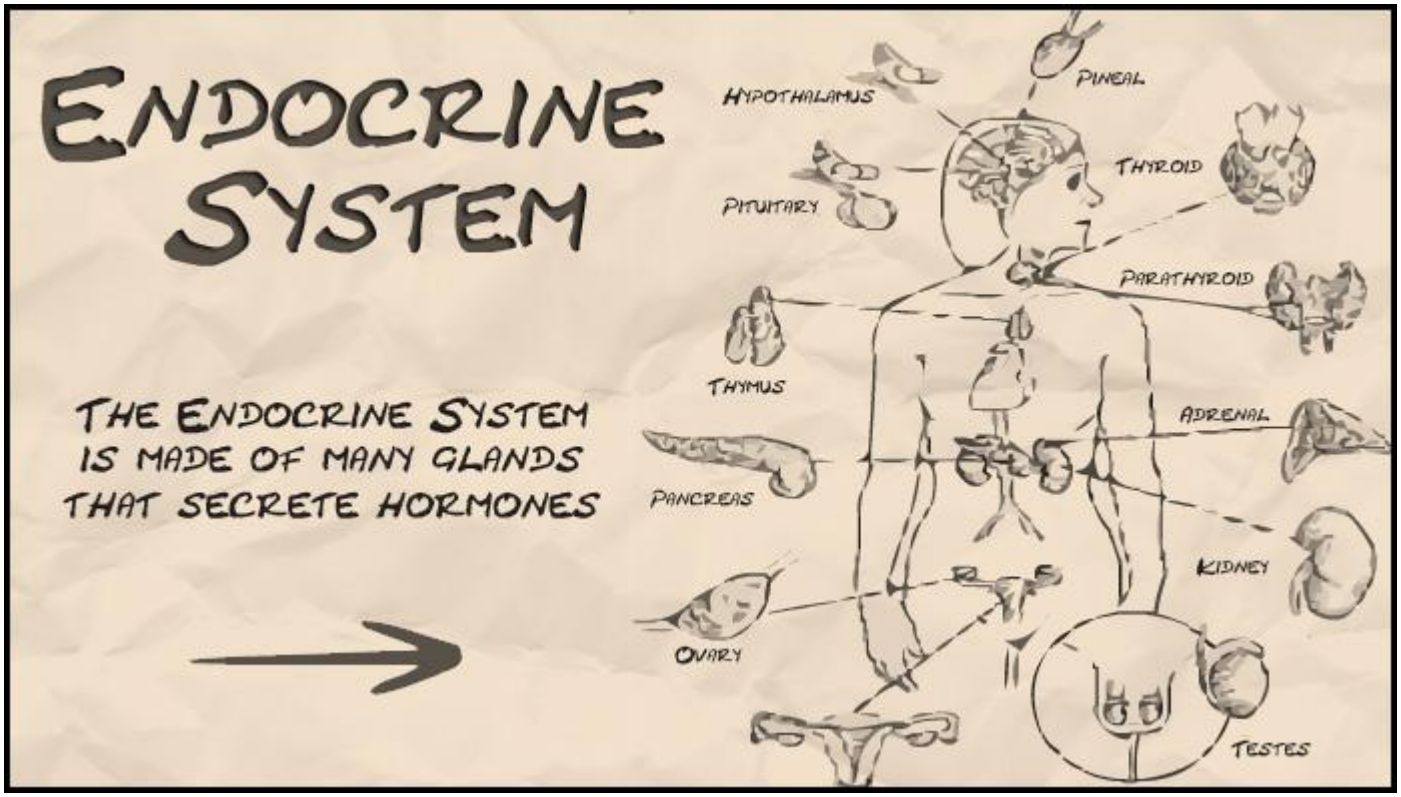
Exposure to environmental endocrine disruptors: What may this mean for bone health?

Jennifer Schlezinger, PhD

Associate Professor of Environmental Health

Boston University
Superfund Research Program

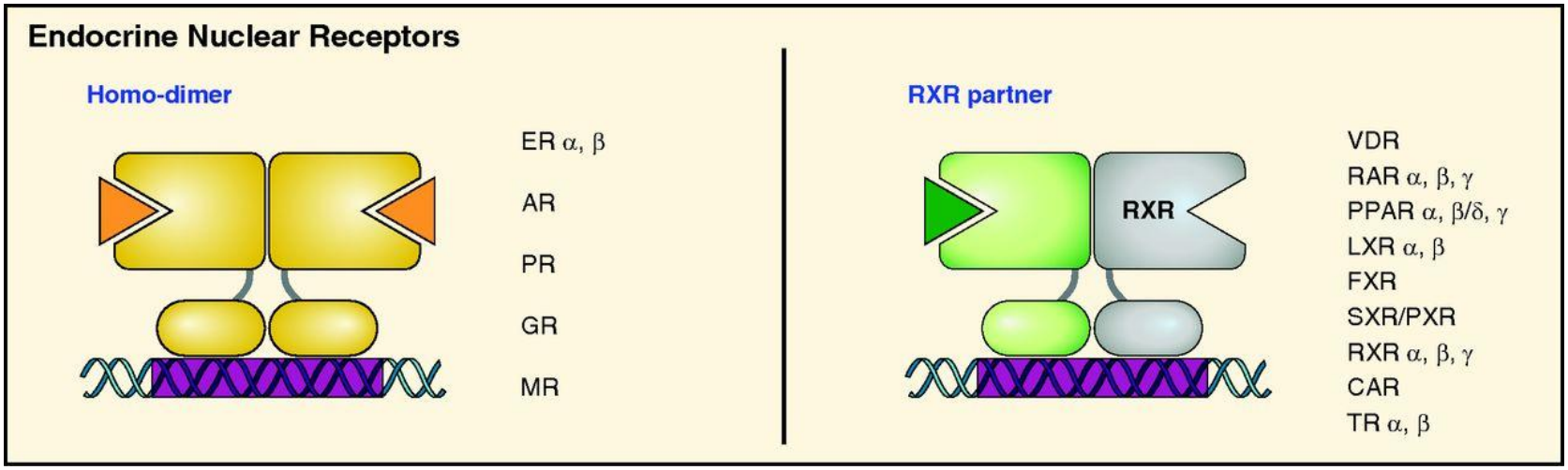
Boston University School of Public Health



Endocrine disruptor: a chemical that can promote or inhibit the production, elimination or action of hormones and hormone-like chemicals.

http://www.untamedscience.com/biology/human/endocrine-system/

Hormones and their receptors regulate bone biology



Steroid receptors

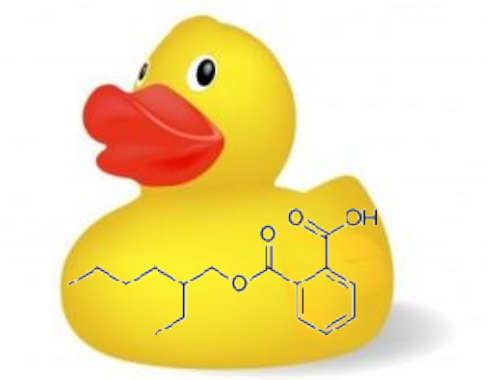
Vitamin/Metabolite/Hormone receptors

Estrogen receptor – Under-activation leads to bone loss
Glucocorticoid receptor – Over-activation leads to bone loss
Vitamin D receptor – Under-activation leads to failure to form bone
PPARγ – Over-activation leads to bone loss

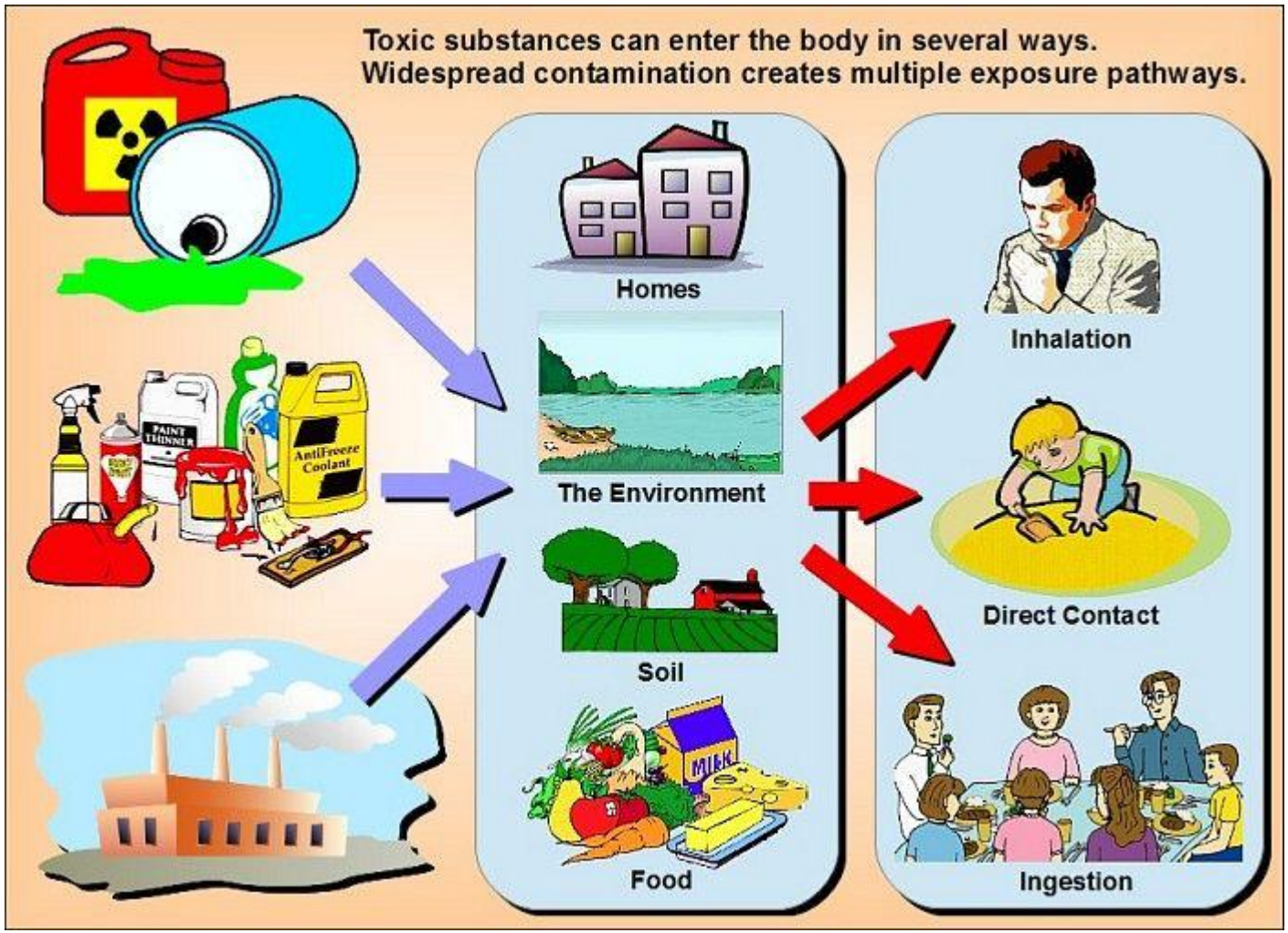
Imai et al., 2013. *Physiol. Rev.* 93:481.

Environmental PPARγ Agonists?

- PPARγ – the master regulator of fat formation. Fat is found under the skin, around the organs and in the bone marrow
- Agonists – turn on fat cell formation and lipid storage programs by binding to PPARγ
- Where do we find PPARγ agonists? Everywhere!



How are we exposed to PPARγ agonists?

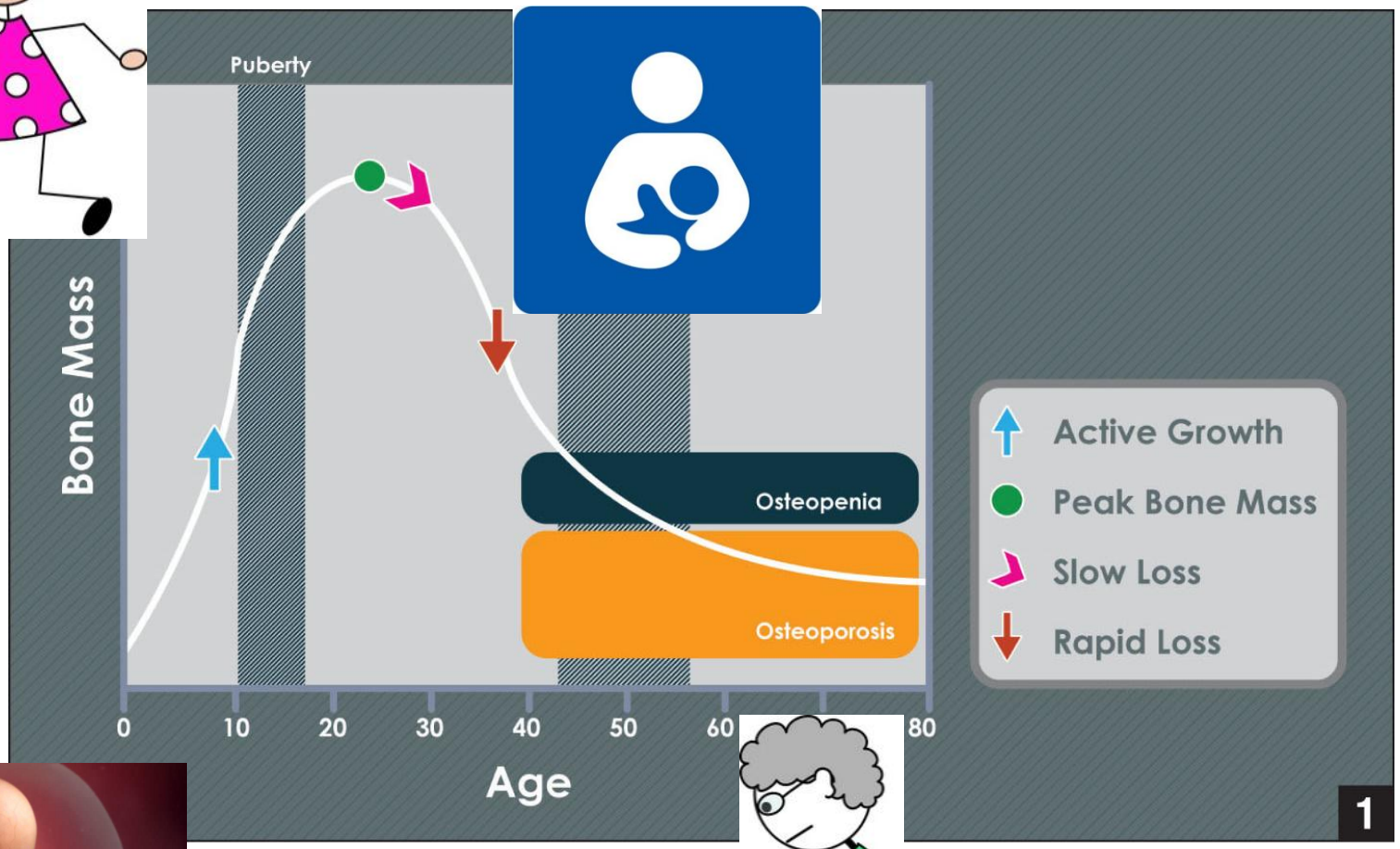


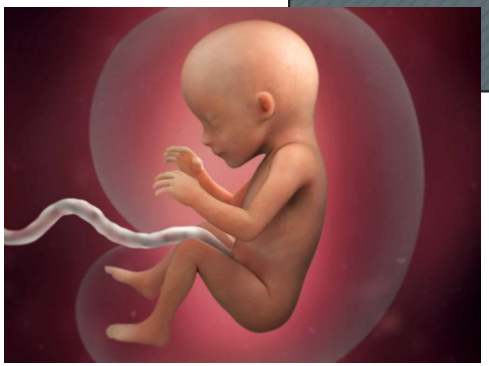
http://experttoxicologist.com/toxicology-toxic-exposures.aspx?cln=1

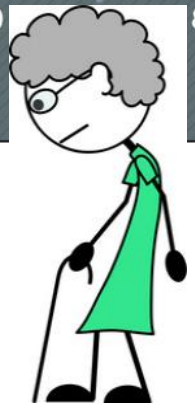
Critical risk factors for developing osteoporosis:

1) Bone loss at menopause
2) Failure to reach peak bone mass

Men are NOT immune to bone loss.



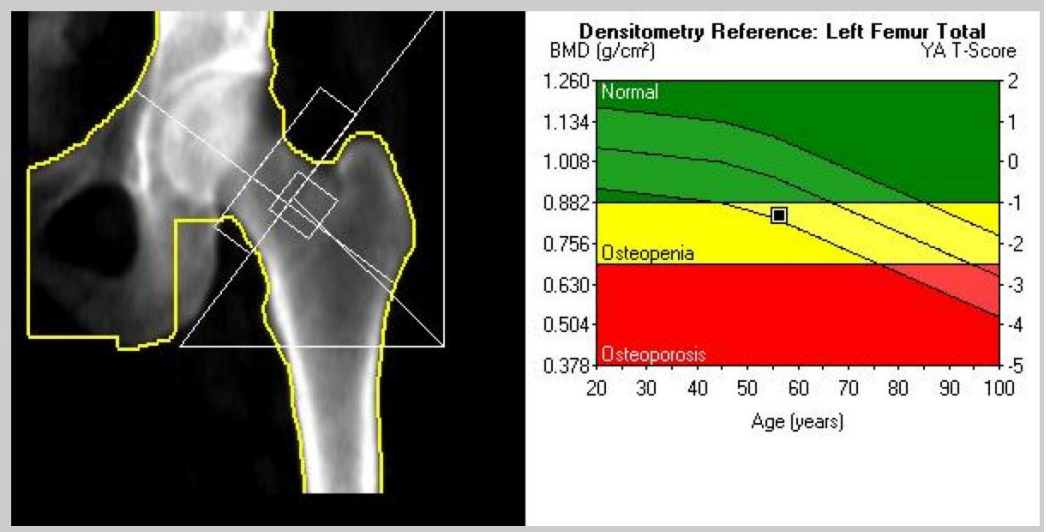




Shuler et al., 2012 *Orthopedics.* 35:798.
NIH Consensus Development Panel, (2001) *JAMA*. 285: 785.
Hui et al., (1990) *Osteoporosis Int*. 1: 30.
Hernandez et al., (2003) *Osteoporos Int*. 14: 843.
www.cdc.gov/nchs/data/hestat/osteoporsis/osteoporosis2005_2010.htm

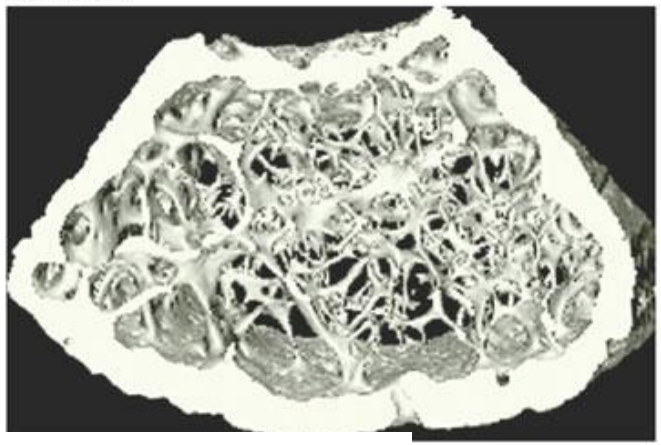
Analyses of bone quality in humans and mice

Dexa Scan – Bone Density

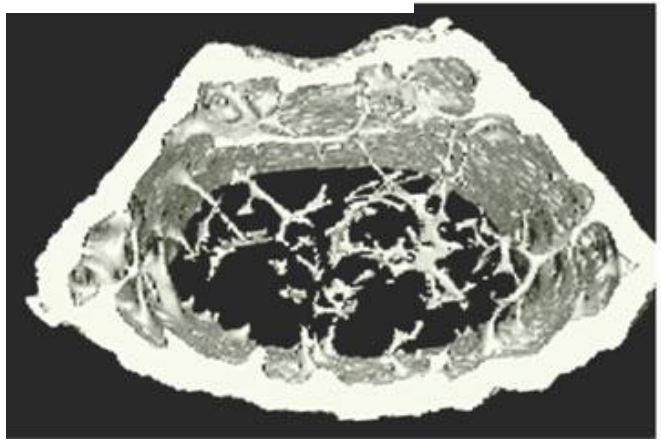


CT– Bone structure/Density

Normal bone



Osteoporotic bone



Serum Markers –

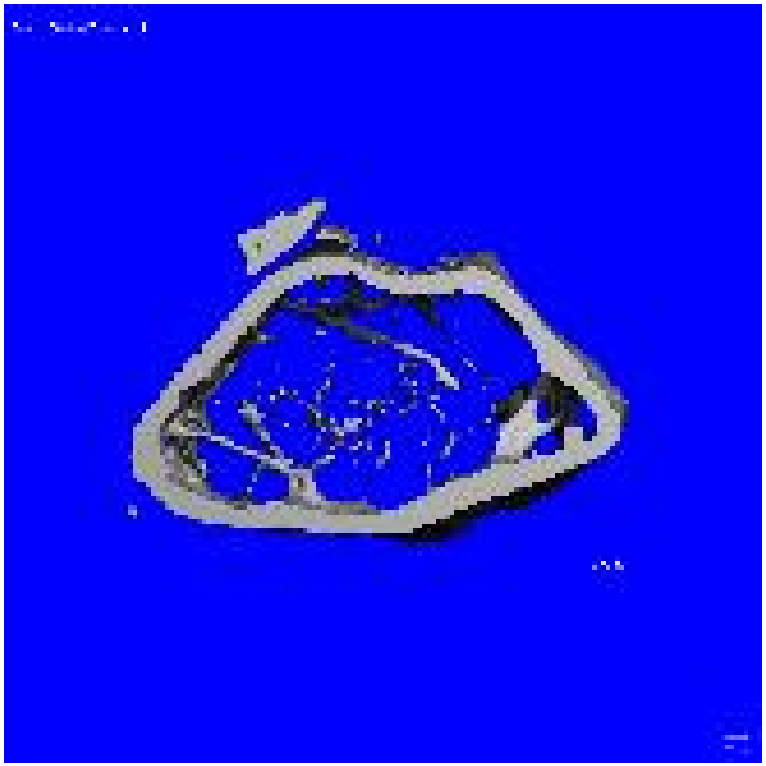
- Bone formation
  - Bone alkaline phosphatase (BALP)
  - N-terminal propeptide of type 1 procollagen (PINP)
- Bone breakdown
  - C-terminal telopeptide of type 1 collagen (CTX)
  - Trap5b

Takada. 2009. *Nat. Rev. Rheumatol*. 5: 442

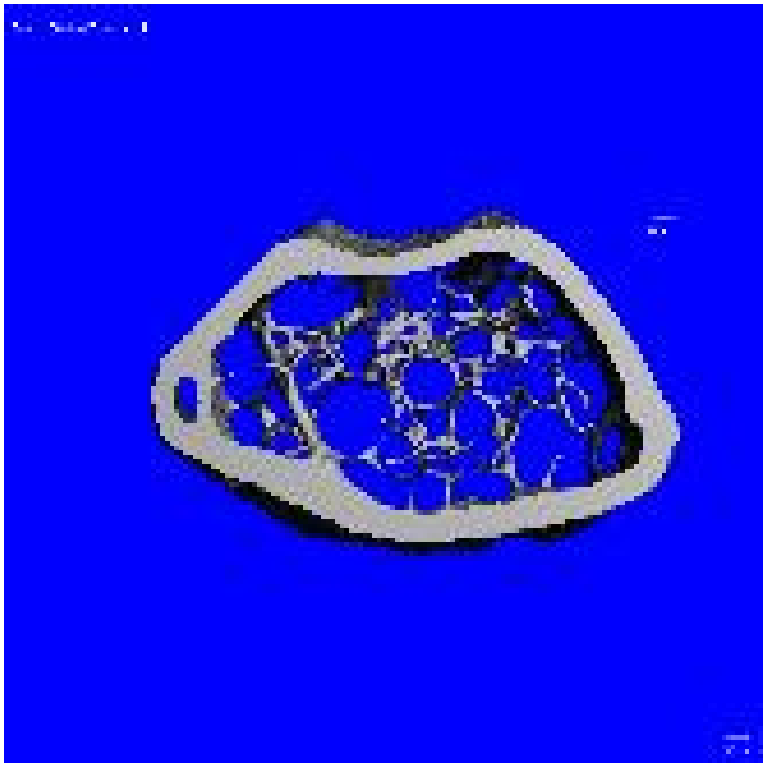
www.food4healthybones.com/blog/dxa-test-must-knows/

Lactation has a dramatic effect on bone

Control - End of lactation



Two week after lactation ends



C57BL/6J mouse – femur

In utero/lactational exposure (Vh or triphenyl phosphate)

Pups are weaned at 21 days of age

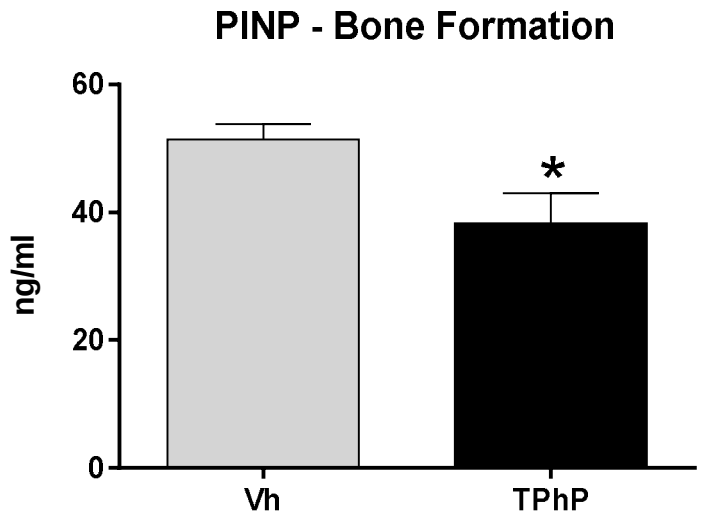
Schlezinger, Unpublished data

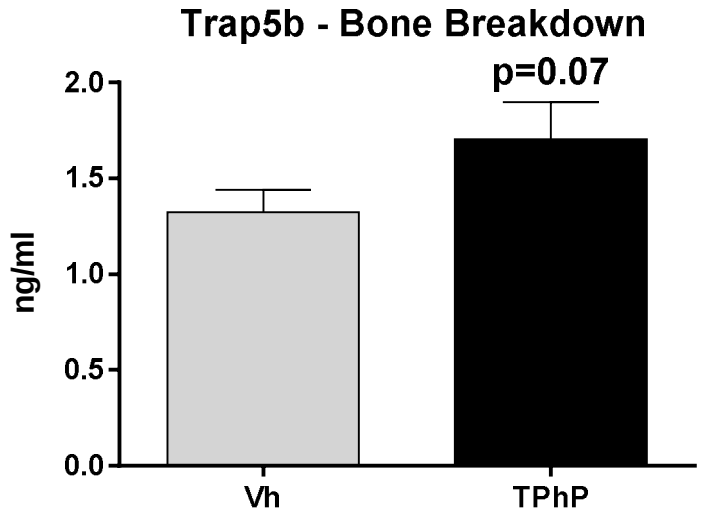
VanHouten and Wysolmerski, (2003) *Endocrinology.* 144: 5521.

Woodrow et al., (2006) *Endocrinology*. 147: 4010.

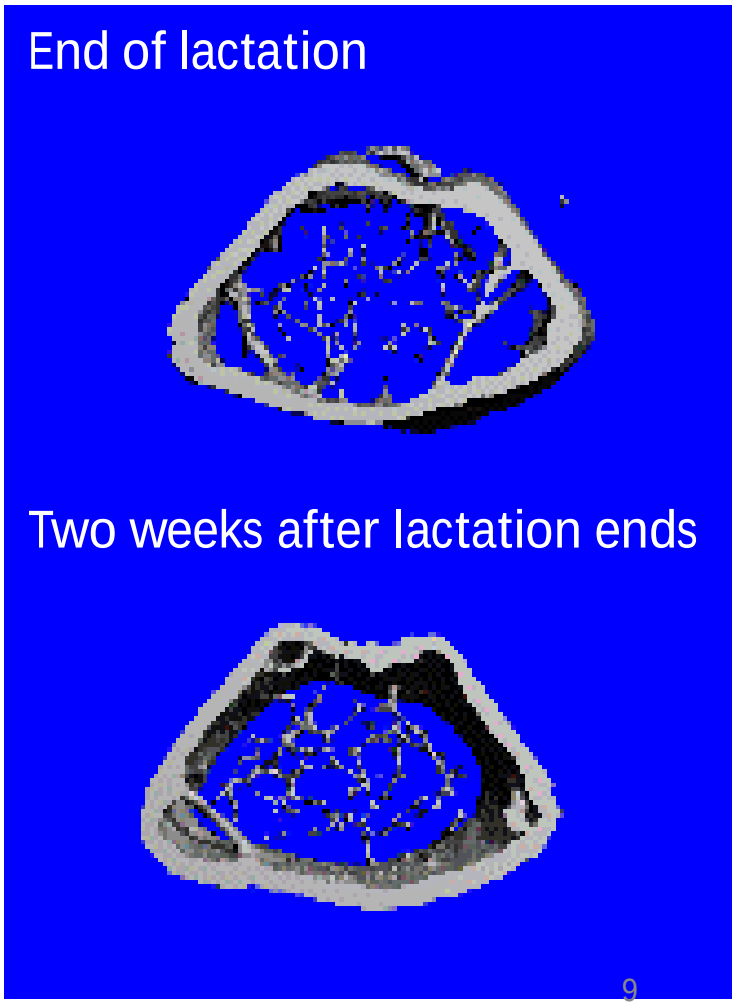
An environmental PPARγ ligand prevents recovery of bone after lactation

Dams





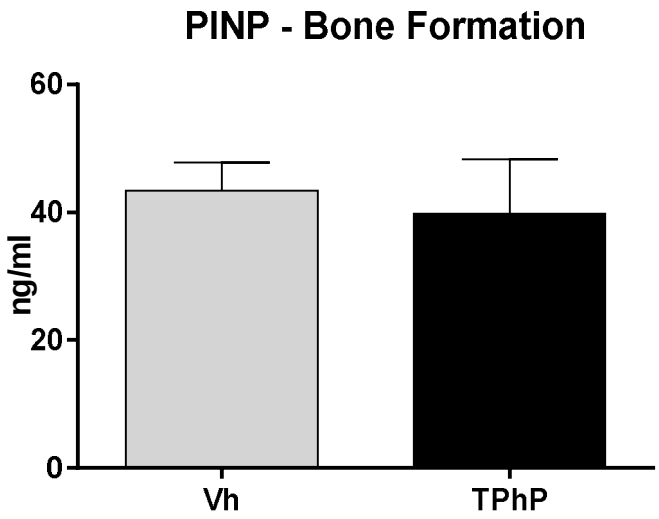
Flame retardant
Triphenyl Phosphate

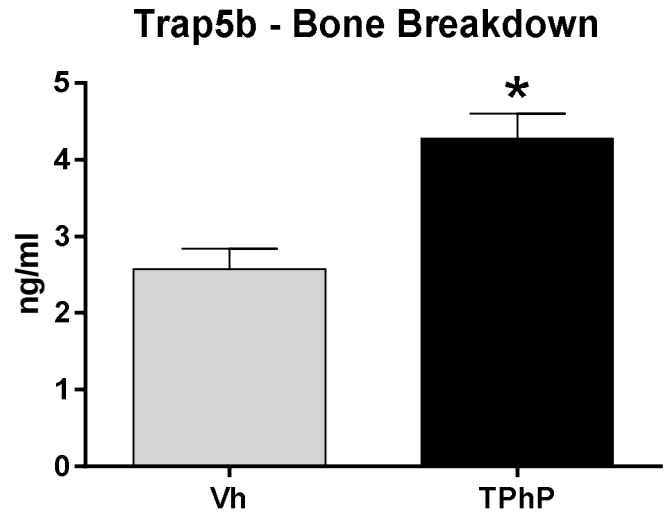


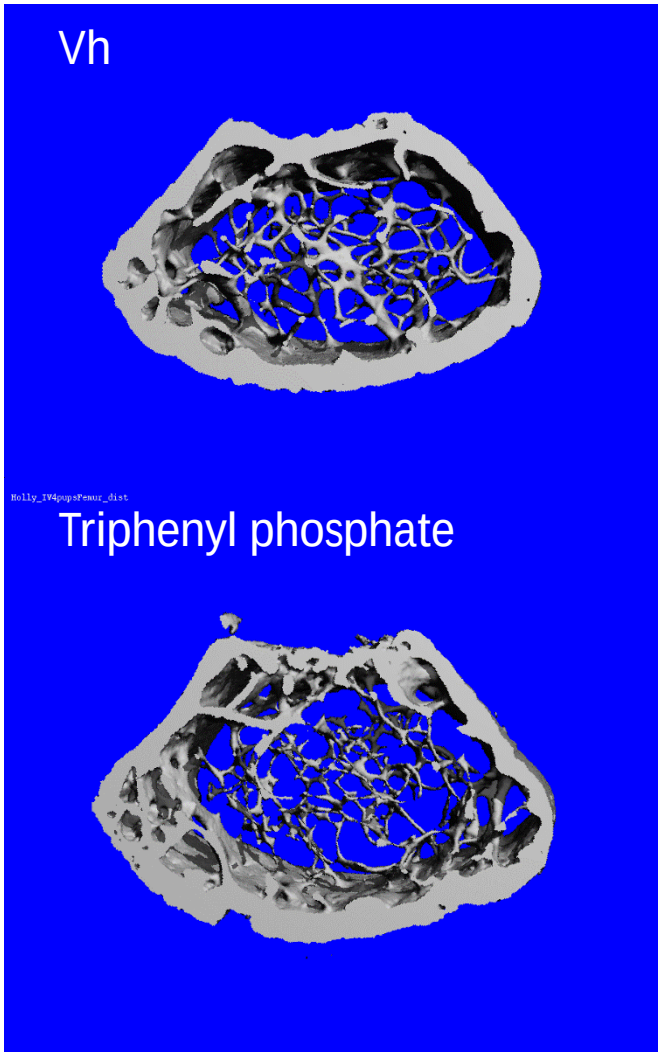
Schlezinger, Unpublished data

Do early life EDC exposures impact bone quality?

Female pups at 16 weeks of age, fed a high fat diet after weaning







Schlezinger, Unpublished data

What do we know? What don't we know?

1. PPARγ, the protein which controls the formation of fat cells, plays an important role in regulating bone quality.
2. Drugs that turn on PPARγ reduce bone quality.
3. Environmental EDCs that turn on PPARγ can decrease bone formation and increase bone resorption. Are there other bone-relevant nuclear receptors that are targets of EDCs?
4. Lactation is a time of bone mobilization. Is recovery from lactation-induced bone loss impaired by EDC exposure?
5. The *in utero* environment is an important factor in determining bone quality. Are early life EDC exposures impairing the ability to achieve peak bone mass?