The Paradox of Progress
Environmental Chemicals & the Origins of Diabetes

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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

Amputations

Cardiovascular Disease
$245 billion annually...and climbing
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 β-cells of the pancreatic islets of Langerhans.
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 β-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.
  - Tolylfluanid

- Strength of evidence varies; however, the diversity and consistency of data suggests that toxicant exposures may represent novel diabetes risk factors.
**Tolylfluanid**

Log $K_{ow} = 3.9$

$LD_{50} = 1000 \text{ mg/kg}$

NOAEL = 76.3 mg/kg/day

Imported Food Tolerances:

30 ppm on Hops

Exposure of 65 ppm
TF Promotes Weight Gain

Male C57BL/6 Mice; 0 or 65 ppm TF x 12 weeks; Mean ± 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

Regnier et al., *Endocrinology*, 2015.
TF Increases Adiposity

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

Dysfunctional Adipokine Secretion

Adipocyte Insulin Resistance

Regnier et al., *Endocrinology*, 2015.
Glucose Intolerance and Insulin Resistance

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

Regnier et al., *Endocrinology*, 2015.
TF Disrupts Circadian Rhythms

Timing of Food Intake Alters Metabolism

Regnier et al., Endocrinology, 2015.

Male C57BL/6 Mice; 0 or 65 ppm TF x 12 weeks; Mean ± S.E.M.; N=4; *P<0.05, **P<0.01.
EDC-Macronutrient Interactions

<table>
<thead>
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<th>Diet</th>
<th>Harlan product code</th>
<th>Protein</th>
<th>% kcal from Carbohydrate</th>
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Chow + TF HFD + TF HCD + TF

![Graph showing Total TF Exposure (mg/mouse)]
Diabetogenic Cocktails

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

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

Adapted from Kahn et al., 2006.
Environmental Injustice

- Air Pollution (PM)
- Polychlorinated biphenyls (PCBs)
- Bisphenol A (BPA)
- Phthalates
- Organochlorine pesticides
- Polybrominated diphenyl ethers (PBDEs)
- Parabens

MMWR, 6/5/2015

Ruiz et al., In press.
Thank you!

Photo Courtesy of
Global Population Speak Out