
# The Role of Polychlorinated Biphenyls in the Development of Diabetes

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University of Kentucky

October 23, 2012

# Dr. Karen Wetterhahn Memorial Award

- Professor of Chemistry at Dartmouth College
- Cofounded Dartmouth's Women in Science Project
- Program Director of Dartmouth College Superfund Research Program

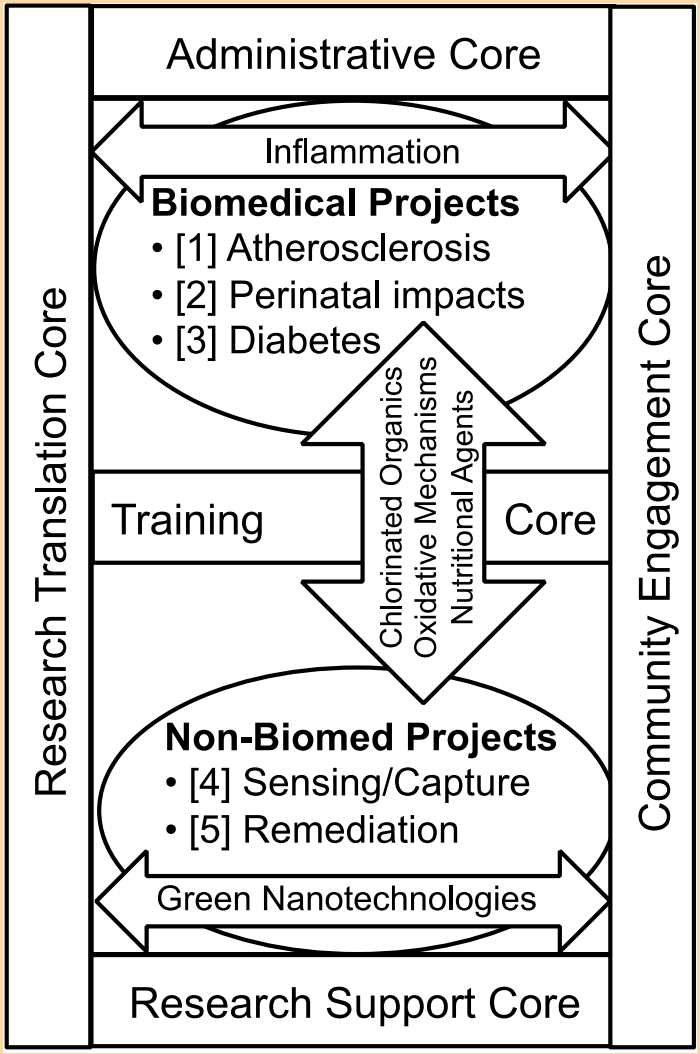
# Dr. Karen Wetterhahn Memorial Award

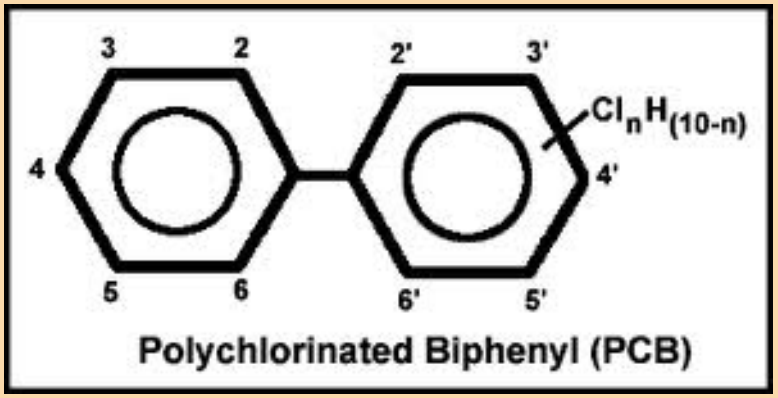
- Dr. Courtney Kozul-Horvath, 2010 Wetterhahn Award Recipient
- Post-doctoral fellow at Dartmouth College studying the immunological effects of arsenic exposure during pregnancy in mice

# Outline

- Polychlorinated biphenyl (PCB) background
- Coplanar PCBs induce diabetes in lean mice
- PCBs in obesity/weight loss model

# Superfund Research Program at the University of Kentucky



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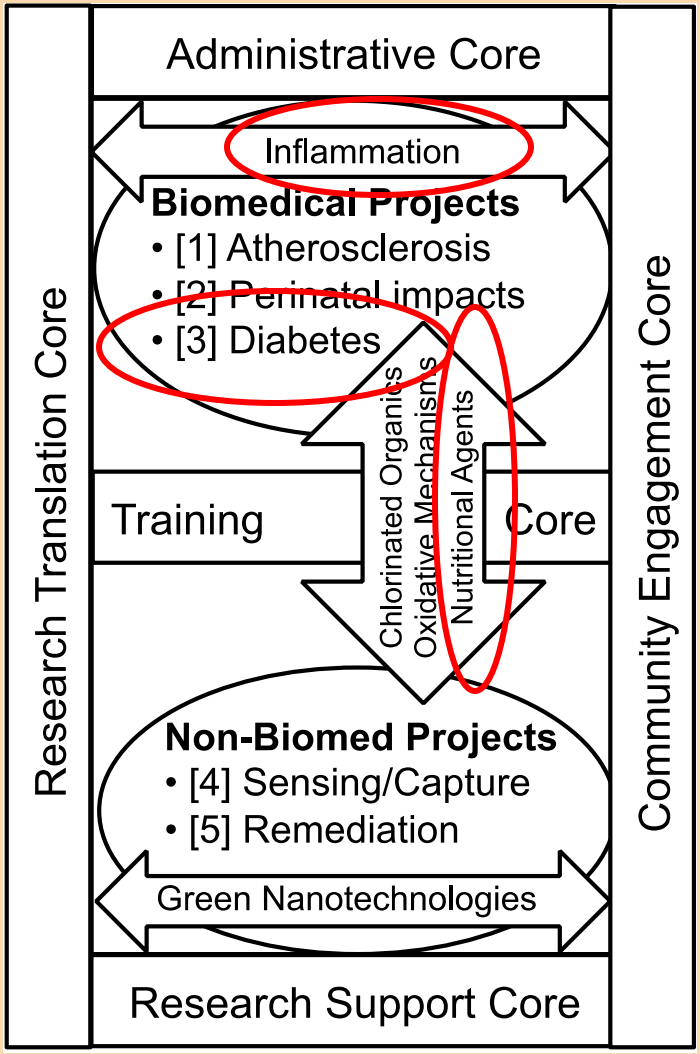
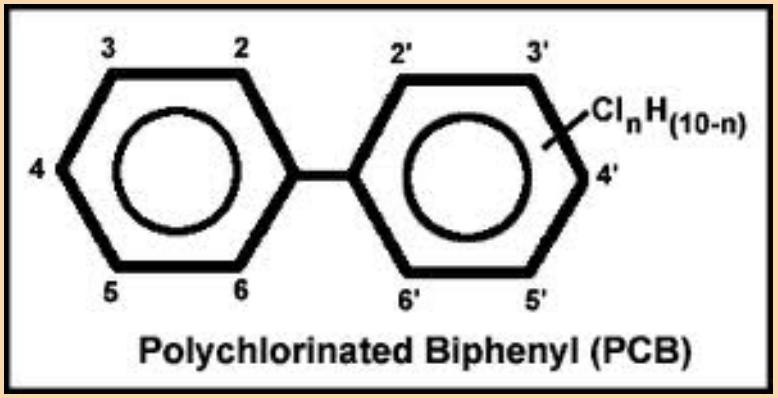
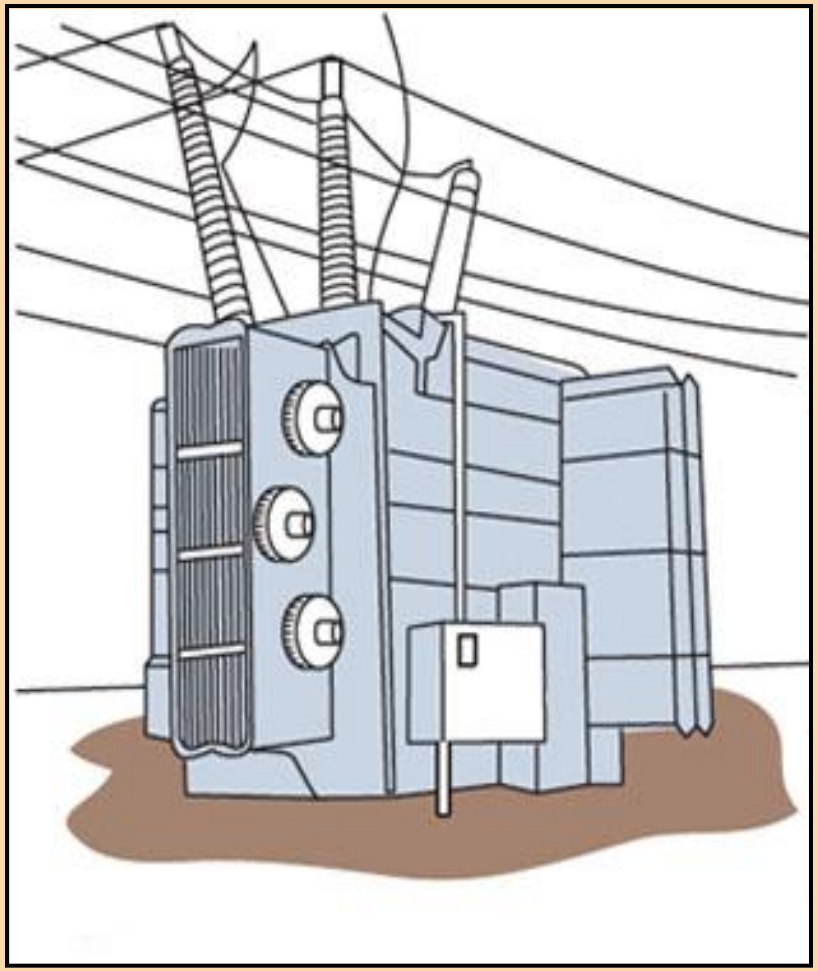



# PCBs: where do they come from?



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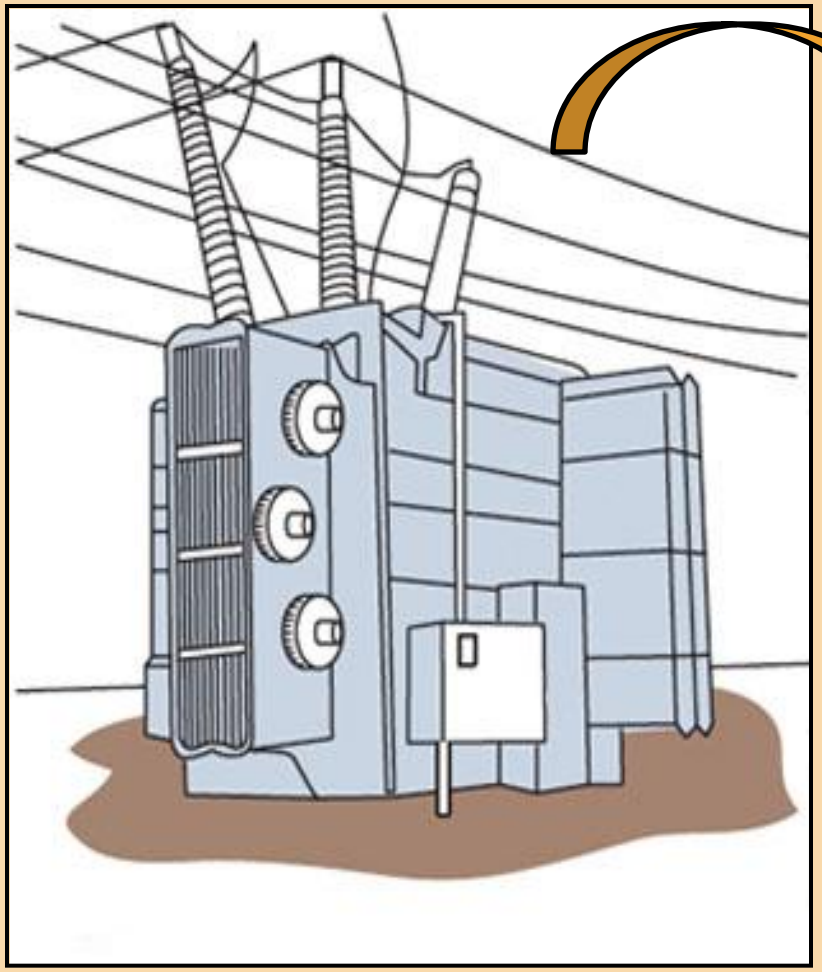
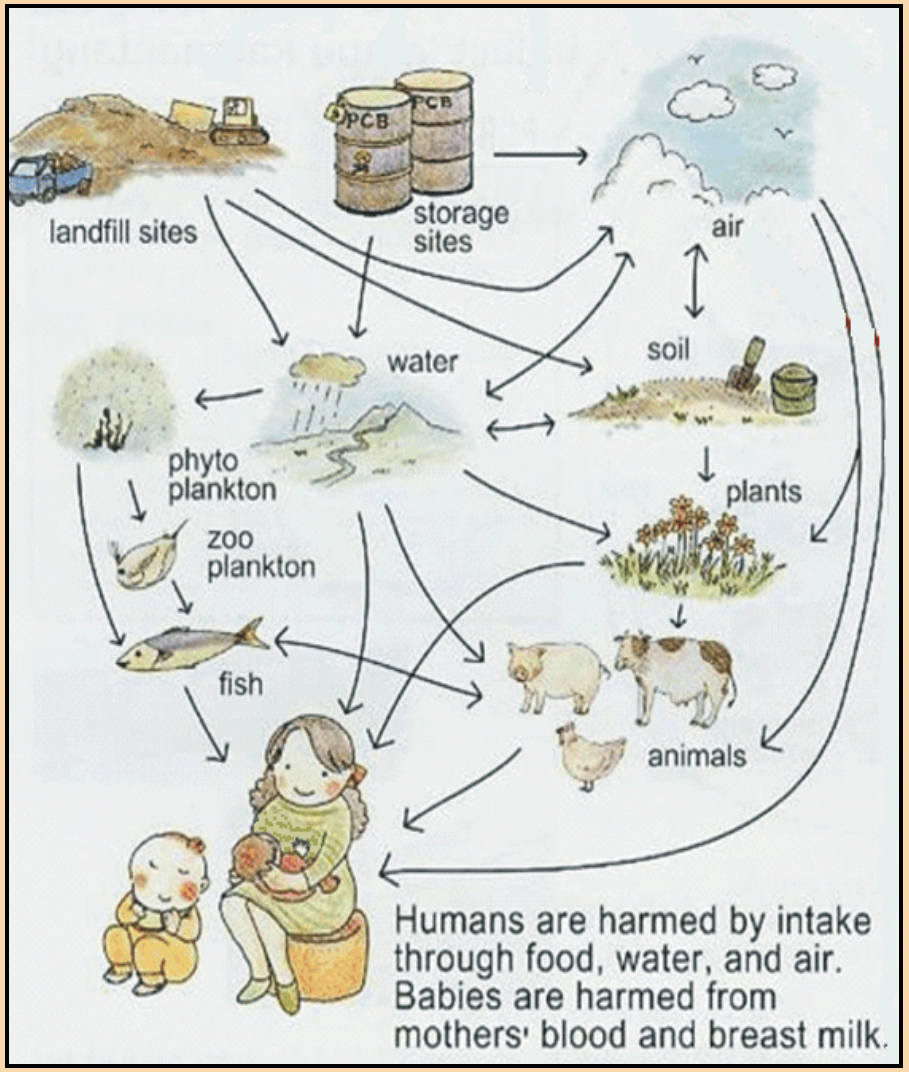
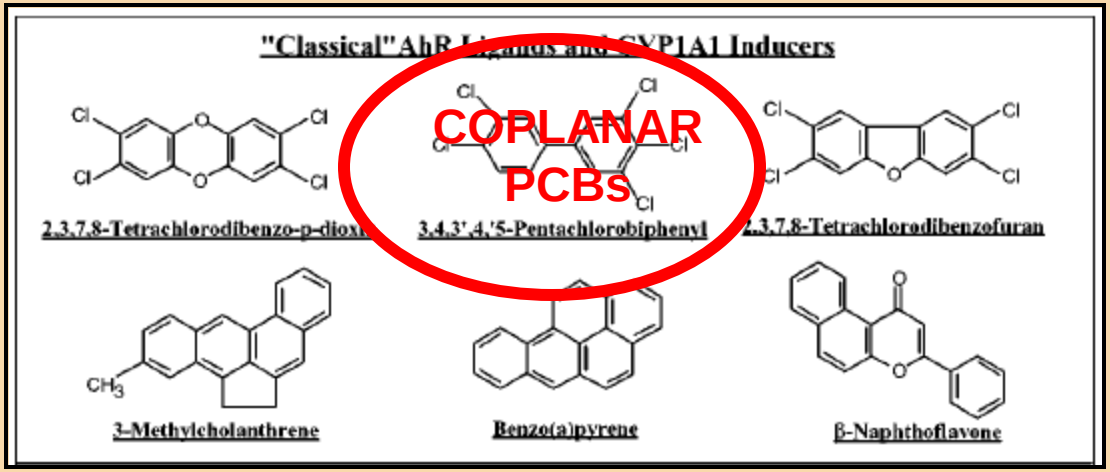




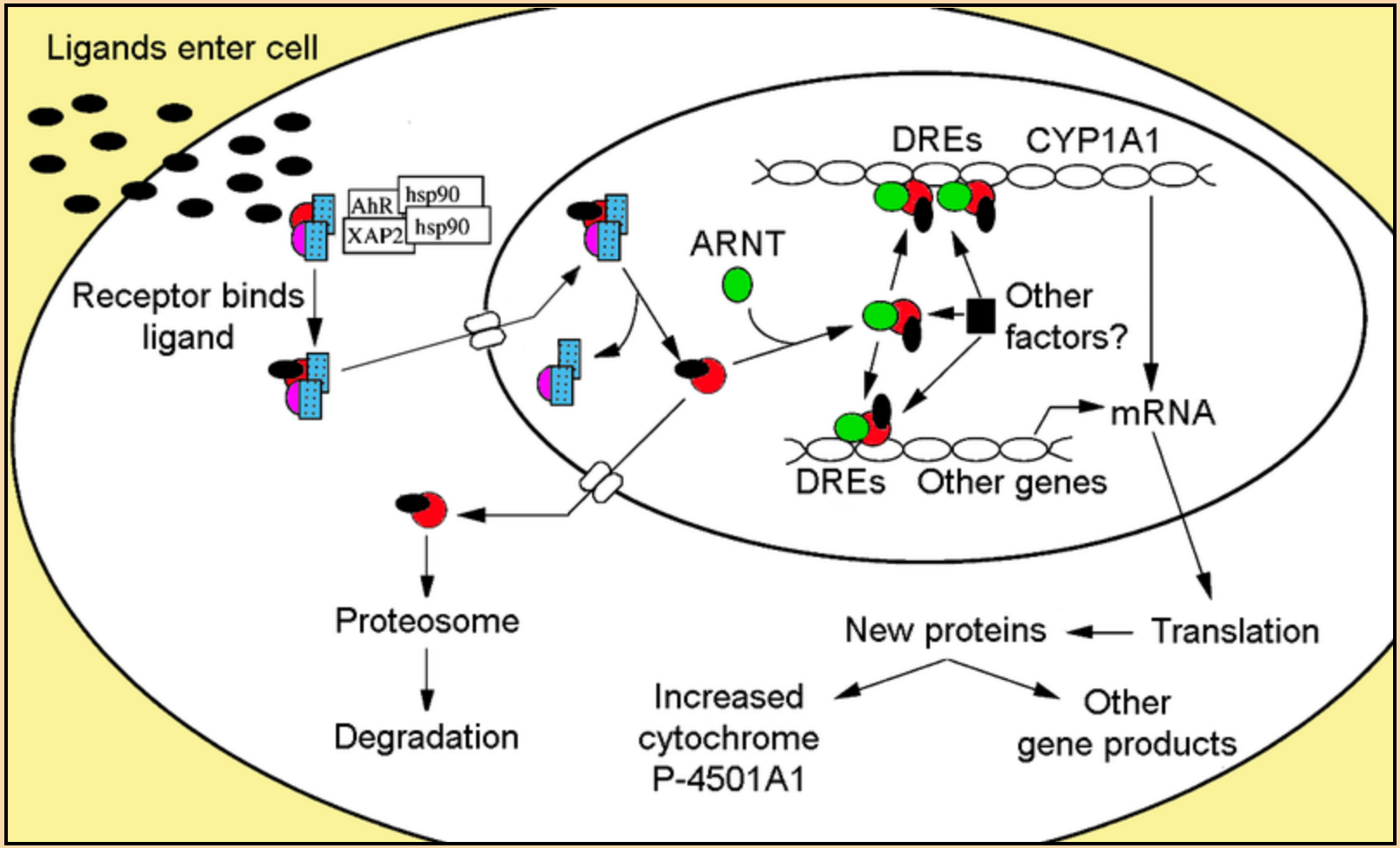
# Aryl hydrocarbon receptor (AhR)

- Evolutionally conserved cytosolic transcription factor.
- Endogenous ligands: derivatives of tryptophan, bilirubin, carotinoids, flavonoids, possibly fatty acids.
- Exogenous ligands: planar halogenated aromatic hydrocarbons and polycyclic aromatic hydrocarbons.




Annu. Rev. Pharmacol. Toxicol. Vol. 43, pp. 309-334, 2003

# Mechanisms of action for PCBs via AhR

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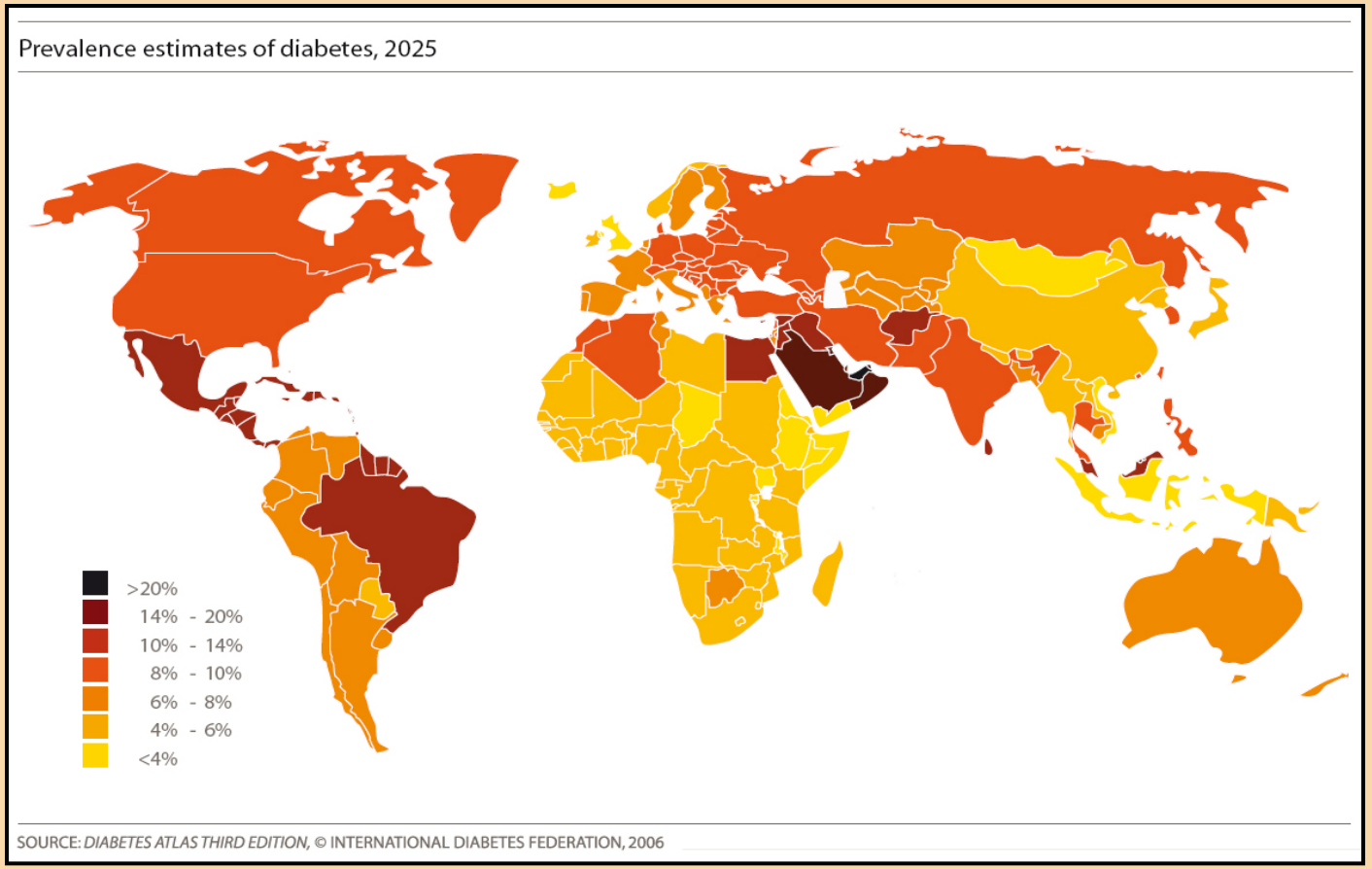
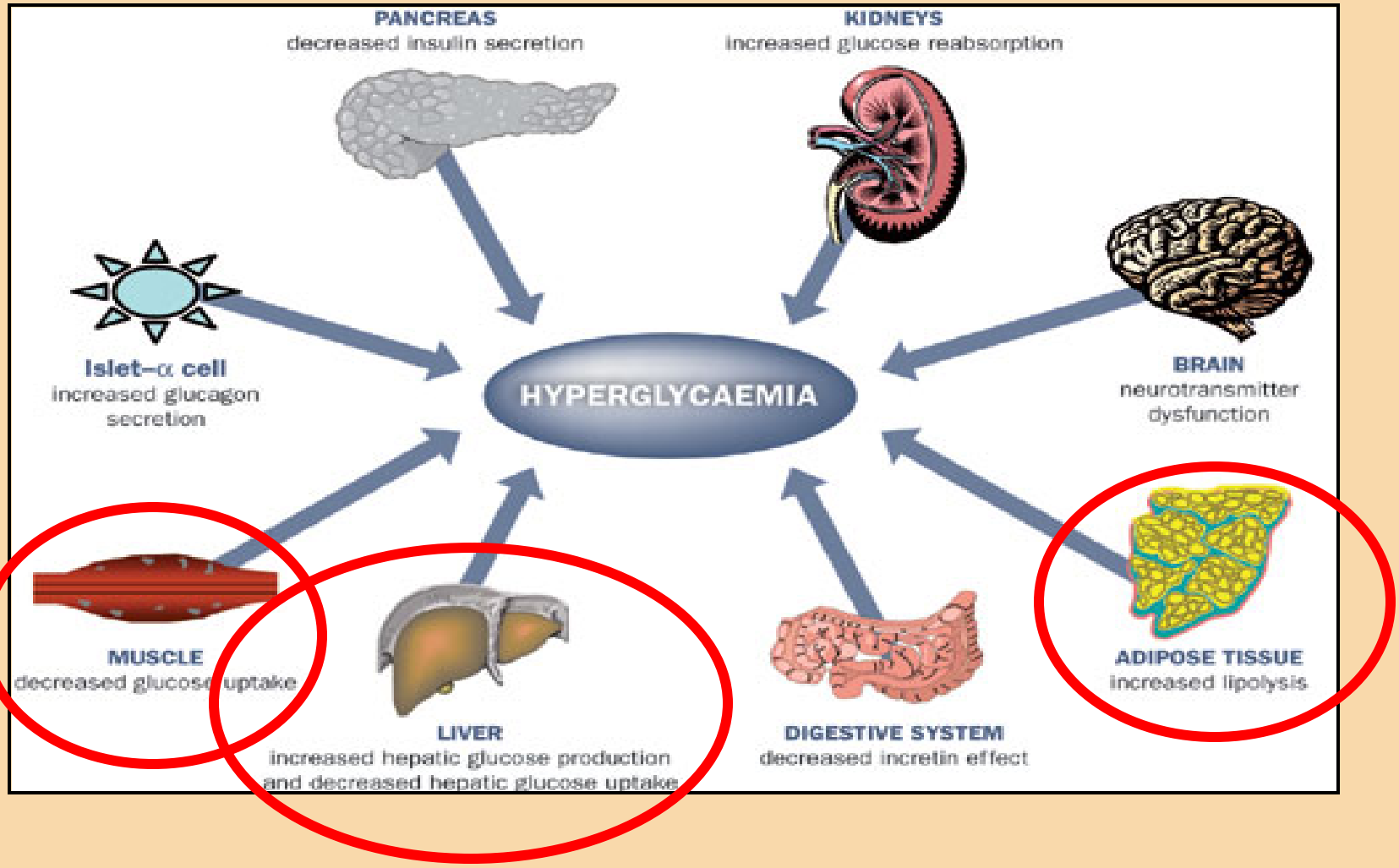
# Diabetes prevalence

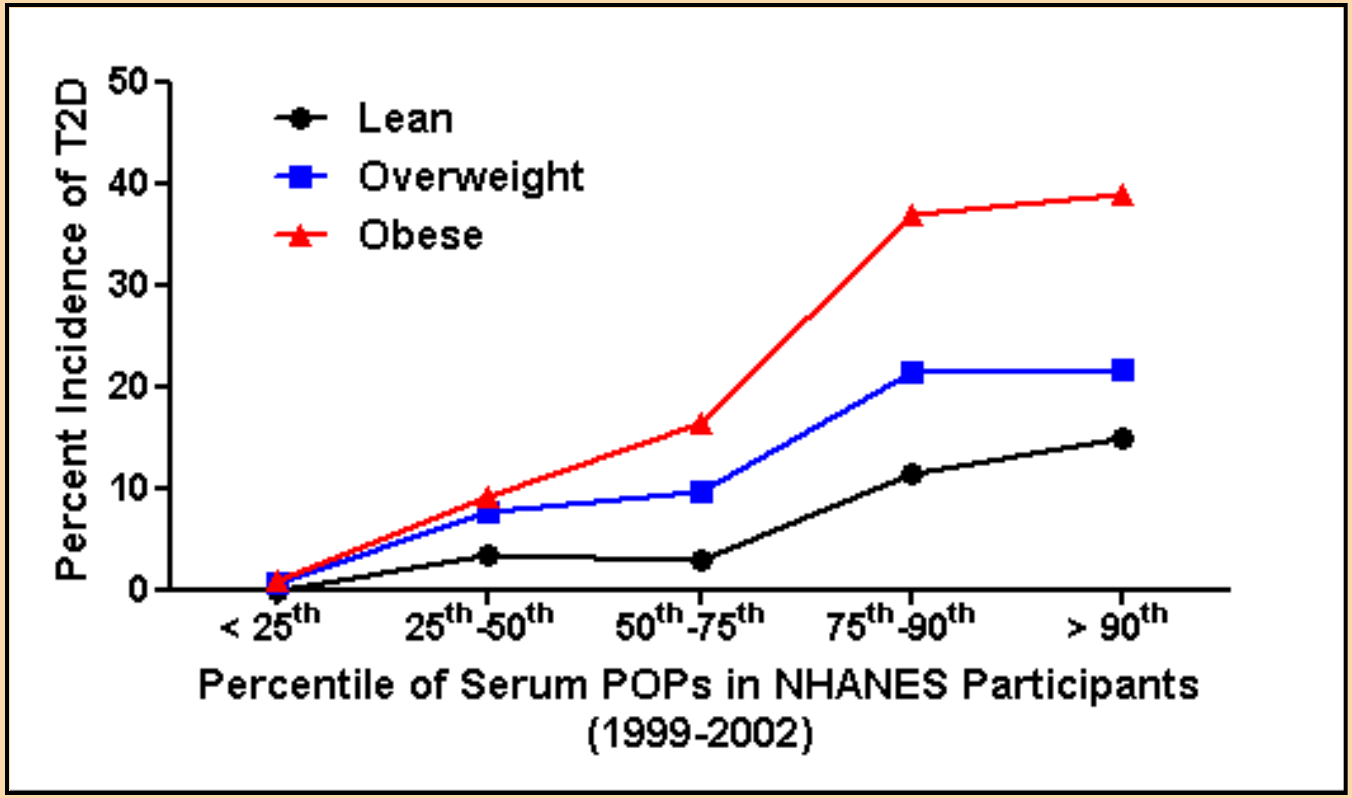
Disease characterized by high plasma glucose, either because the body does not produce enough insulin, or because cells do not respond to insulin that is produced.



# KEY ORGANS OF DIABETES

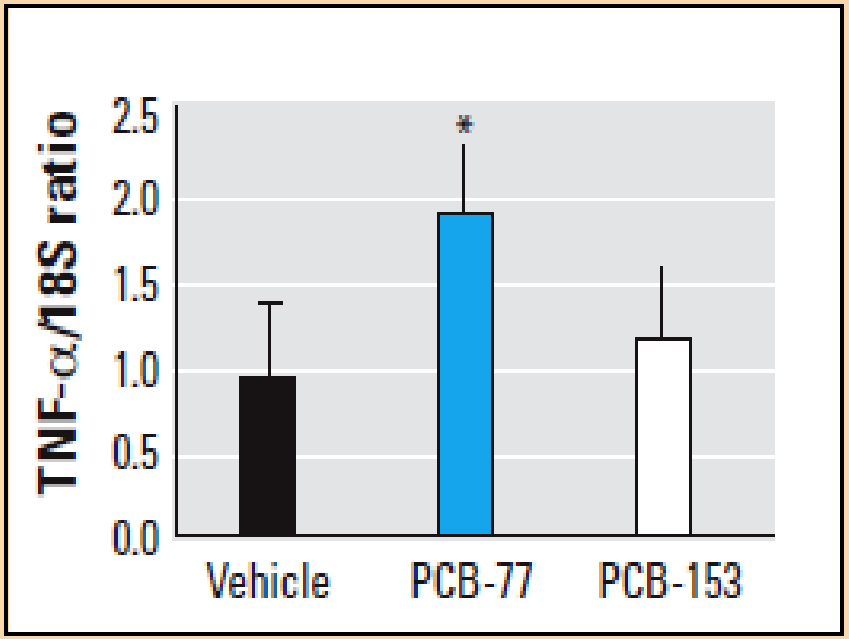


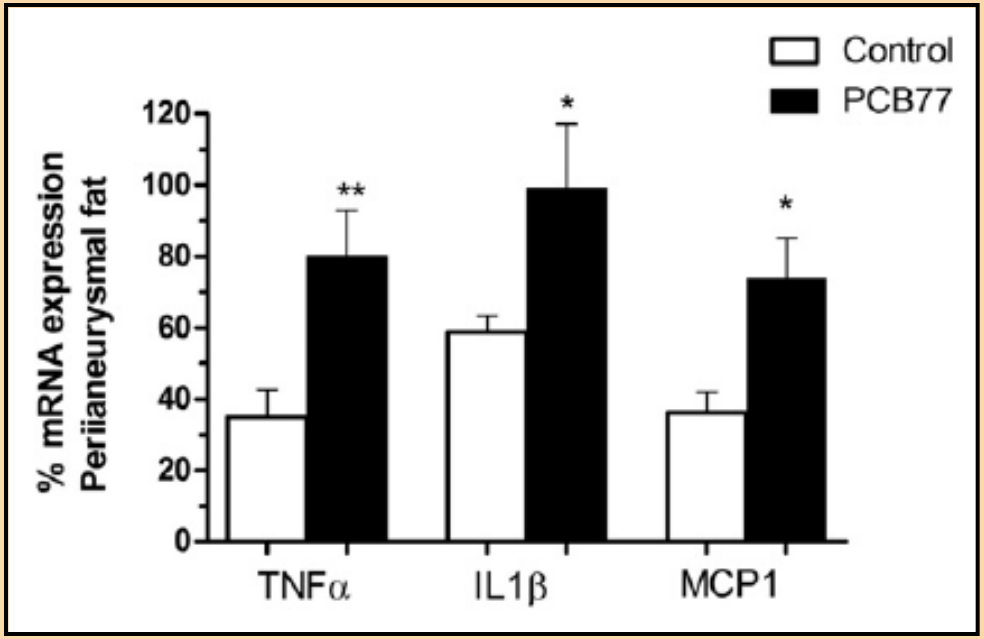
# Exposure to POPs correlates to the incidence of type 2 diabetes




D-H Lee et al, Diabetes Care 29: 1638–1644 (2006)

# PCB77 induces expression of proinflammatory cytokines in adipose tissue




Arsenescu, et al, Environ Health Perspect, 116:761-768 (2008)

Arsenescu, Baker N, et al, Toxicology and Applied Pharmacology, 257:148-154 (2011)

# Working Hypothesis

The working hypothesis of these studies is that exposure of lean mice to PCB77 induces diabetes by stimulating production of adipose TNF-α.


# Does PCB77 result in dose-dependent glucose and insulin intolerance?

Male
C57BL/6, Low Fat Diet

- **Vehicle**
- **PCB77 (2.5 mg/kg)**
- **PCB77 (50 mg/kg)**
- **PCB77 (248 mg/kg)**

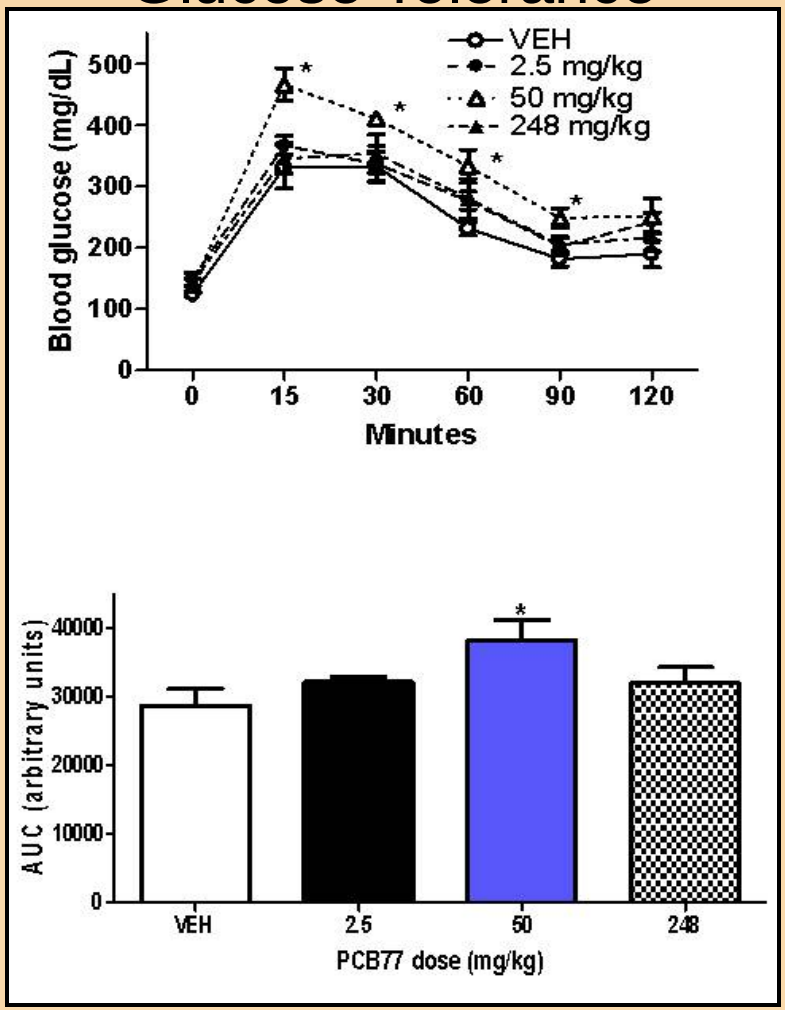
| Week: | 1 2 |
| --- | --- |
| Oral Gavage | Weeks 1 & 2 |
| Animals Sacrificed | Week 2 |

Prior to sacrifice:

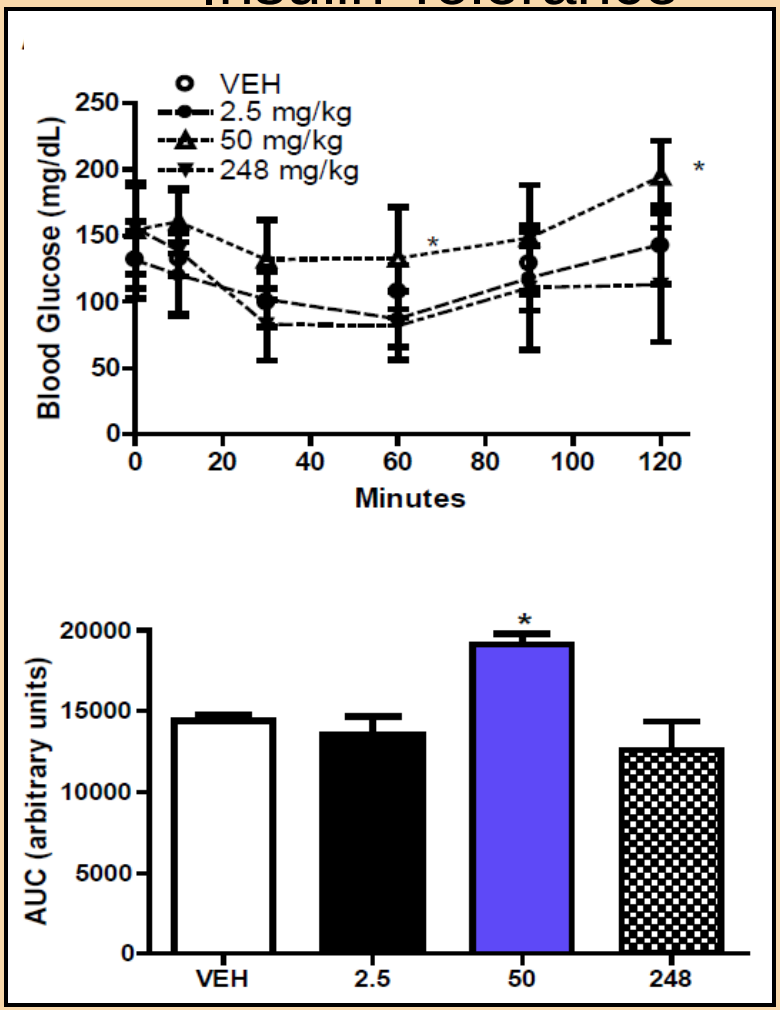
- Glucose Tolerance Test
- Insulin Tolerance Test

# PCB77-induced impairment of glucose and insulin tolerance is dose-dependent

Glucose Tolerance



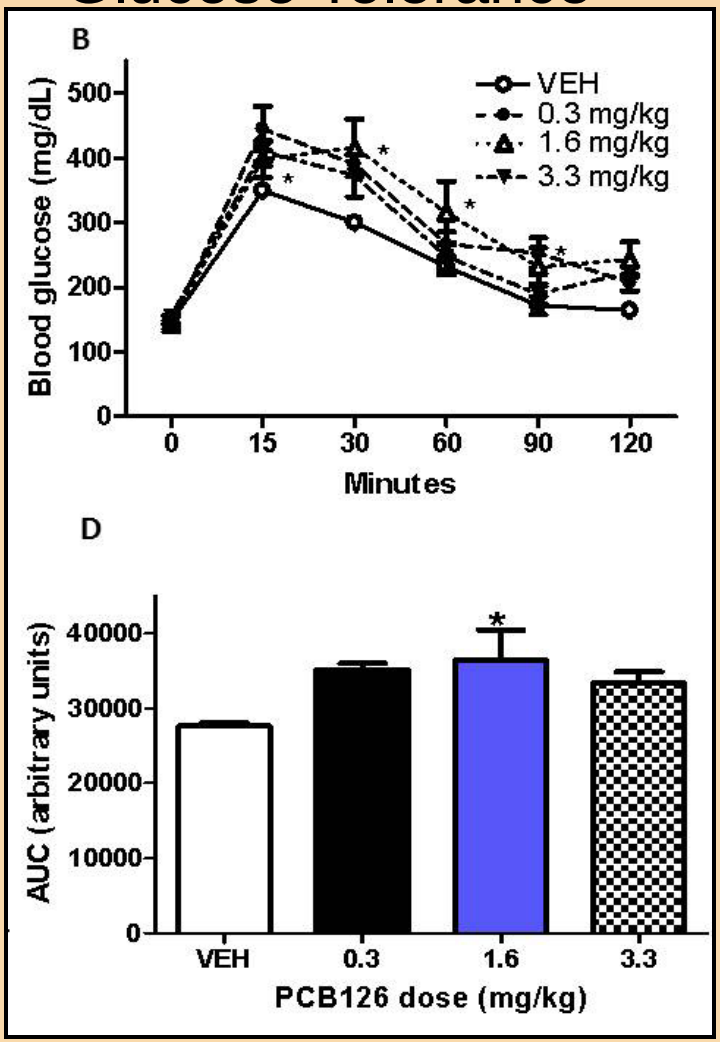

Insulin Tolerance



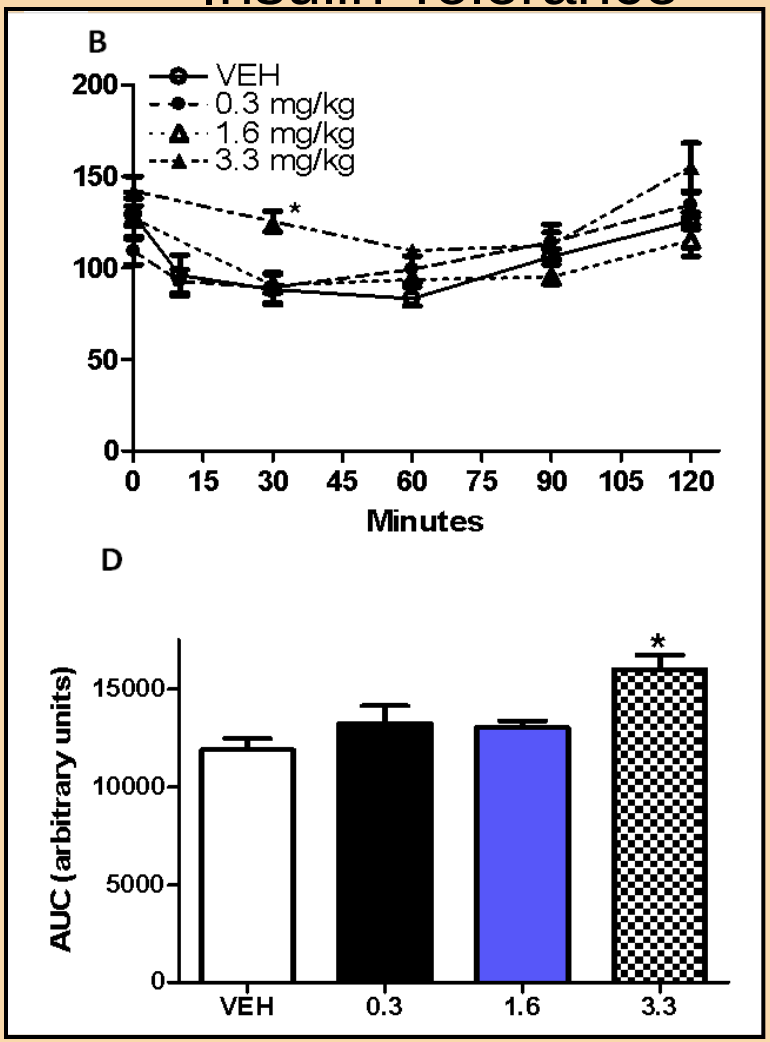

Baker N, et al, *Environ Health Perspect*, (2012, in revision)

# PCB126-INDUCED IMPAIRMENT OF GLUCOSE AND INSULIN TOLERANCE IS DOSE-DEPENDENT

## Glucose Tolerance




## Insulin Tolerance




Baker N, et al, *Environ Health Perspect*, (2012, in revision)

# Is PCB77-induced impairment of glucose and insulin tolerance AhR-dependent?

- CH223191, a potent AhR antagonist
- Mice gavaged with CH223191 (10 mg/kg/day, oil) for 1 week prior to and for duration of study

Male
C57BL/6, Low Fat Diet

- **Vehicle**
- **CH223191**
- **PCB77 (50 mg/kg)**
- **PCB77 + CH223191**

Experimental Design

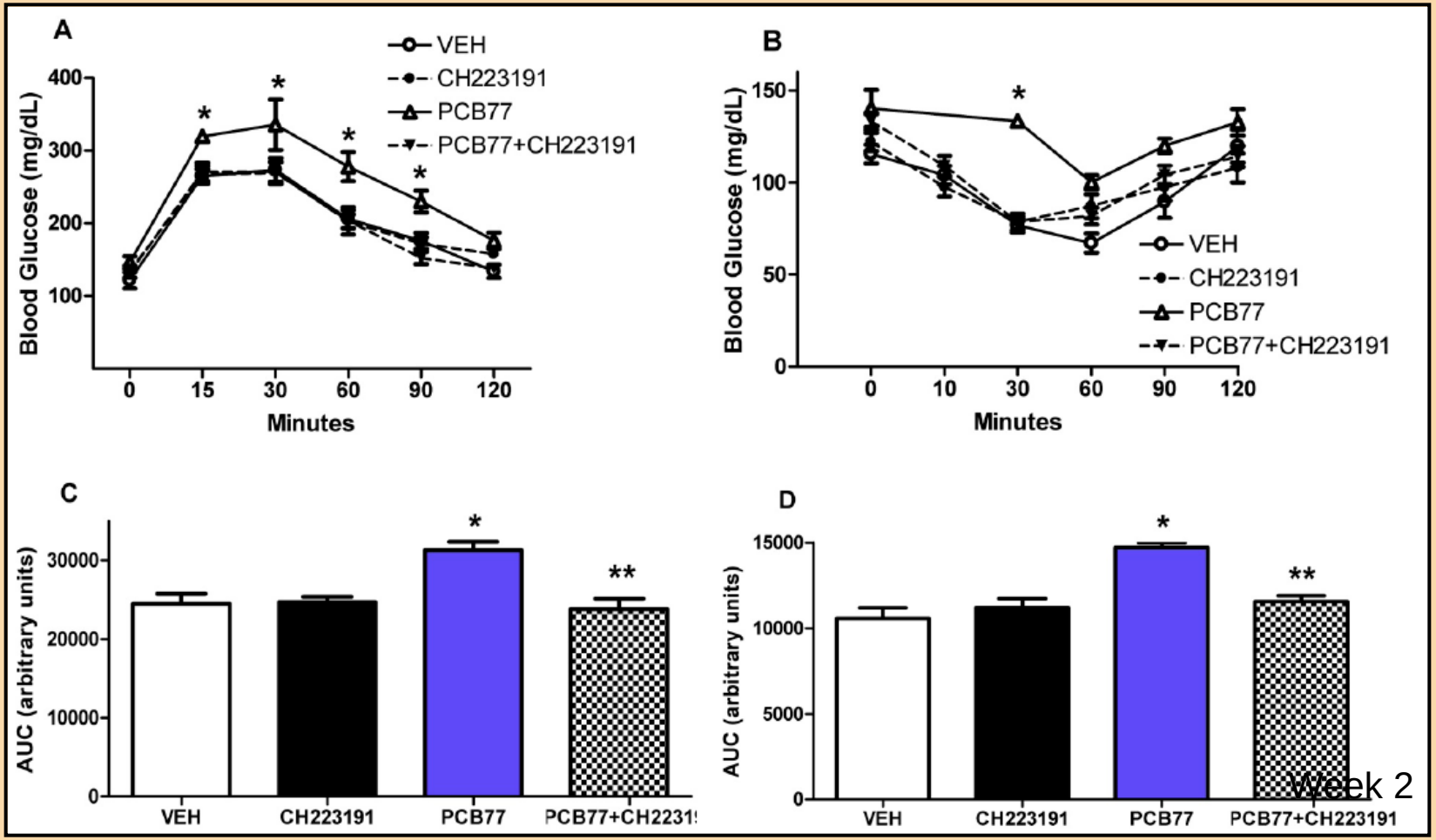
| Week: | 0 1 2 |
|---|---|
| Gavage CH223191 | Week 0, 1, 2 |
| Gavage PCB77 | Weeks 1 & 2 |
| Animals Sacrificed | Week 2 |

Kim SH, et al, *Mol Pharmacol*, 69(6):1871-8 (2006)
Choi, et al, *Mol Pharmacol*, 81(1):3-11 (2012)

# Is PCB77-induced impairment of glucose and insulin tolerance AhR-dependent?

Glucose Tolerance

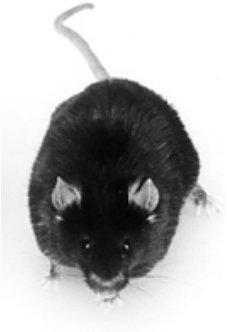
Insulin Tolerance




Week 2

Baker N, et al, *Environ Health Perspect*, (2012, in revision)

# Is PCB77-induced impairment of glucose homeostasis sustained?



Male
C57BL/6,
Low Fat Diet

**Vehicle**

**PCB77 (50 mg/kg)**

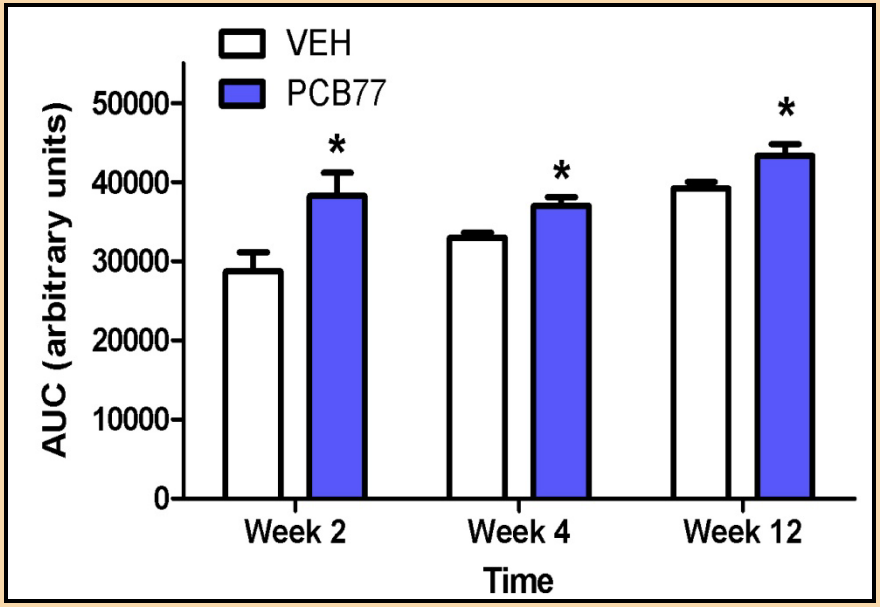
Monthly:

- Glucose Tolerance Test
- Insulin Tolerance Test

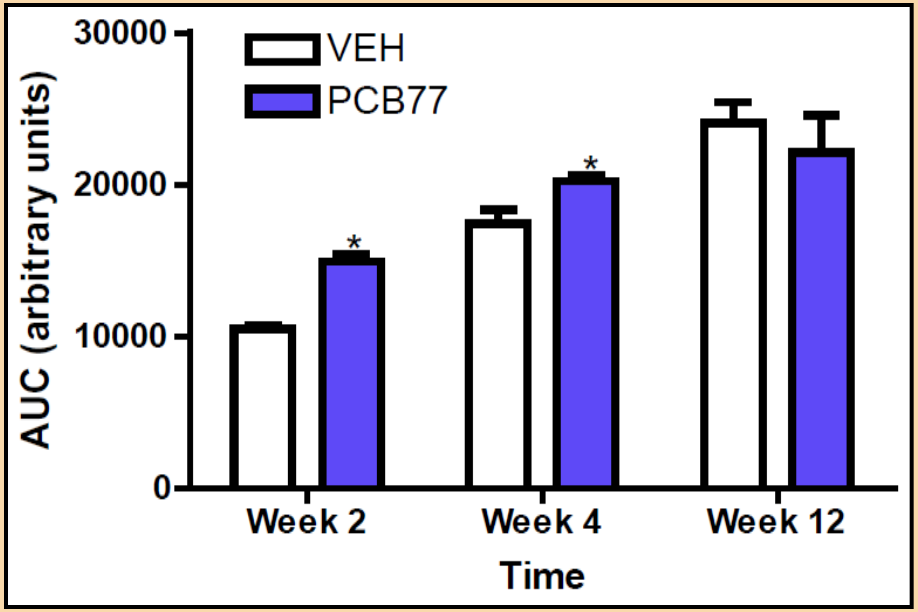
| Week: | 1 2 3 4 5 6 7 8 9 10 11 12 |
|---|---|
| Oral Gavage | Weeks 1 & 2 — Weeks 9 &10 |
| Animals Sacrificed | Week 2 — Week 4 — Week 12 |

# PCB77 promotes sustained glucose and insulin intolerance

Glucose Tolerance

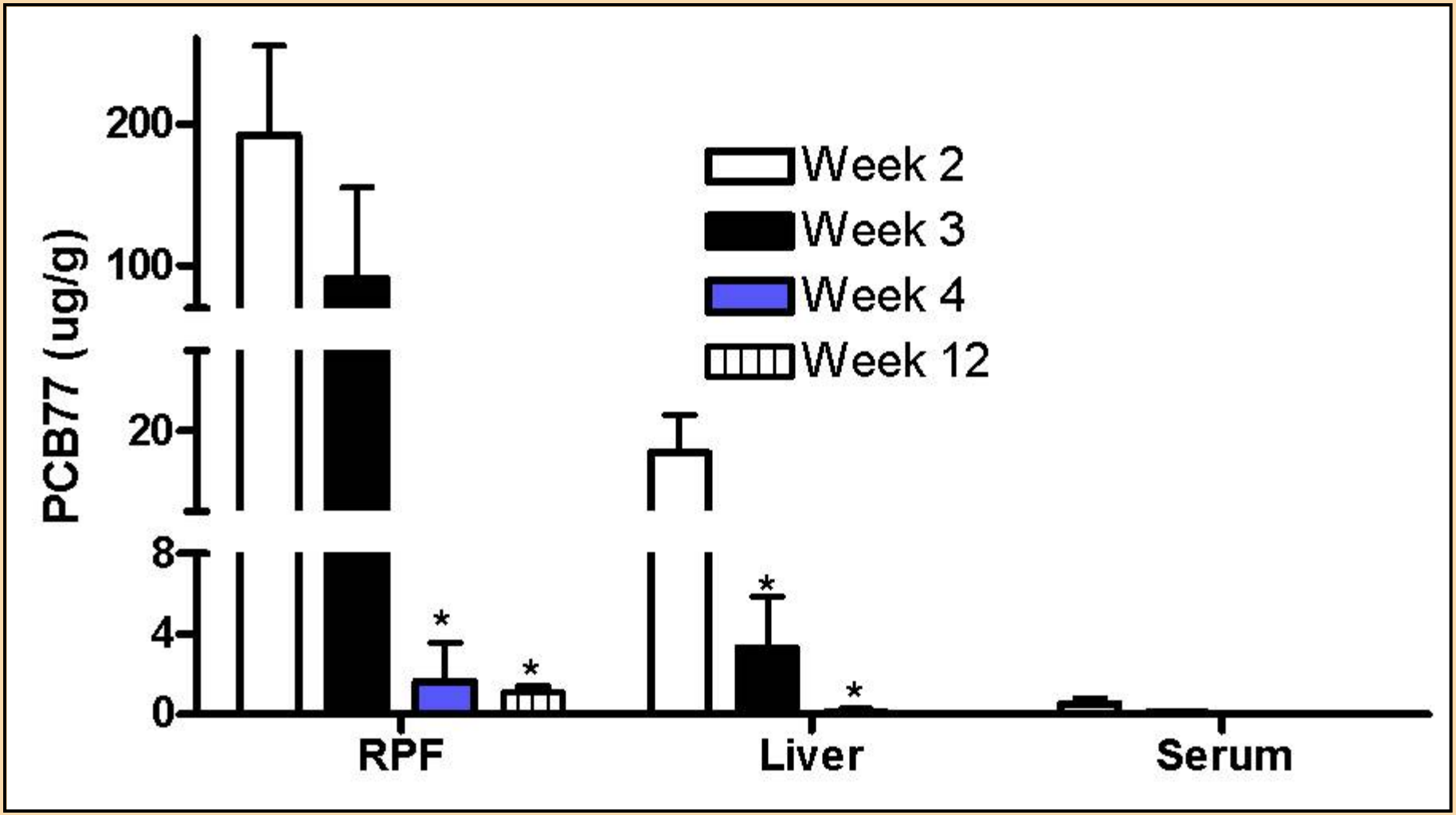



Insulin Tolerance



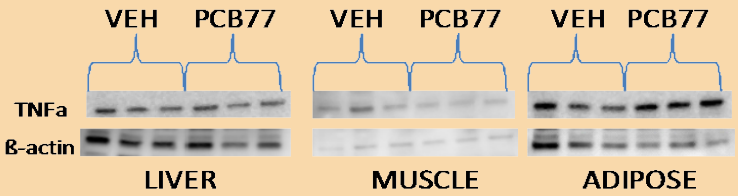

Baker N, et al, *Environ Health Perspect*, (2012, in revision)

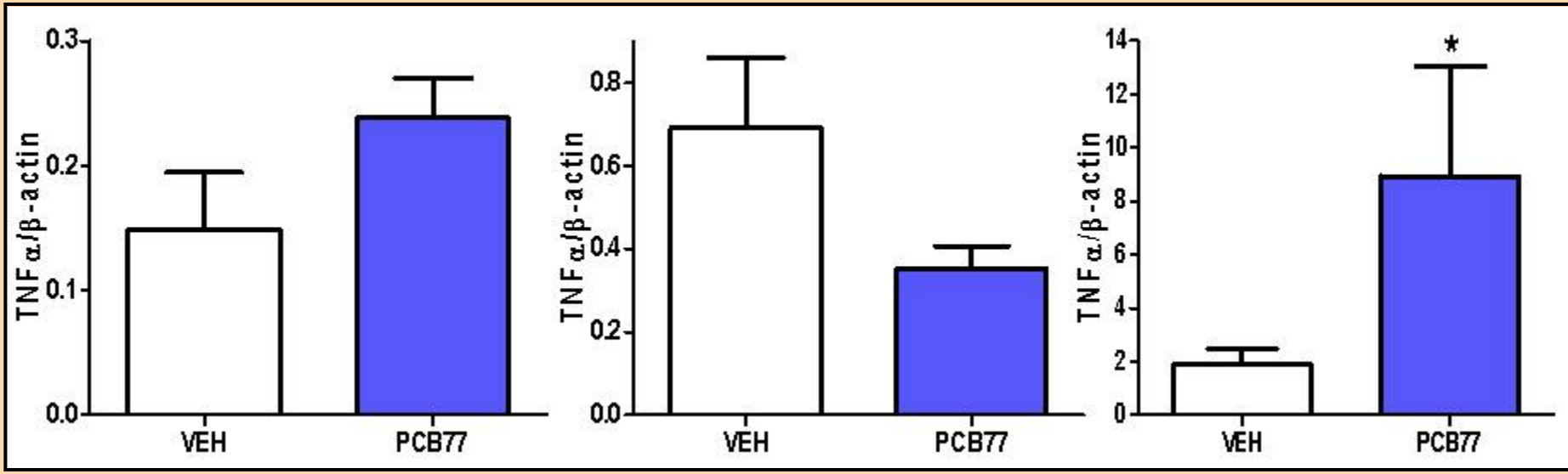
# PCB77 accumulates in adipose tissue




Baker N, et al, *Environ Health Perspect*, (2012, in revision)

# PCB77 causes an adipose-specific increase in TNF-α in lean mice




Baker N, et al, *Environ Health Perspect*, (2012, in revision)

# Studies in Obese Mice - Hypothesis

With obesity, PCB77-induced diabetes is mitigated due to sequestration in lipid pools of adipose tissue. During weight loss, release of stored PCB77 from adipose tissue will blunt the beneficial effects of weight loss on glucose and insulin homeostasis.

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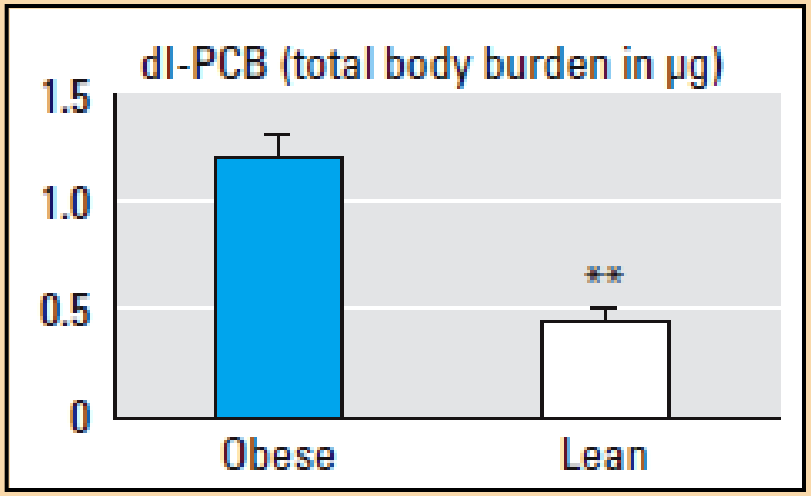
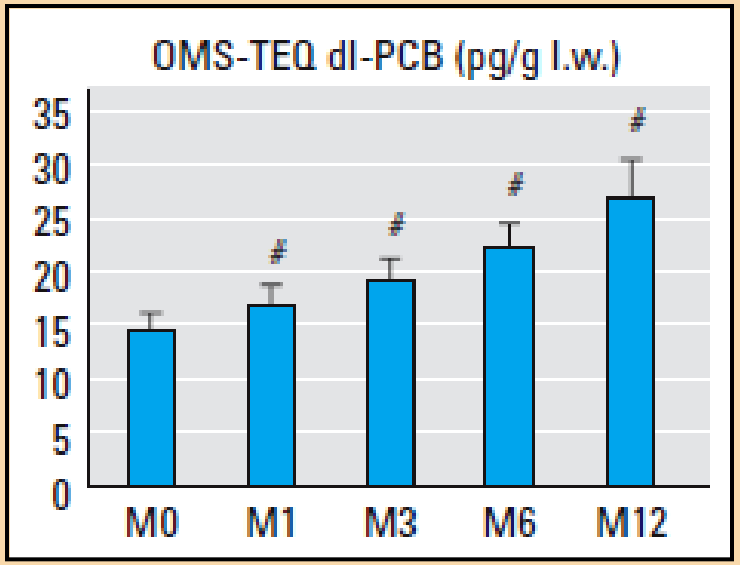
ADIPOSE




SERUM




Kim M-J, et al, *Environ Health Perspect*, 119:377-383 (2011)

# What does PCB77 do to glucose homeostasis during weight gain *versus* weight loss?

Groups:
Male
C57BL/6

## High fat diet

- 60% kcal from fat
- Fat sources: Lard > soybean oil
- Energy: 5.24 kcal/g

**Vehicle**

**PCB77 (50 mg/kg)**

Measurements:
Monthly:

- Glucose Tolerance Test
- Insulin Tolerance Test

| Week: | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 |
|---|---|
| Oral Gavage | Weeks 1 & 2 — Weeks 9 &10 |
| Start LF Diet | Week 12 |
| Animals Sacrificed | Week 12 — Week 16 |

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**Weight Gain Phase**

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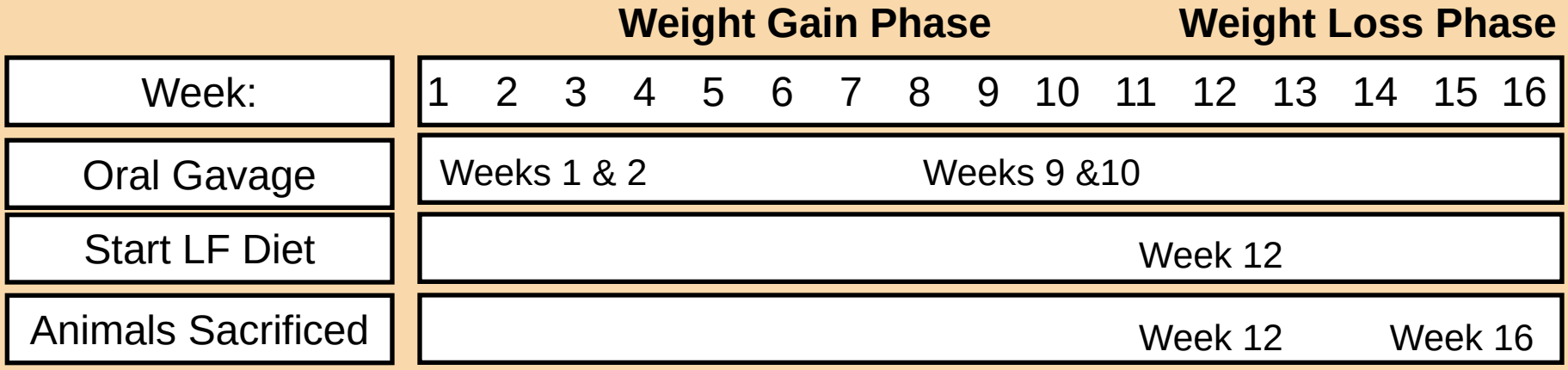
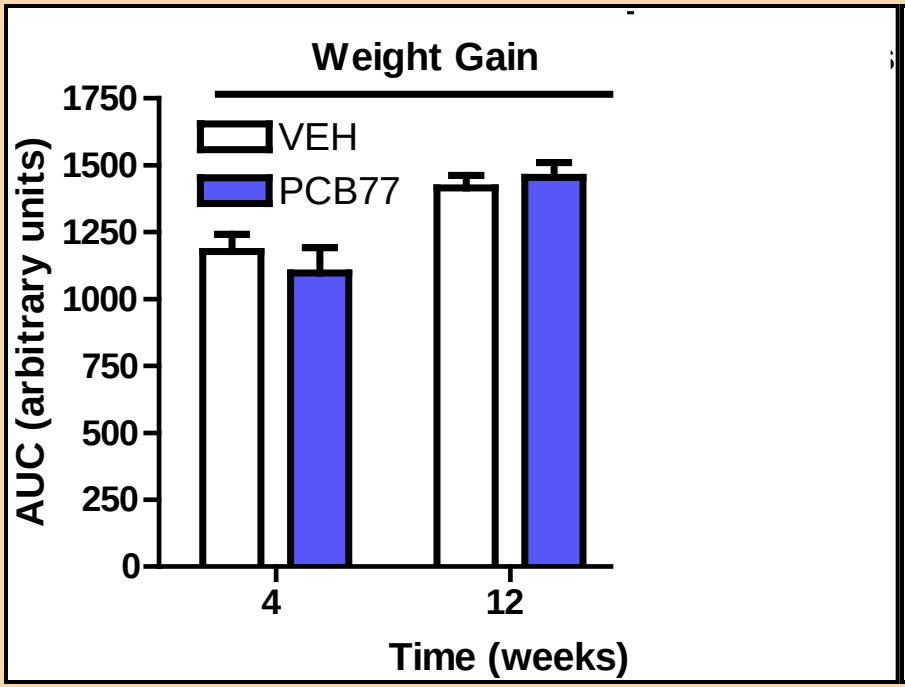
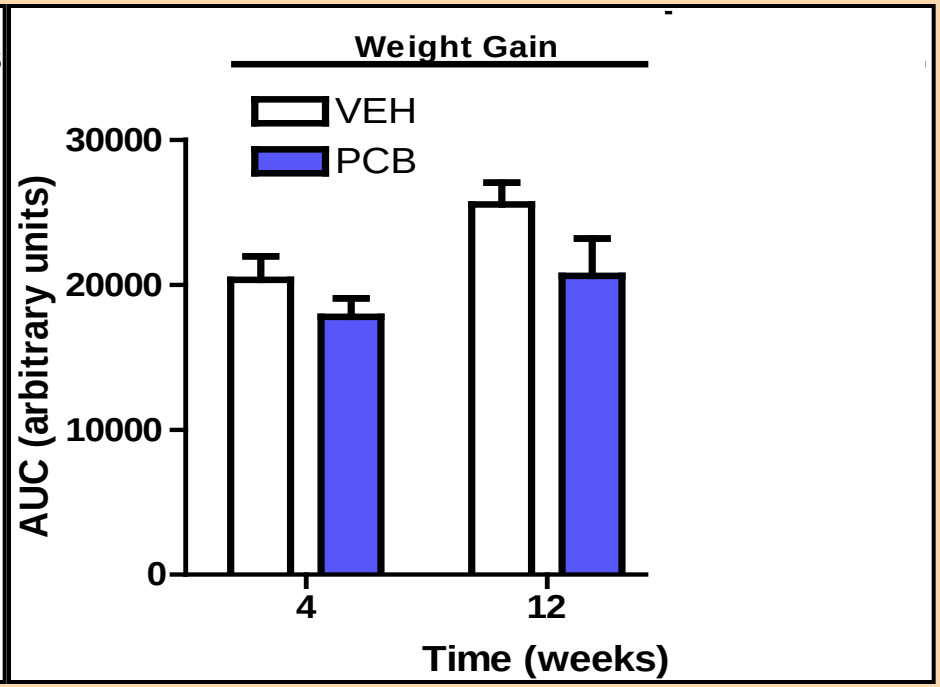


# PCB77-induced glucose intolerance is blunted in obese mice, but appears following weight loss

Glucose Tolerance




Insulin Tolerance




Baker N, et al, *Environ Health Perspect*, (2012, in revision)

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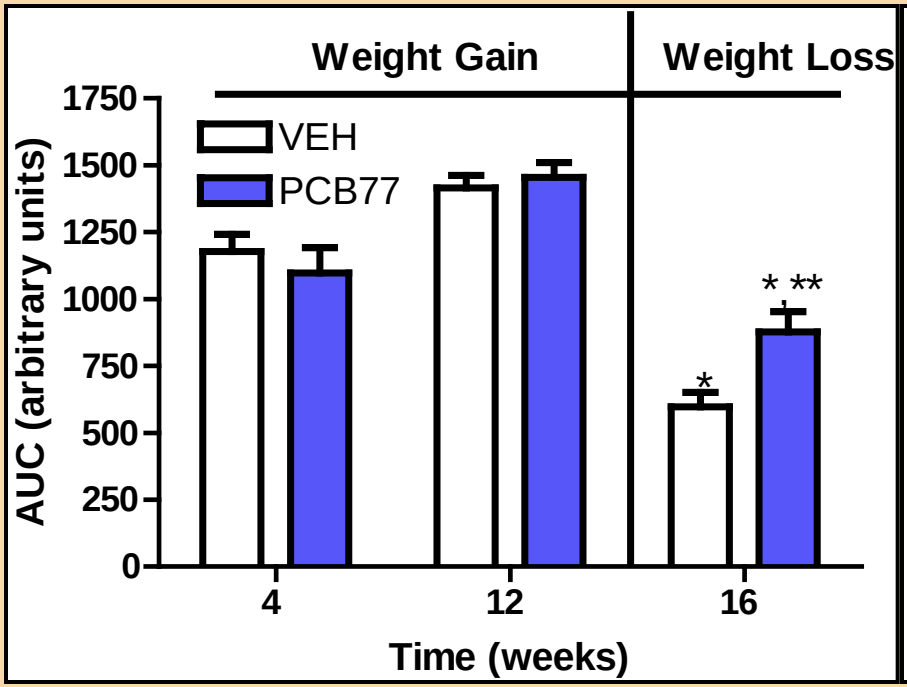
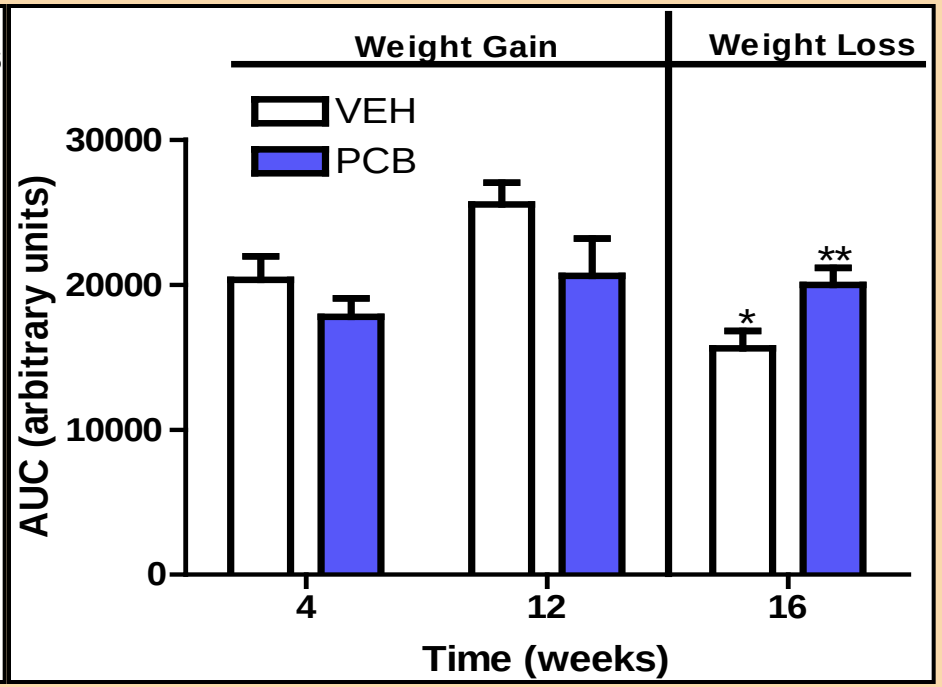



Insulin Tolerance

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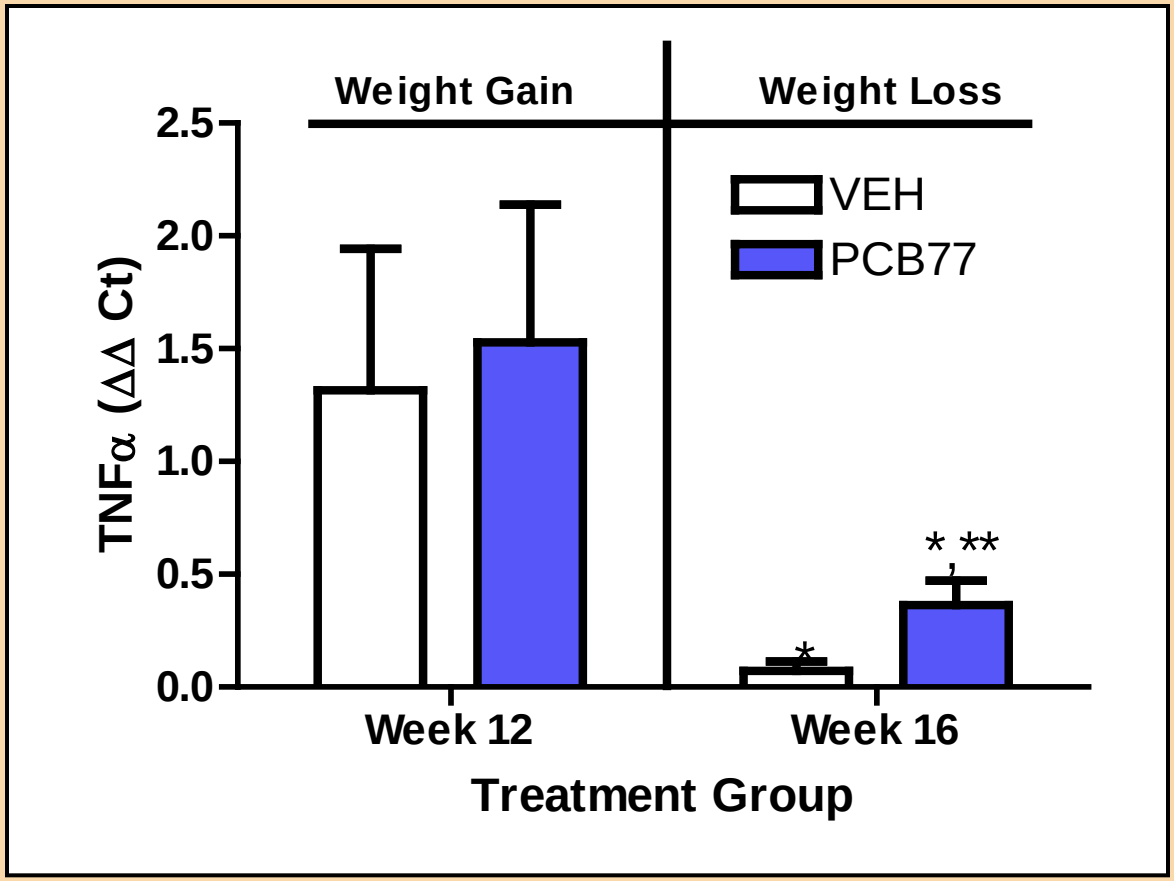


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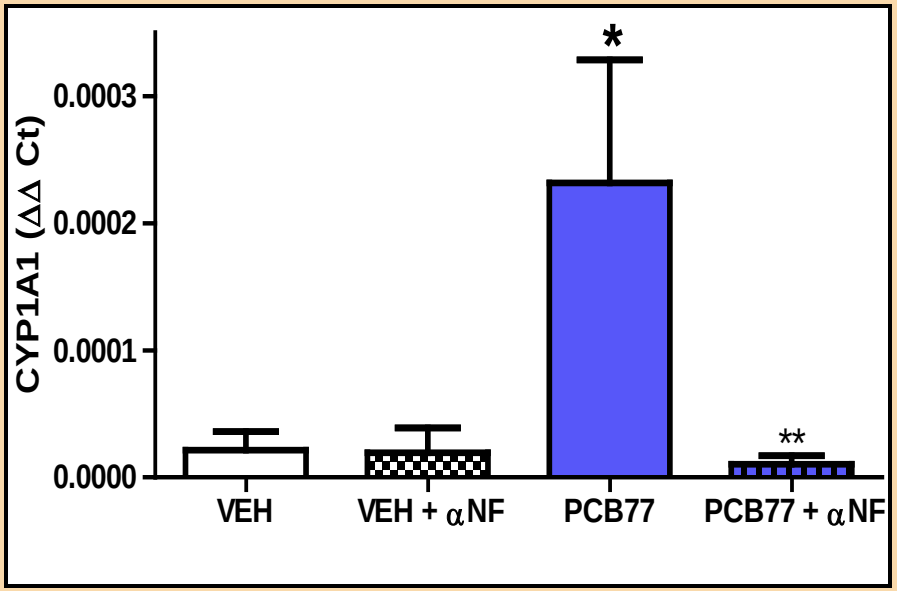
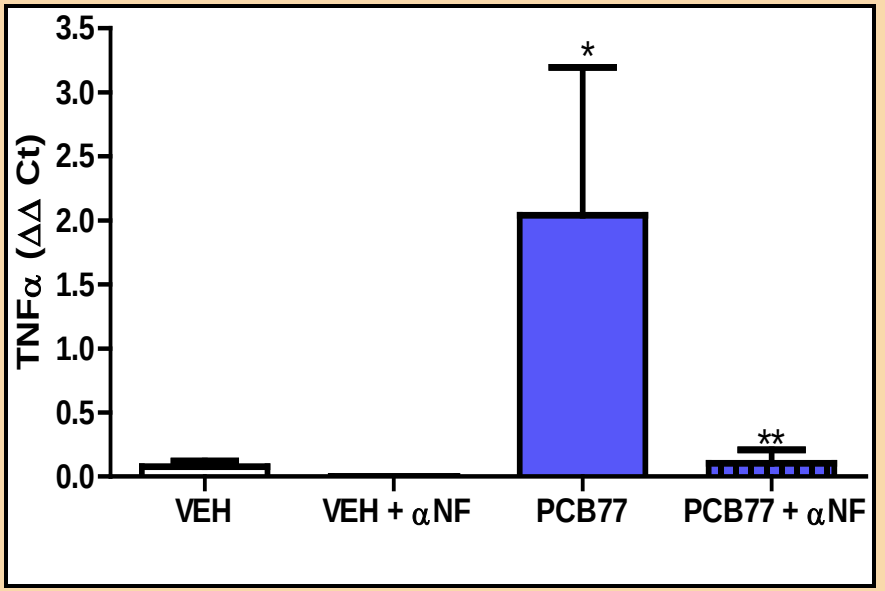
# PCB77 induces CYP1A1 and TNF-α mRNA abundance via the AhR in 3T3-L1 adipocytes

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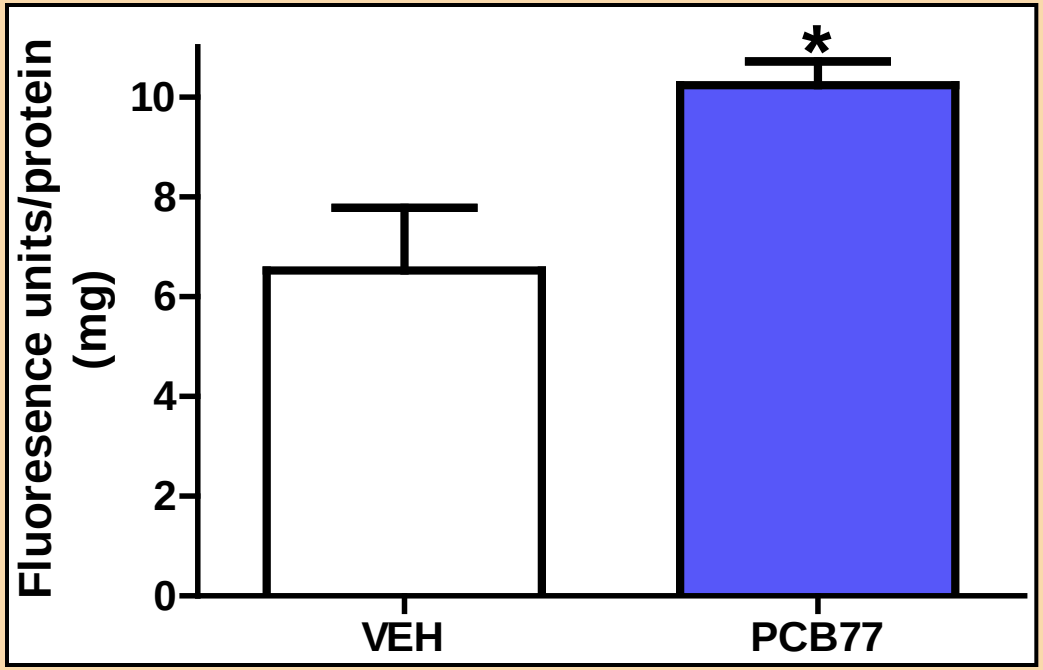


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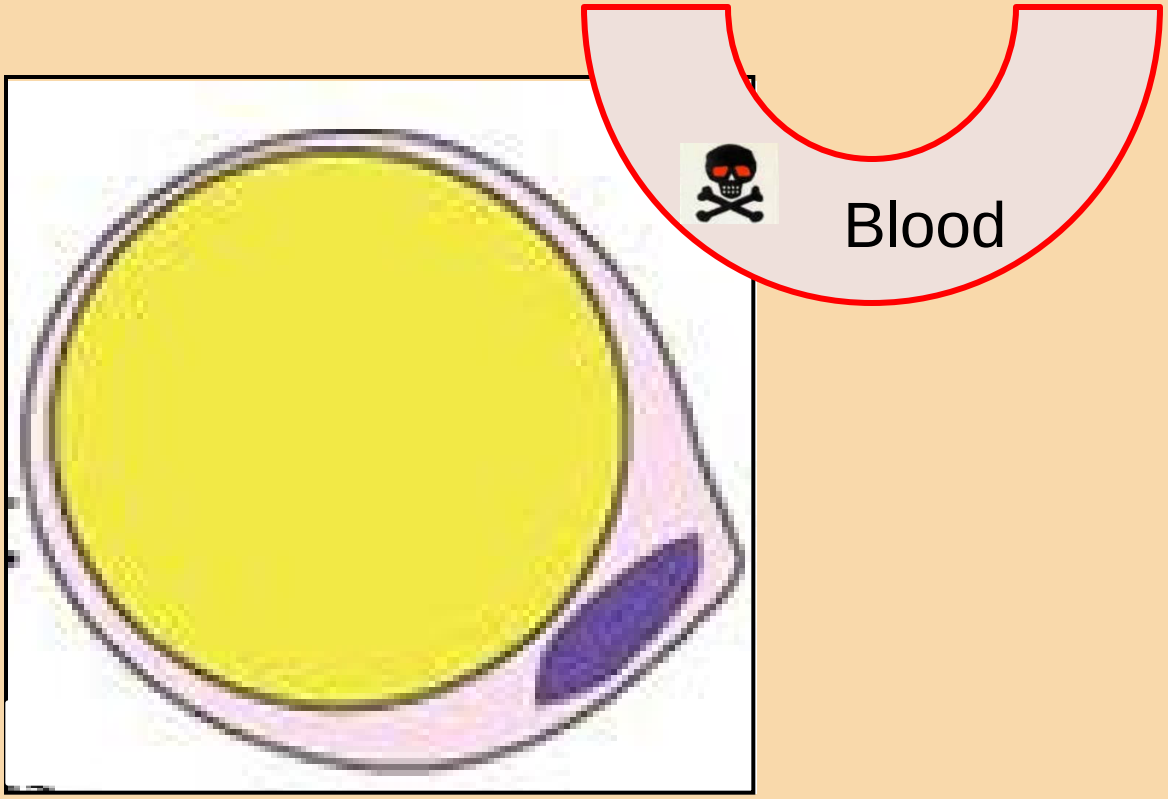
# A proposed adipocyte-specific mechanism for PCB-induced insulin resistance



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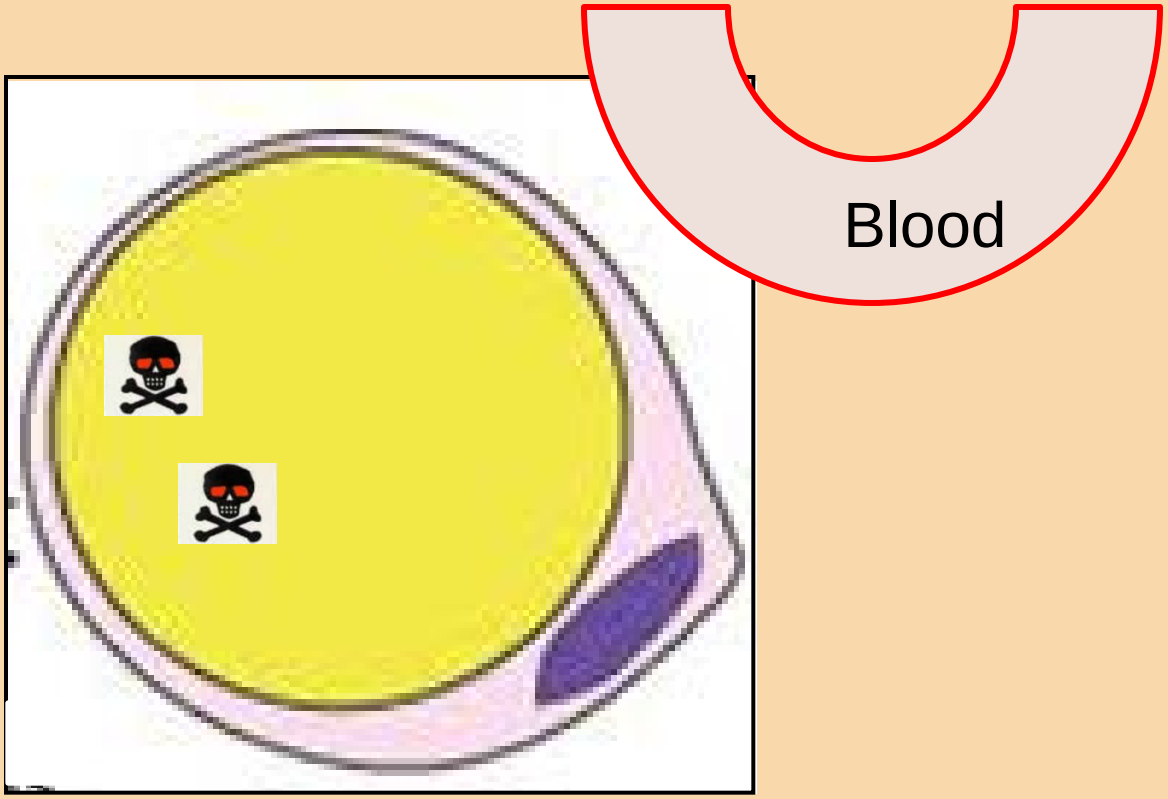

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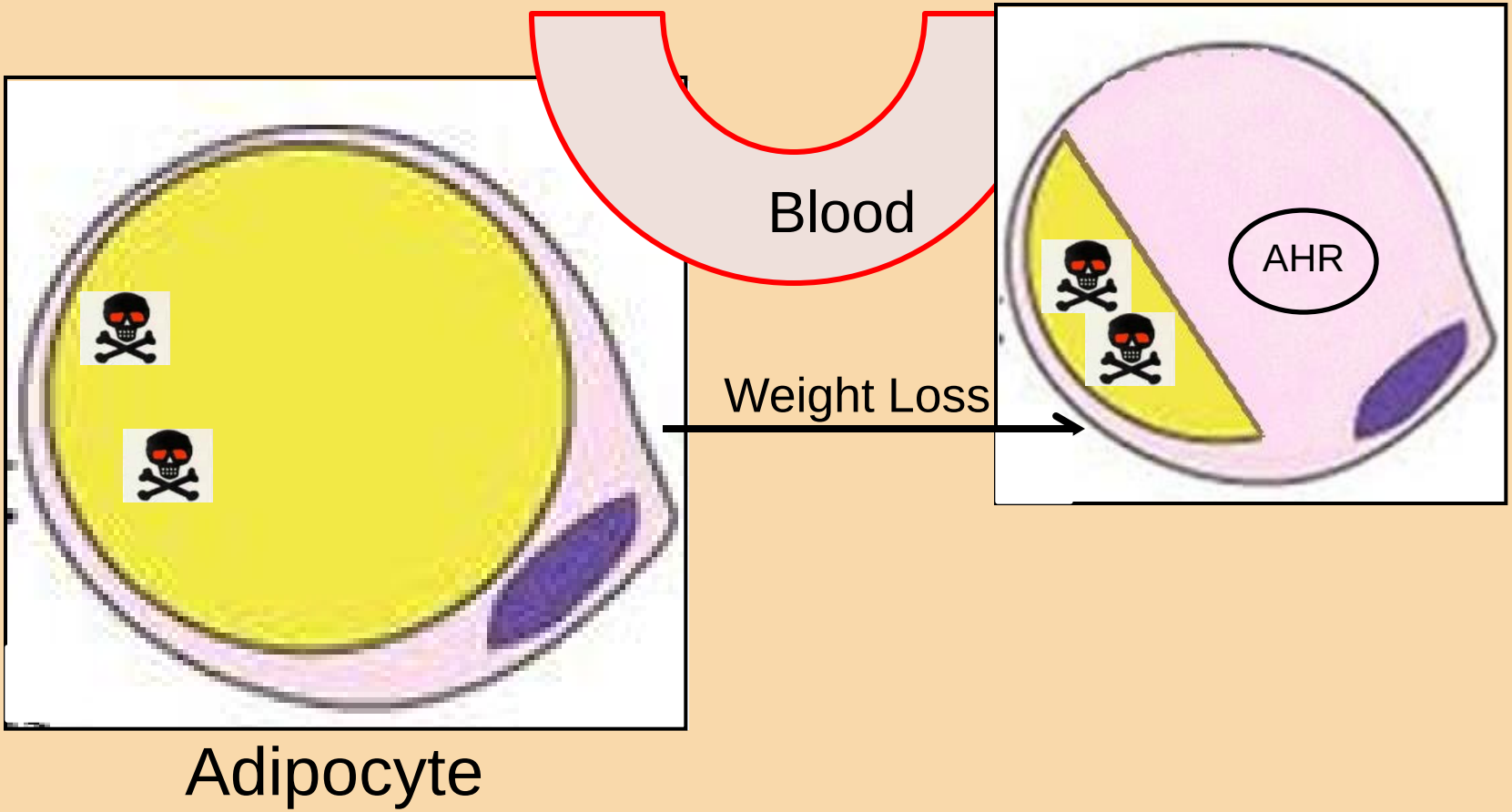

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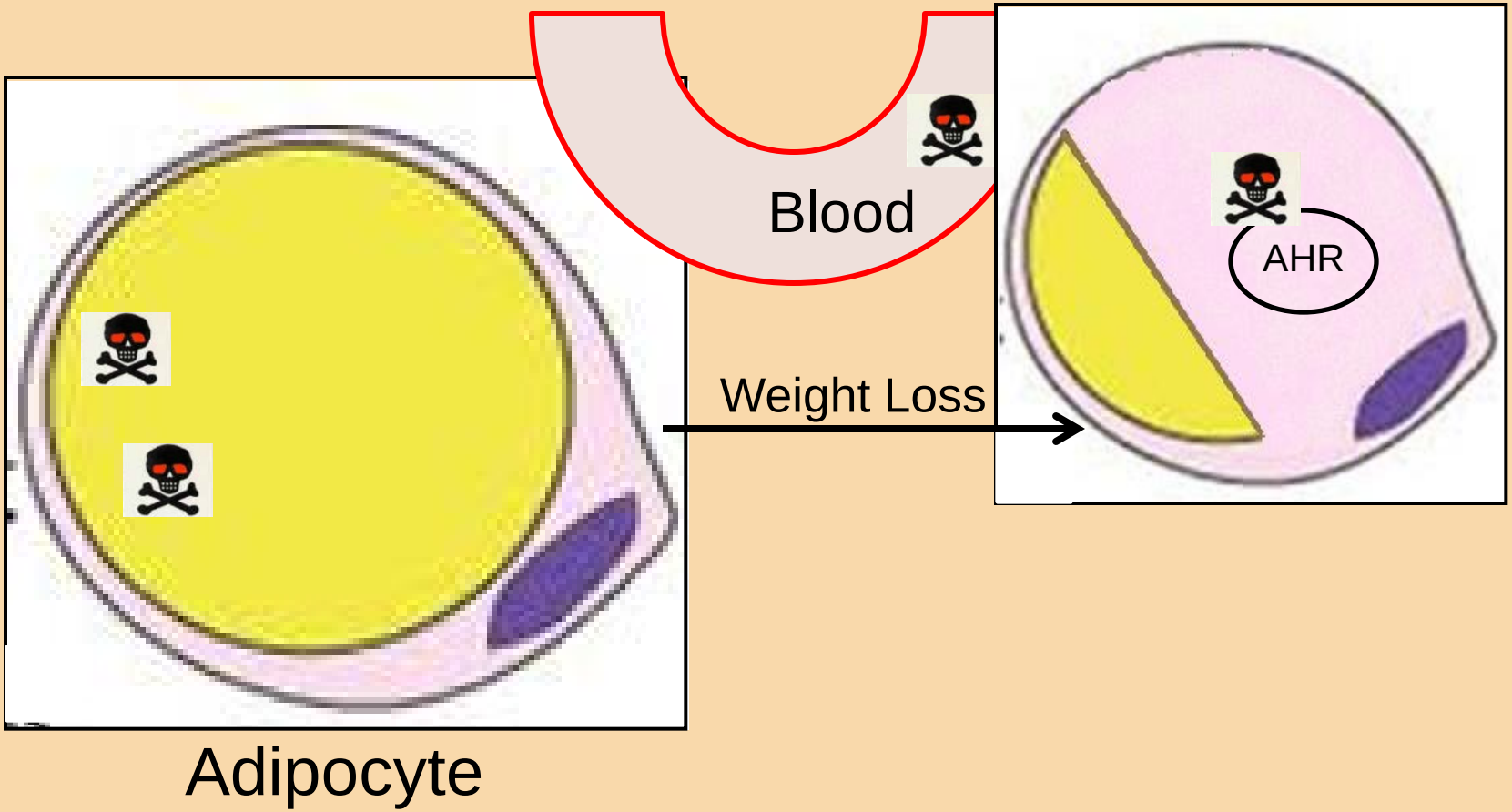

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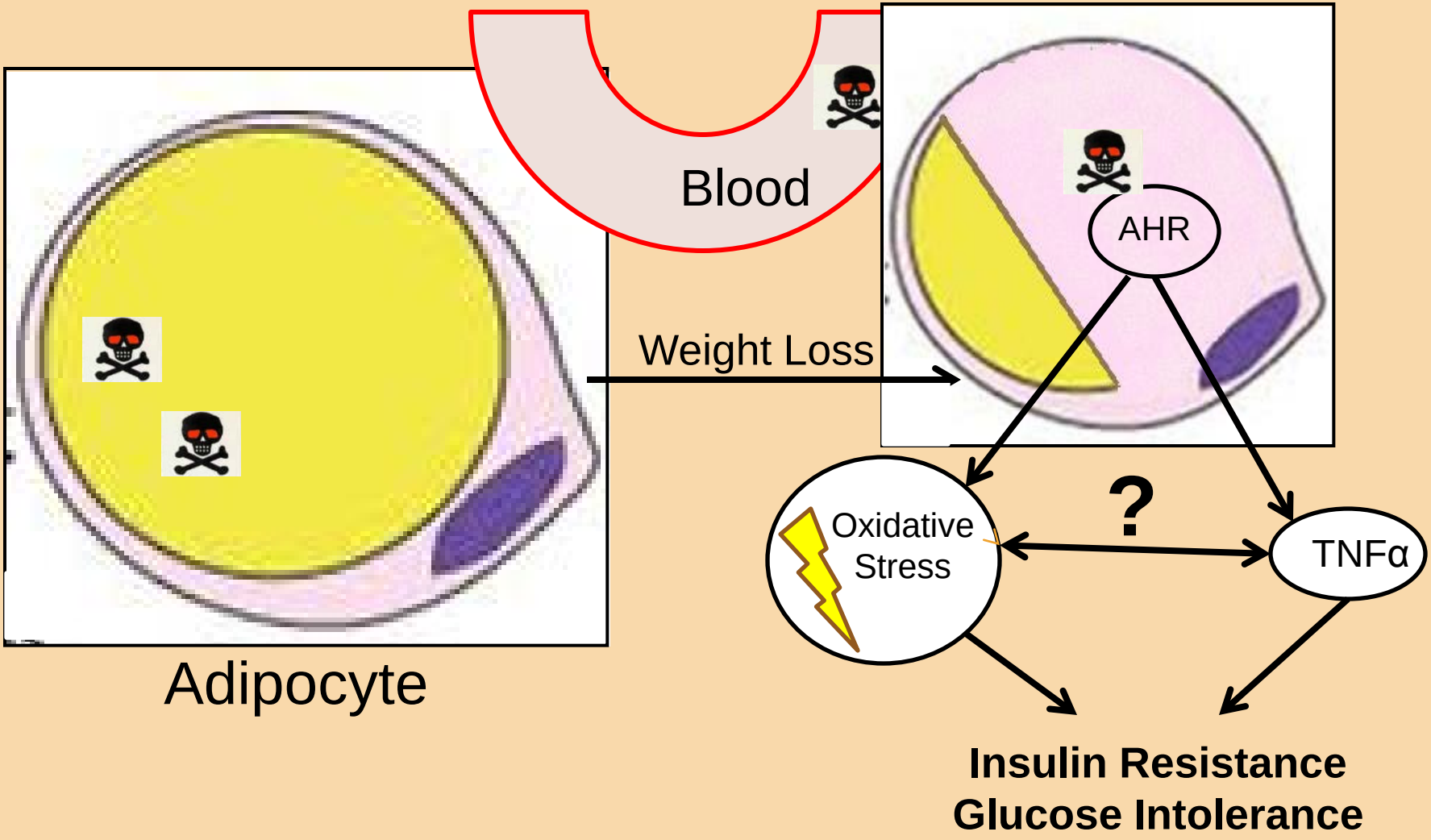

# Acknowledgements


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Cassis Lab:

- Vicki English
- Wendy Katz
- Eboni Lewis
- Robin Shoemaker
- Sean Thatcher
- Yu Wang
- Frederique Yiannikouris
- Xuan Zhang

Committee Members:

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- Dr. Hollie Swanson

Wei Lab:

- Dr. Yinan Wei
- Dr. Jun Fang

Walker Lab, UNM:

- Dr. Mary Walker

Morris Lab:

- Dr. Andrew Morris
- Manjula Sunkara

Statistics Help:

- Dr. Arnold Stromberg

Family:

- Rory Baker
- Ava Parker Baker

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