



Ares: Vita  
catSci Exco:  
entia latur

# The Paradox of Progress

Environmental Chemicals & the Origins of Diabetes

Robert M. Sargis, MD, PhD

Assistant Professor of Medicine

Section of Endocrinology, Diabetes, and Metabolism

University of Chicago

# Diabetes

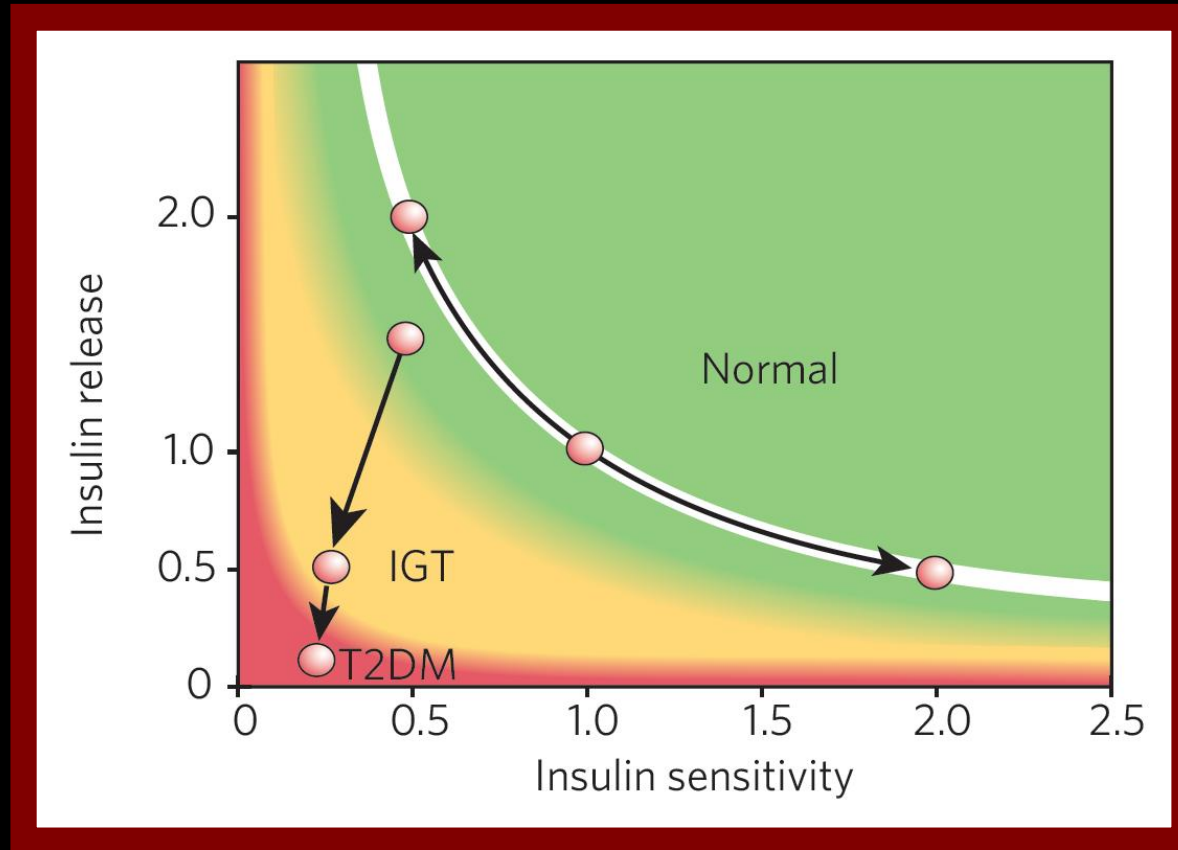
---



- Defined phenotypically by elevations in blood glucose levels.
- Constellation of diseases with various pathogeneses
  - Type 2 Diabetes (~90-95%)
  - Type 1 Diabetes (~5-10%)
  - Monogenic Diabetes (~1%)
  - Gestational Diabetes (9.2%)
  - Others

# Diabetes: Loss of Glucose Regulation...and More

←β-cell Dysfunction



←Insulin Resistance



## Blindness

## Kidney Failure



## Cardiovascular Disease



## Amputations



# **Economic Costs of Diabetes in the U.S. in 2012**

---

AMERICAN DIABETES ASSOCIATION

---

\$245 billion annually...and climbing

### North America and Caribbean

2015 **44.3 million**  
2040 **60.5 million**

### Europe

2015 **59.8 million**  
2040 **71.1 million**

### Middle East and North Africa

2015 **35.4 million**  
2040 **72.1 million**

### Western Pacific

2015 **153.2 million**  
2040 **214.8 million**

### South and Central America

2015 **29.6 million**  
2040 **48.8 million**

### Africa

2015 **14.2 million**  
2040 **34.2 million**

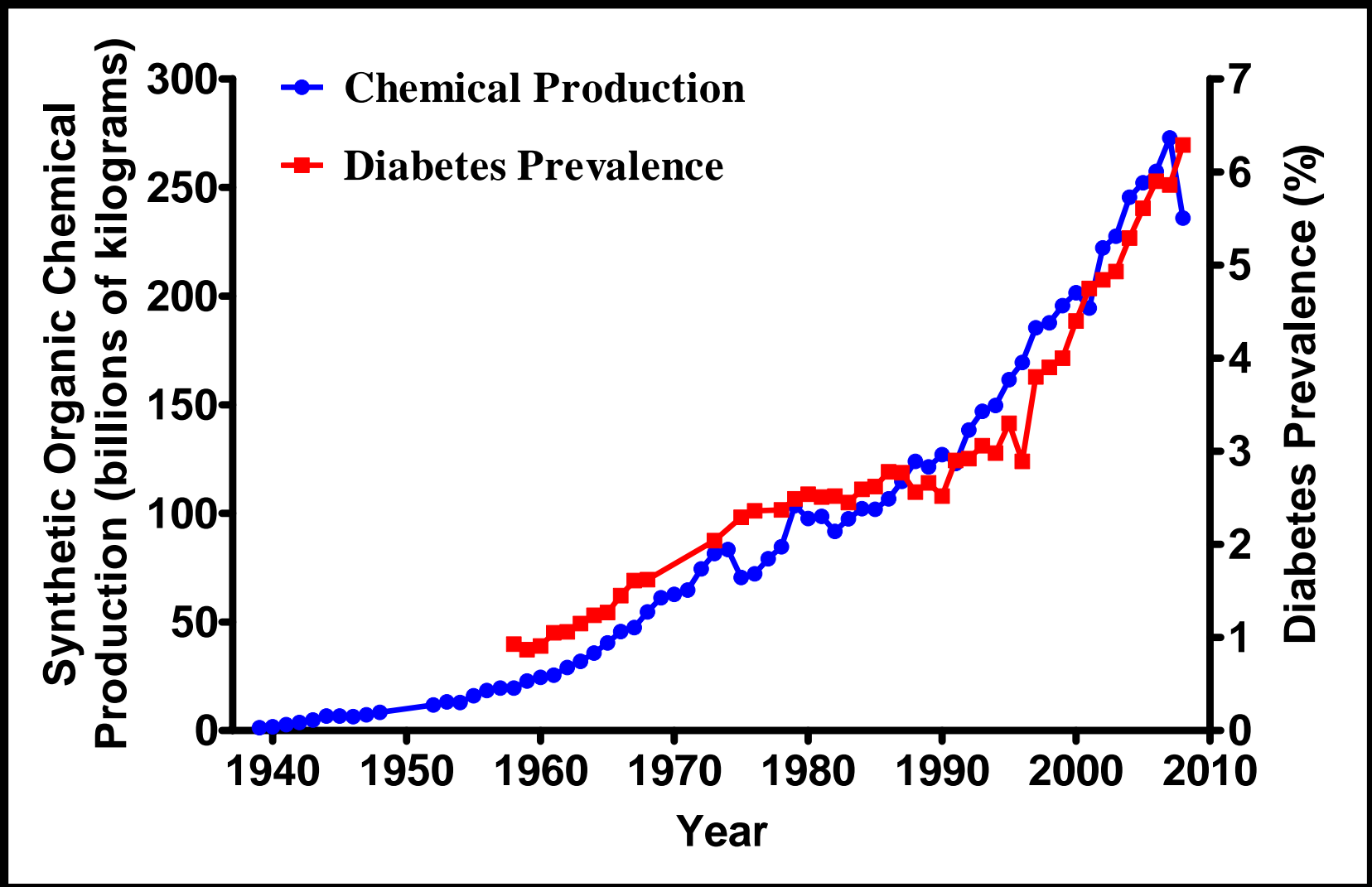
### South East Asia

2015 **78.3 million**  
2040 **140.2 million**

## World

2015 **415 million**  
2040 **642 million**







# EXPERIMENTAL ALLOXAN DIABETES IN THE RAT

J. SHAW DUNN  
M D GLASG

PROFESSOR OF PATHOLOGY

*(From the Pathological Department of the University and  
Western Infirmary, Glasgow)*

N. G. B. McLETCHE  
M B GLASG

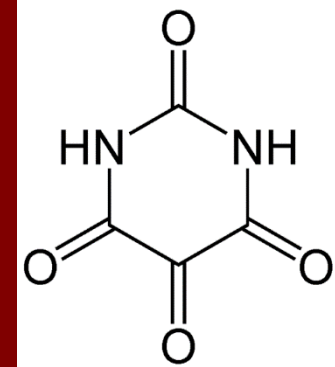


Fig. 4—Islet from diabetic rat No. 7. The cells are disordered in arrangement, the central ones being enlarged and the peripheral ones smaller than normal. (x 350.)

First synthesized in 1818 by Brugnatelli.

Used in the production of the purple dye murexide.

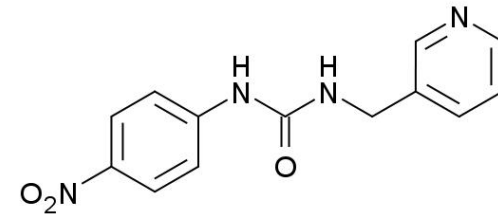
First described as a diabetogen in 1943.

Selective destruction of insulin-producing  $\beta$ -cells of the pancreatic islets of Langerhans.

*The Lancet*, 25 September 1943.

# Diabetes Mellitus and Autonomic Dysfunction After Vacor Rodenticide Ingestion

LEONA V. MILLER, JOHN D. STOKES, AND CHUTIMA SILPIPAT



52 yo man developed diabetic ketoacidosis after ingesting 1 gram of Vacor in a suicide attempt.

Vacor (Pyrinuron, Pyriminil) was a rodenticide voluntarily removed from the market in 1979.

First reported case of toxin-induced diabetes in humans.

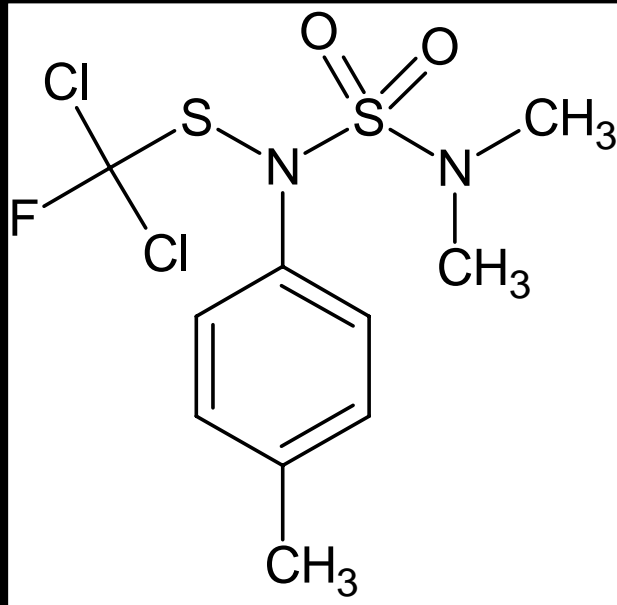
Diabetic ketoacidosis results from a specific destruction of insulin-producing  $\beta$ -cells in pancreatic islets of Langerhans.

*Diabetes Care*, March/April 1978.

# Diabetogenic Endocrine Disruptors

---

- Increasing number of environmental contaminants have been shown to modulate the key factors regulating glucose homeostasis:
  - Insulin Secretion
  - Insulin Action
- These include both inorganic and organic compounds of natural and synthetic origin.
  - Tolyfluanid
- Strength of evidence varies; however, the diversity and consistency of data suggests that toxicant exposures may represent novel diabetes risk factors.



# Tolyfluanid

$\text{Log } K_{ow} = 3.9$

$\text{LD}_{50} = 1000 \text{ mg/kg}$

$\text{NOAEL} = 76.3 \text{ mg/kg/day}$

Imported Food Tolerances:  
30 ppm on Hops

Exposure of 65 ppm



Civileats.com



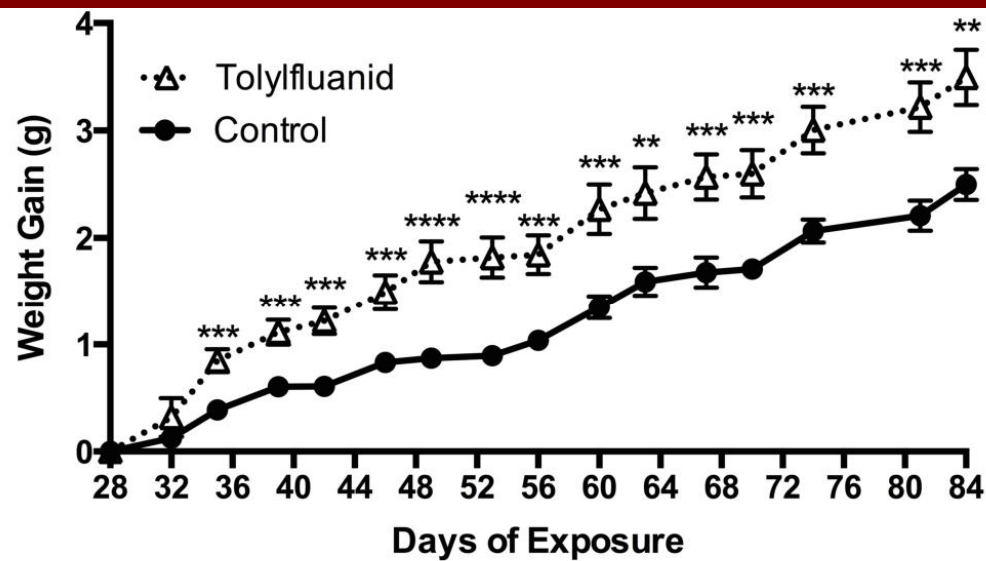
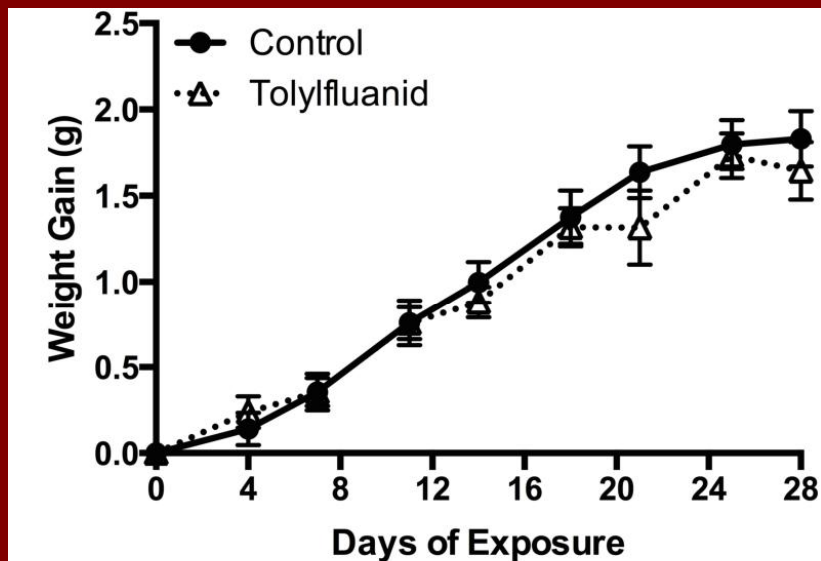
Viewzone.com



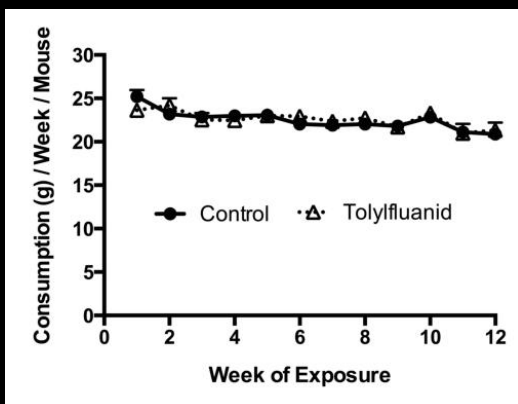
12

Drinks.seriousseats.com

# TF Promotes Weight Gain



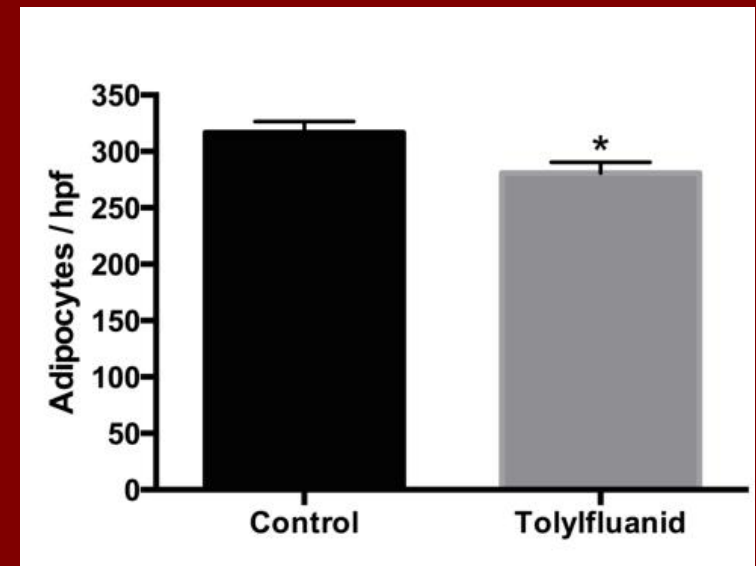
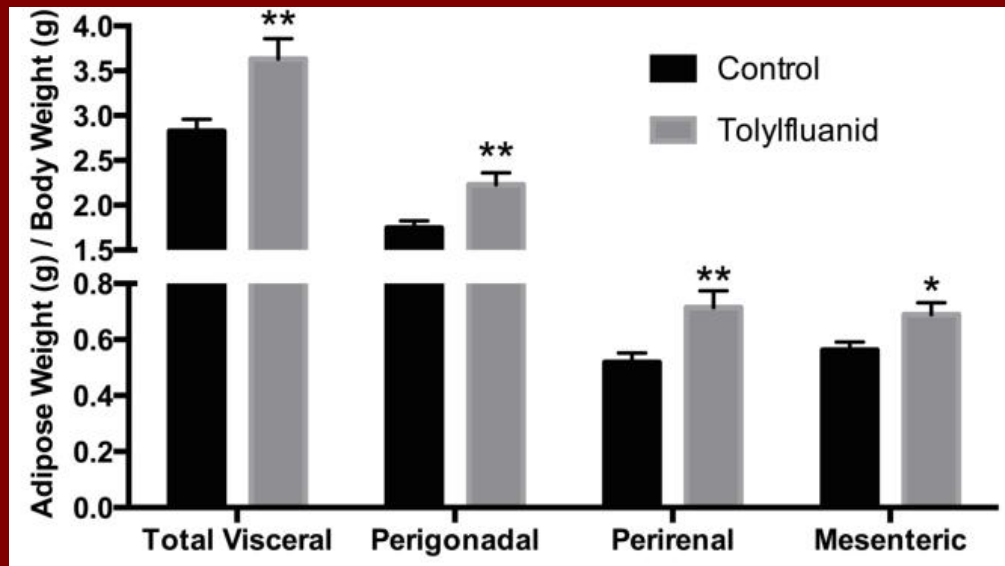
Male C57BL/6 Mice; 0 or 65 ppm TF x 12 weeks; Mean  $\pm$  S.E.M.; N=28; \*P<0.05, \*\*P<0.01; \*\*\*P<0.001; \*\*\*\*P<0.0001.



↑ Inflection Point in Weight Gain

← No Change in Food Intake

# TF Increases Adiposity

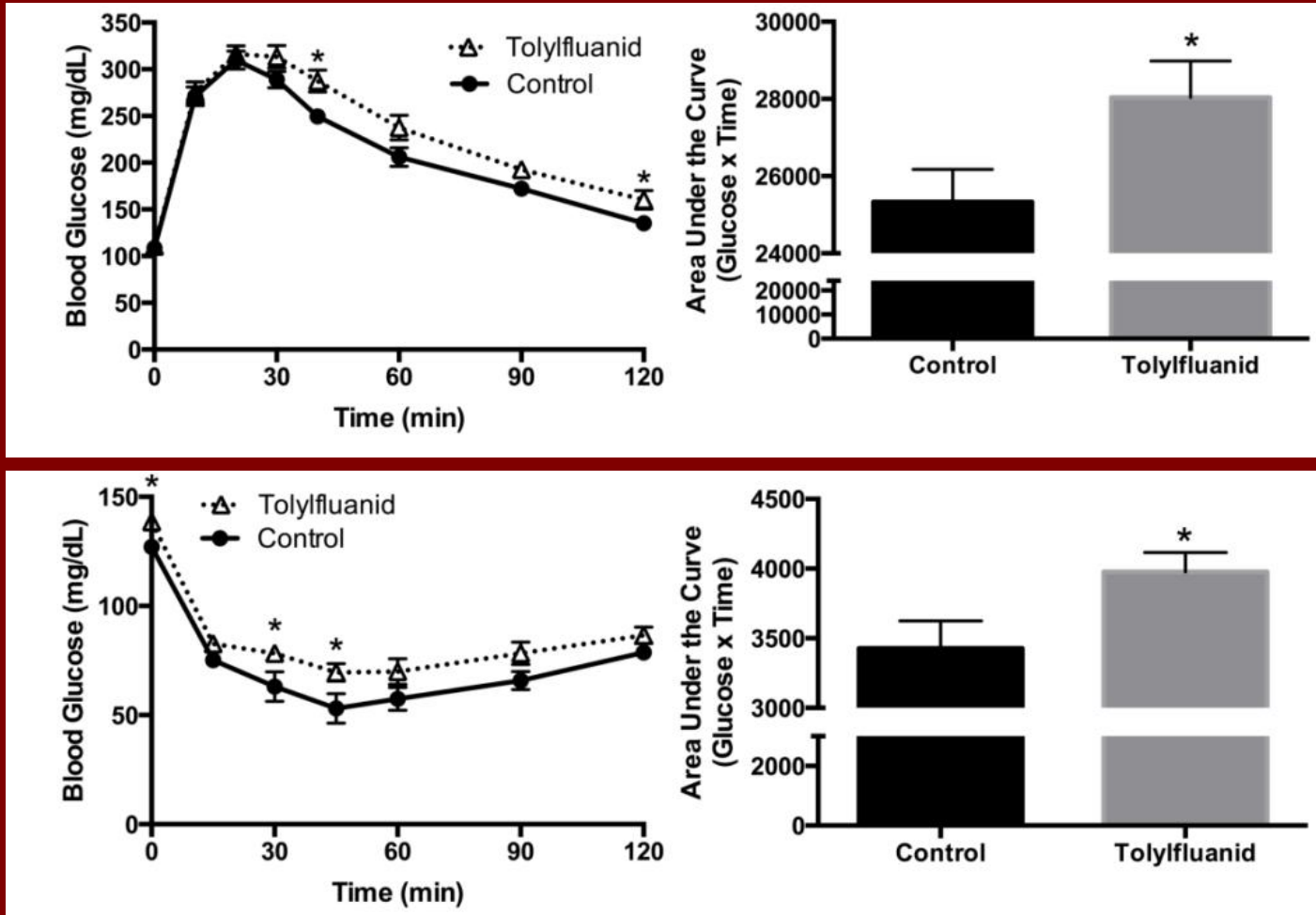


Male C57BL/6 Mice; 0 or 65 ppm TF x 12 weeks; Mean  $\pm$  S.E.M.; N=28 (for adipocytes/hpf, N=8); \*P<0.05, \*\*P<0.01.

**Dysfunctional Adipokine Secretion**

**Adipocyte Insulin Resistance**

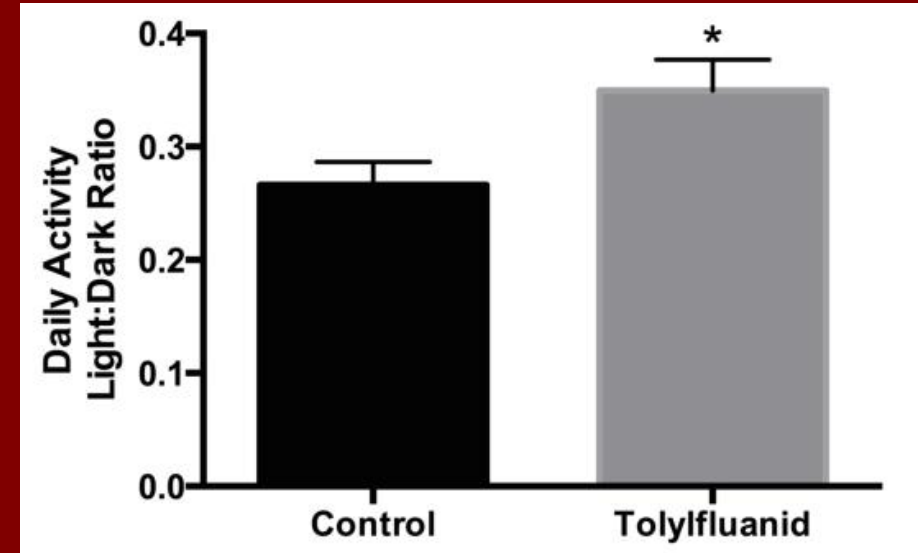
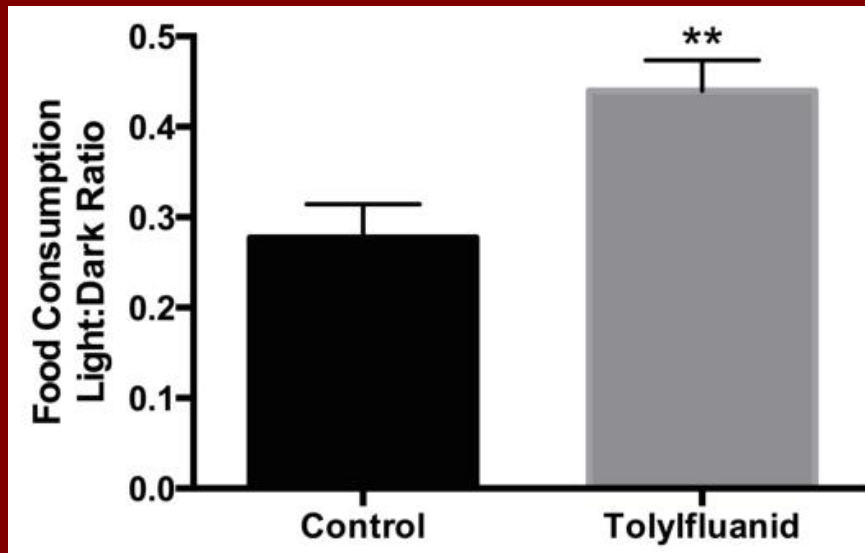
# Glucose Intolerance and Insulin Resistance



**Male C57BL/6 Mice; 0 or 65 ppm TF x 12 weeks; Mean  $\pm$  S.E.M.;  
For GTT at 9 wks, N=9-10; for ITT at 10 wks, N=7-8; \*P<0.05.**



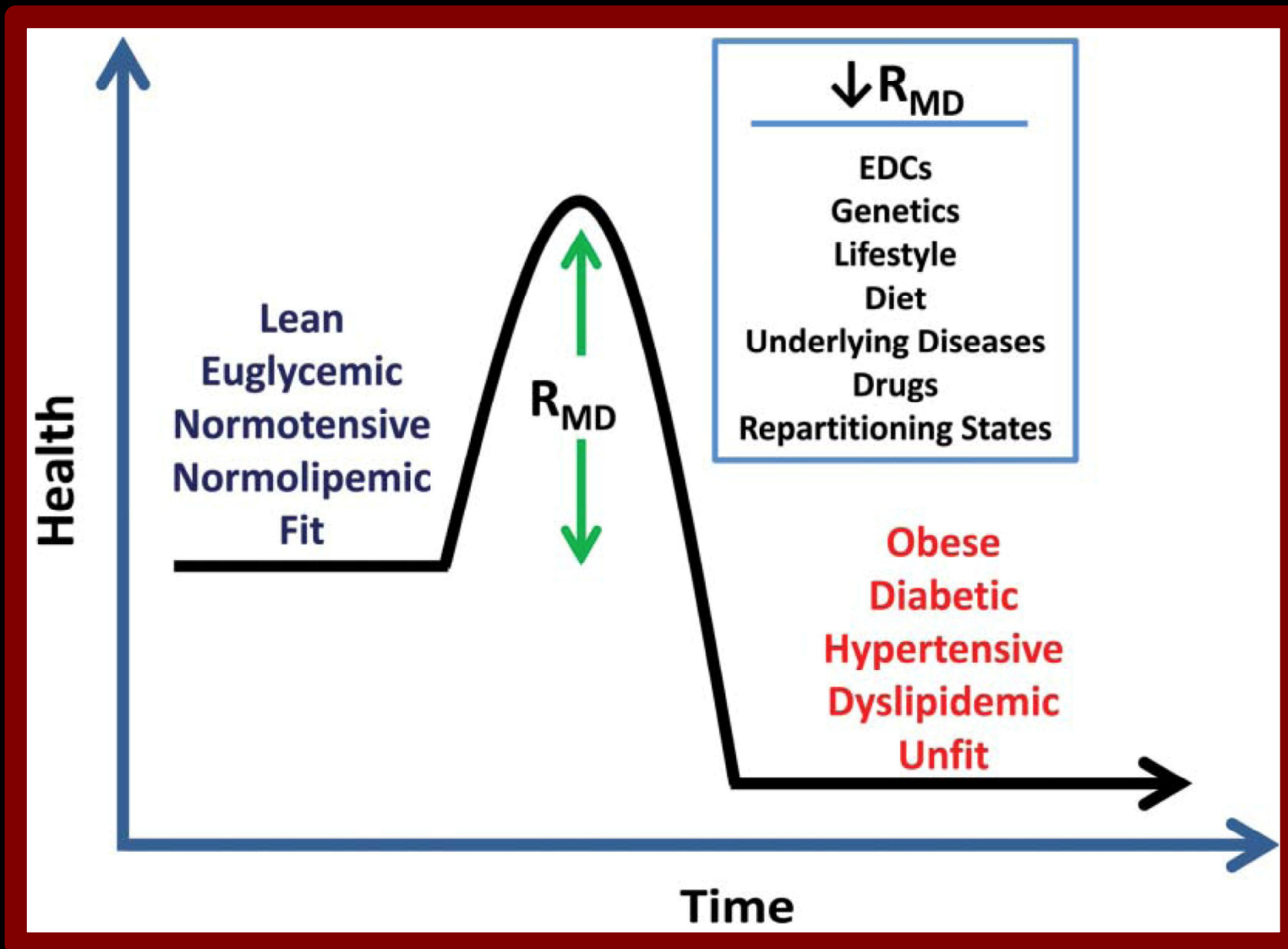
# TF Disrupts Circadian Rhythms



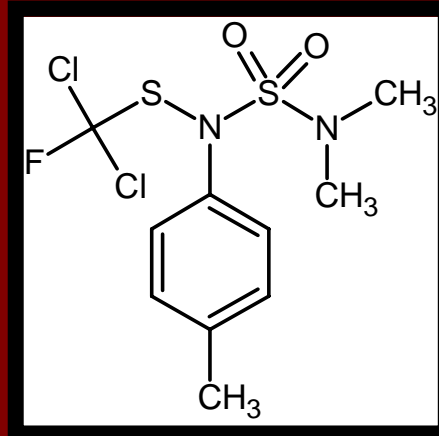
**Male C57BL/6 Mice; 0 or 65 ppm TF x 12 weeks;  
Mean  $\pm$  S.E.M.; N=4; \*P<0.05, \*\*P<0.01.**

**Timing of Food Intake  
Alters Metabolism**

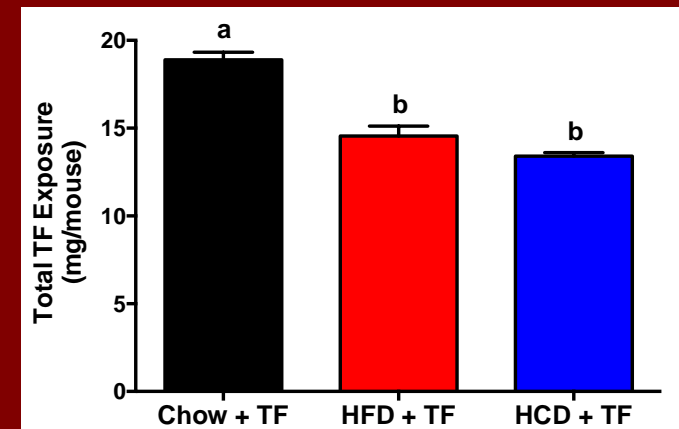




# EDC-Macronutrient Interactions



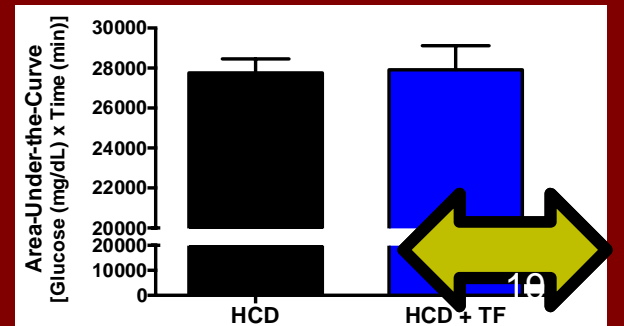
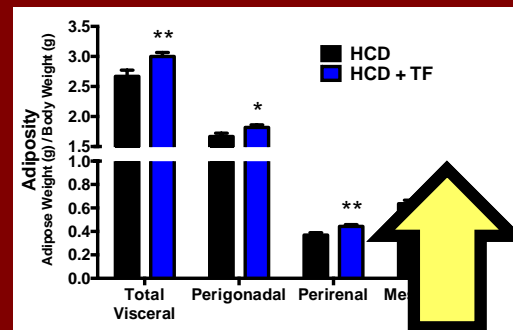
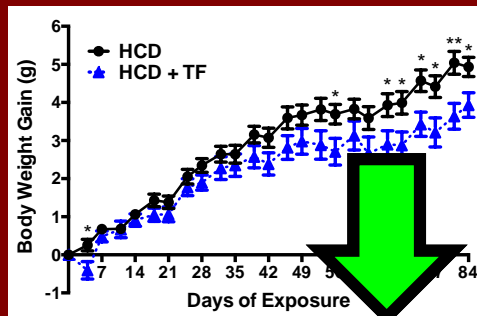
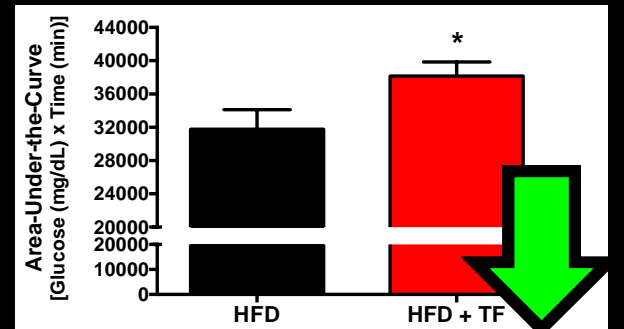
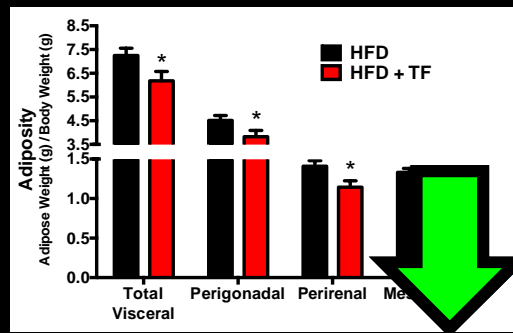
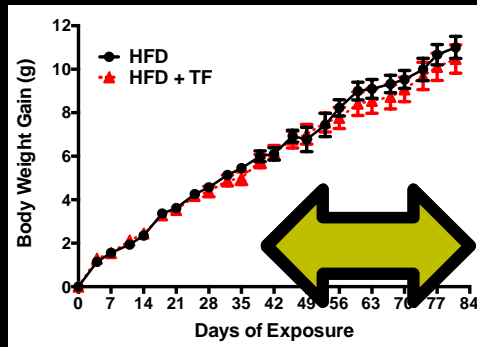
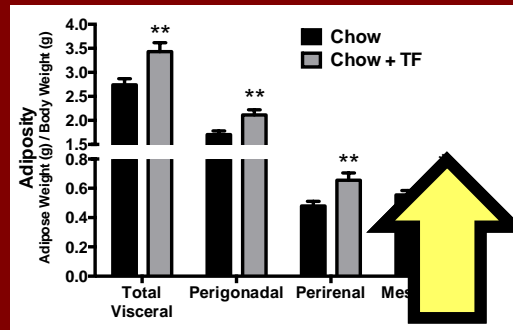
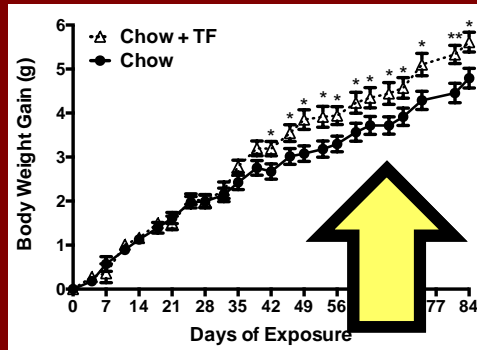
Diet	Protein	% kcal from Carbohydrate	Fat
Harlan product code			
Chow			
Control: TD.00588	24.0	58.0	18.0
TF: TD.120075			
HFD			
Control: TD.120438	14.8	47.6	44.6
TF: TD.120439			
HCD			
Control: TD.140437	14.7	75.5	9.70
TF: TD.140438			



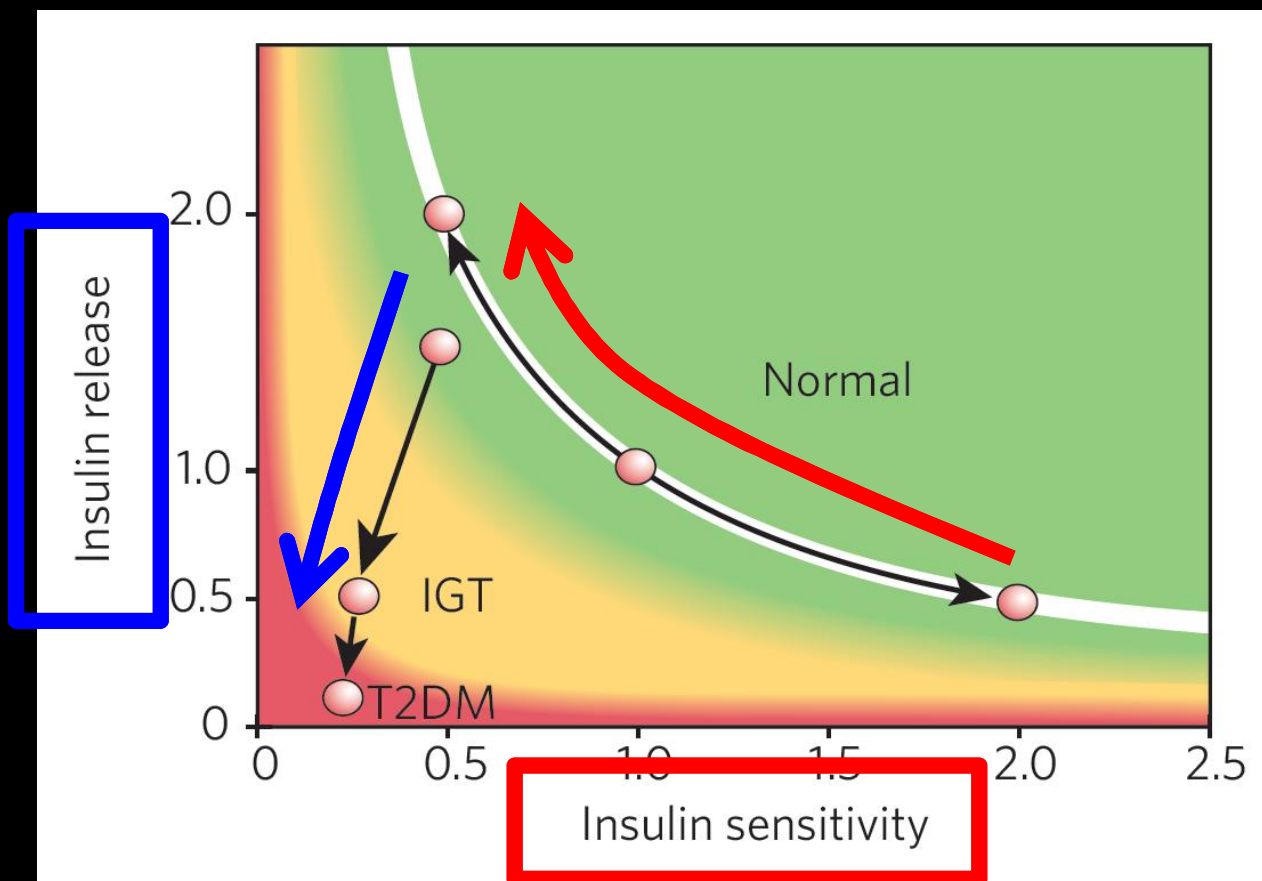
# Weight Gain

# Adiposity

# Glucose Tolerance



# Diabetogenic Cocktails

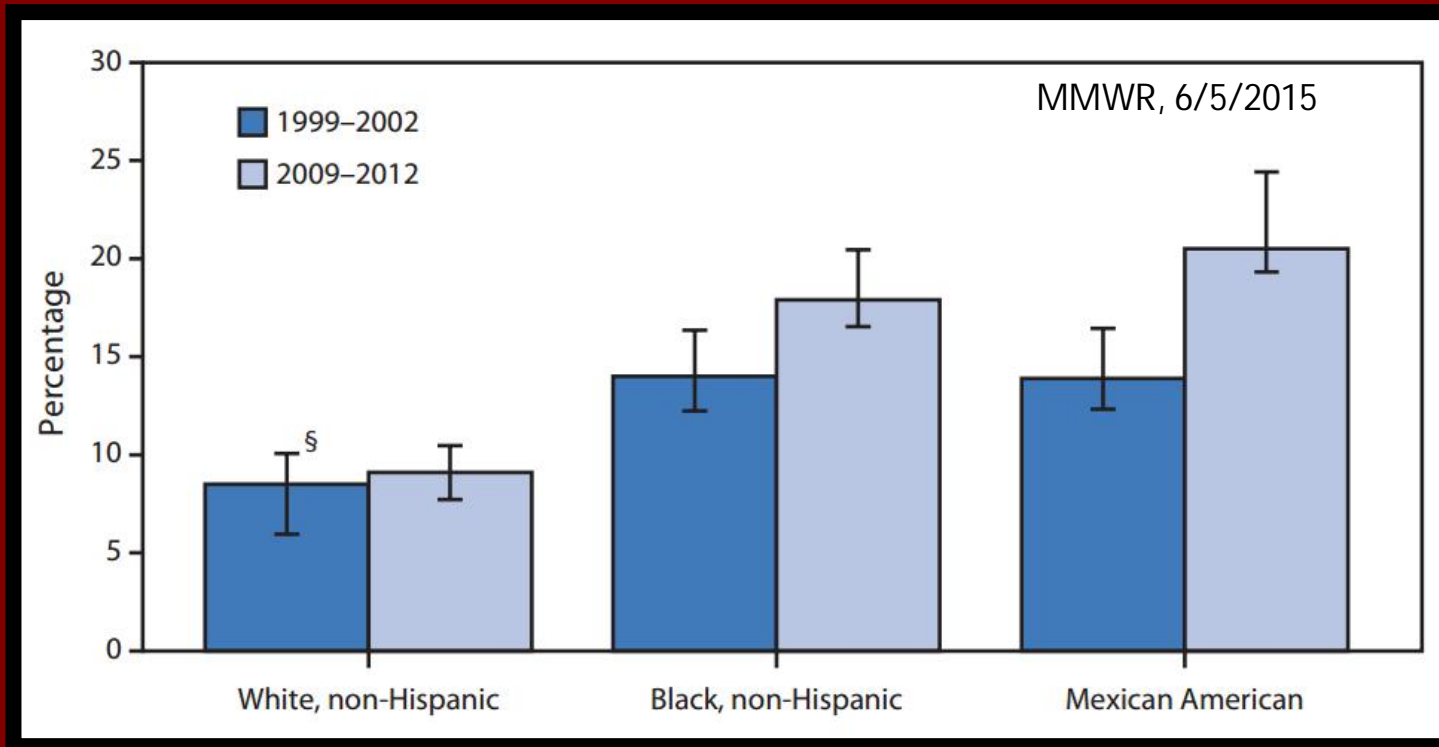


- Arsenic
- TCDD
- Cadmium
- Mercury
- PCBs
- Vacor
- BPA
- TPT
- Alloxan

- Tolyfluanid
- TCDD
- BPA
- DEHP
- Particulate Matter
- Arsenic
- PCB-77
- Cadmium

Adapted from Kahn et al., 20  
Nature, 2006.

# Environmental Injustice



- Air Pollution (PM)
- Polychlorinated biphenyls (PCBs)
- Bisphenol A (BPA)

- Phthalates
- Organochlorine pesticides

- Polybrominated diphenyl ethers (PBDEs)
- Parabens



Thank you!

Photo Courtesy of  
Global Population Speak Out 22