)
Cadmium + ICI	**69.0** (+/- 5.4, n = 8)	**72.2** (+/- 2.8, m = 8)
Estradiol	**84.1*** (+/- 3.2, n = 20)	**112.6*** (+/- 6.9, n = 11)

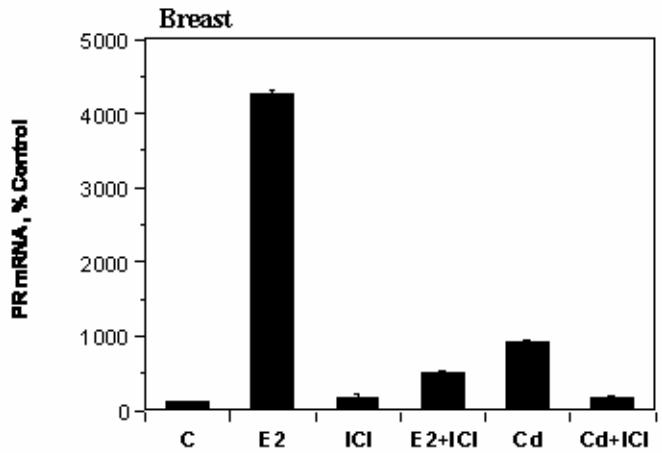
Significantly different from controls: *, $p<0.05$

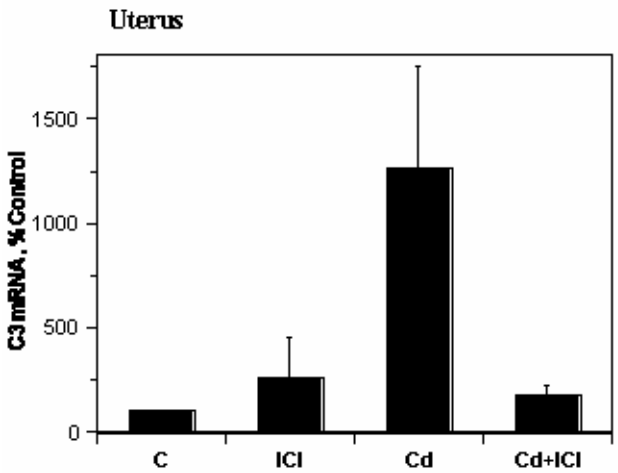
Effects of cadmium on the mammary gland

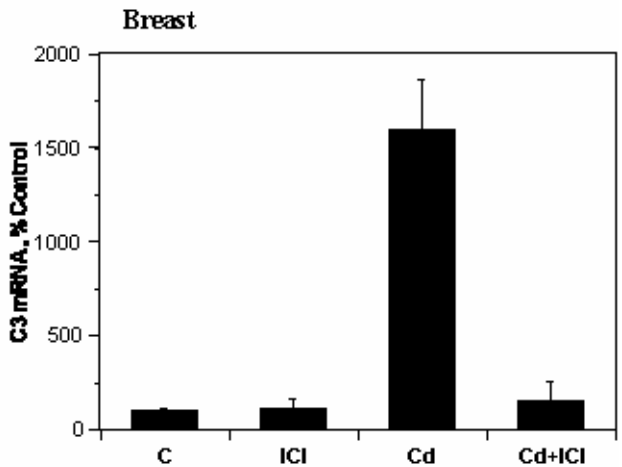


Effects of cadmium on PR and complement C3









Early life effects of cadmium

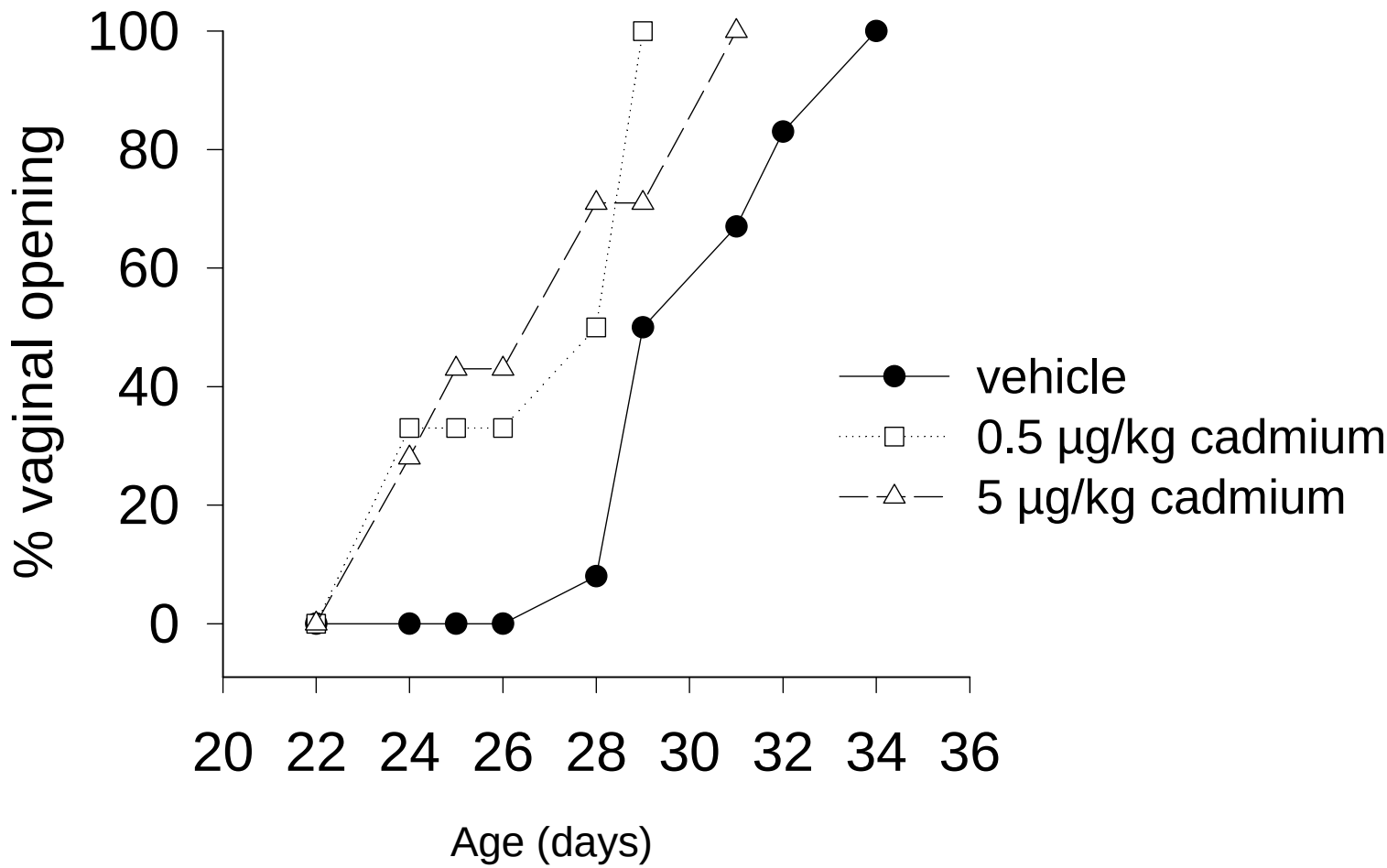
Pregnant female Sprague-Dawley treated with 0.5 or 5 ug/kg body weight on days 12 and 17 of gestation

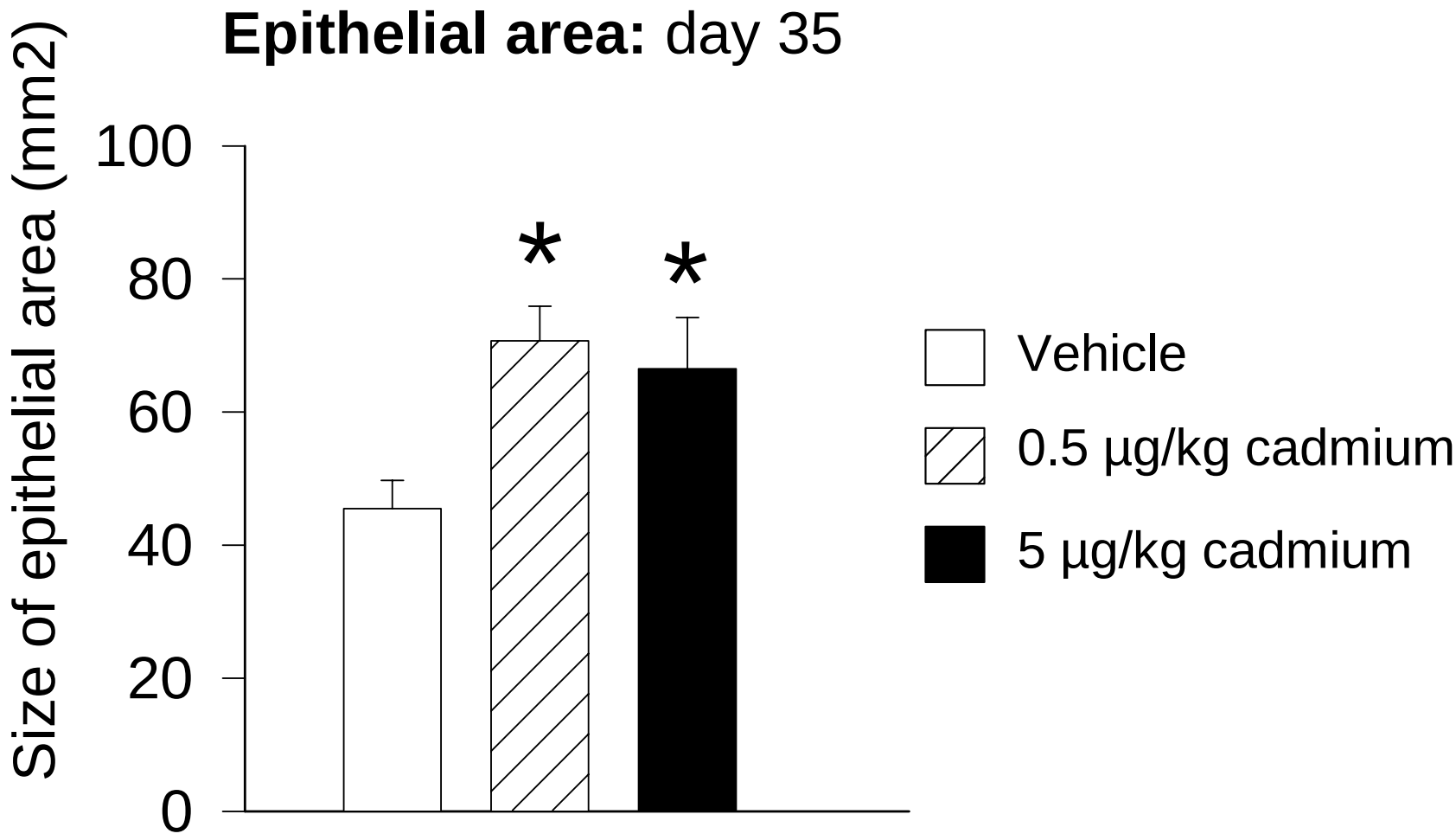
Female offspring were cross-fostered

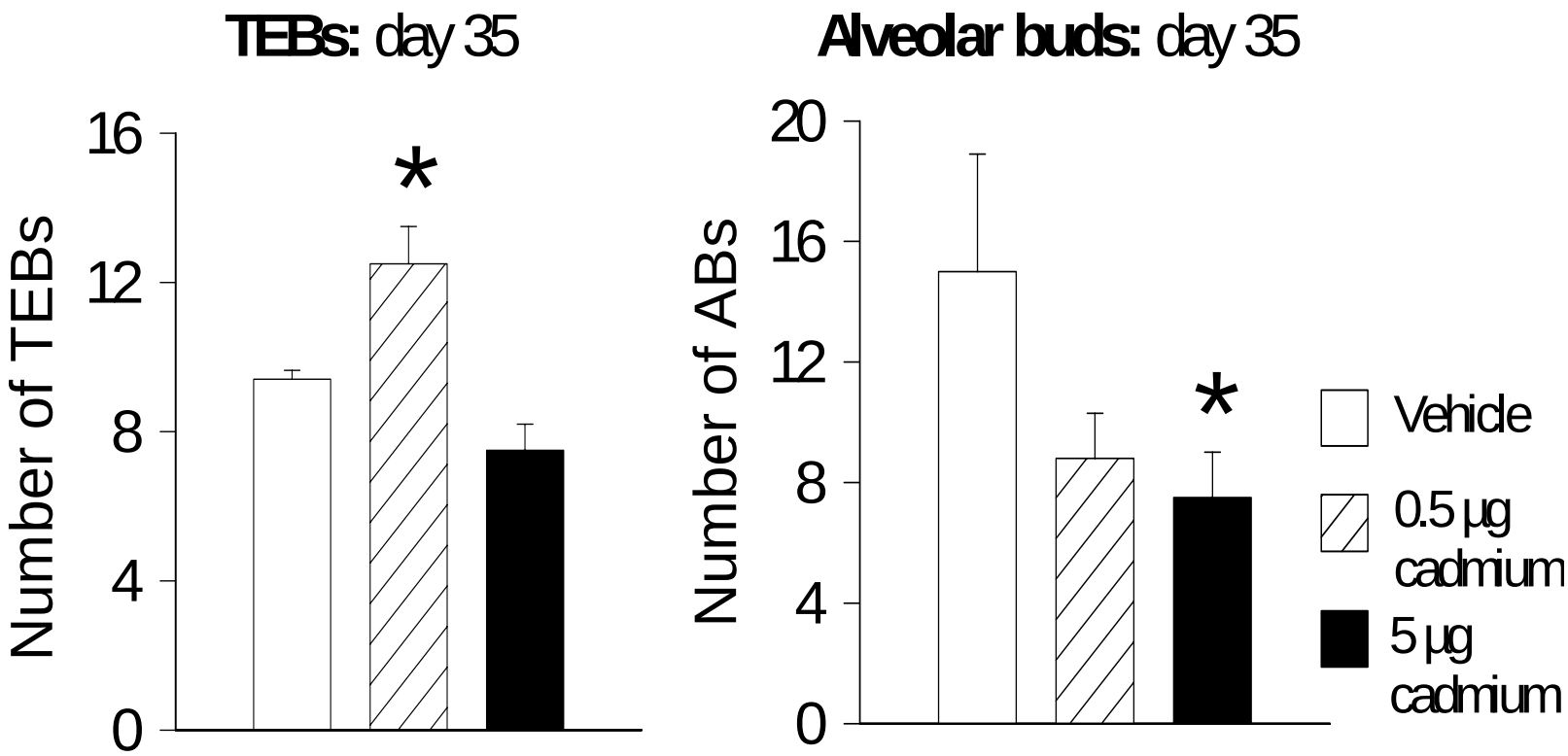
WHO Provisional Tolerable Weekly Intake

= 7 ug/kg bw/week

In utero cadmium exposure: vaginal opening




Epithelial area: day 35
Size of epithelial area (mm2)
100
80
60
40
20
0
*
*
Vehicle
0.5 µg/kg cadmium
5 µg/kg cadmium


TEBs: day 35
Number of TEBs
16
12
8
4
0
*
Alveolar buds: day 35
Number of ABs
20
16
12
8
4
0
*
Vehicle
0.5 µg cadmium
5 µg cadmium

Summary

- Cadmium mimics the effects of estradiol in vivo and following in utero exposure

“Metalloestrogens ?”

Bivalent Cations:

- Cd
- Co
- Cu
- Cr
- Hg
- Ni
- Pb
- Sn

Anions:

- AsO_2
- SeO_3
- VO_4

Summary

Some, but not all, bivalent metals & anions activate ER-α through the formation of a high affinity complex with the HBD

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