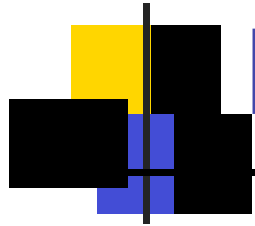




NIEHS: How We Think with Regards to Endocrine Disruption

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National Institute of Environmental Health Sciences
NIH/DHHS

EED Gordon Conference, june 2008



EED Gordon Conference

- Terrific
 - Interactions
 - Group discussions
 - Posters
 - Students
- Sponsor
 - R13



Scientific Program Administrator

- Develop portfolio of grants to address major public health concerns of American people... focusing on environmental exposures
- Reproduction/development/endocrine/SBIR
- Listen and learn...and transmit info back to NIEHS
 - Initiatives
 - Funding decisions
 - Guidance to applicants



Trends We Support...

- Define sensitive windows of exposure
- Low environmentally relevant doses
- Low dose experiment
- Multiple doses
- Relevant numbers of animals and repetitions
- Mechanisms
- Biomarkers of exposure, susceptibility and effect
- Disease endpoints
- Mixtures...but
- Interdisciplinary, collaborative, team research
- Translational research



Trends to Stimulate...

- Focus on communication to community
- Cross species extrapolation...importance to humans
- Examination of cross pathway interactions (hub proteins)
- Development of better animal models of disease
- Measure internal doses...animals and humans
- Use of databanks and cohorts for Febad studies
- Use of NHANES database
- Lifespan approach
- Focus on aged
- New diseases and ...cardiovascular, lung, neurodegeneraton, ADHD, bone, obesity,diabetes, metabolic syndrome
- Focus on other EDCs,
- Define where EDCs are coming from...

ENDOCRINE DISRUPTING CHEMICALS

HERBICIDES

2,4,-D
2,4,5,-T
Alachlor
Amitrole
Atrazine
Linuron
Metribuzin
Nitrofen
Trifluralin

FUNGICIDES

Benomyl
Ethylene thiourea
Fenarimol
Hexachlorobenzene
Mancozeb
Maneb
Metiram - complex
Tri-butyl-tin
Vinclozolin
Zineb

INSECTICIDES

Aldicarb
beta-HCH
Carbaryl
Chlordane
Chlordecone
DBCP
Dicofol
Dieldrin
DDT and metabolites
Endosulfan
Heptachlor / H-epoxide
Lindane (gamma-HCH)
Malathion
Methomyl
Methoxychlor
Oxychlordane
Parathion
Synthetic pyrethroids
Transnonachlor
Toxaphene



INDUSTRIAL CHEMICALS

Bisphenol - A
Polycarbonates
Butylhydroxyanisole (BHA)
Cadmium
Chloro- & Bromo-diphenyl ether
Dioxin (2,3,7,8-TCDD)
Furans
Lead
Manganese
Methyl mercury
Nonylphenol
Octylphenol
PBDEs
PCBs
Pentachlorophenol
Penta- to Nonylphenols
p-tert-Pentylphenol
★ **Phthalates**
Styrene

Testosterone synthesis inhibitor
Thyroid hormone transport inhibitor

Estrogen receptor agonist
Androgen receptor antagonist



Obesity

Newbold *et al.* 2005, 2007

Same strain of mice
Same caloric intake
Same activity levels

Obesogens - Just the Tip of the Iceberg ?

PFOA

Estradiol

Genistein

Tributyl Tin

Phthalates

DES

Nicotine

Organophosphate
pesticides

Bisphenol A

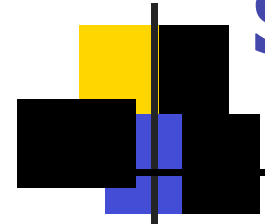
PCBs ?

PBDEs?

others?

Could it be that we are exposed to all of these at low levels and we get something from nothing when they interact?

Strategy for Assessing Risk



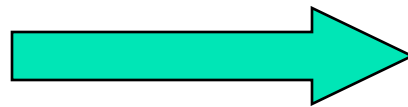
Animal Expt

Internal Dose

Epigenetic biomarker



Disease



Met/disp

validate

Human

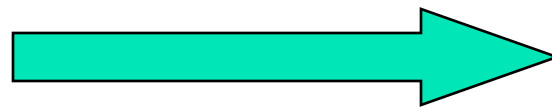
Internal Dose

Epigenetic Biomarker



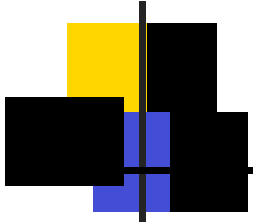
Predict

Disease



Same physiology

Quotes...



-
- There may be mER diseases
 - Neonatal BPA impairs estrous cyclicity but it takes weeks to show up
 - Development is the most sensitive time
 - I walked in NITC and saw nurses with milk in polycarbonate bottles for feeding the neonates
 - We need to have more clinicians at these meetings
 - Neonates had triclosan, MEHP and BPA....



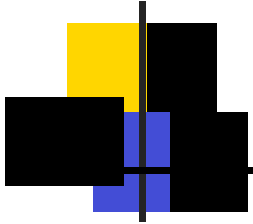
Quotes...

- NHANES data shows that BPA either has a long half life or there is continuous chronic exposure
- Since women aren't going to stop taking contraceptives and peeing....
- Think outside the estrogenic box
- We need to know the sperm counts of normal american men as a starting point
- We are missing a lot...only testing estrogen, androgen and thyroid hormone systems
- Males prefer females with a beak color similar to their mothers
- Epigenetics drives mutations
- We need real world low concentrations for long periods
- We have to learn to work outside our comfort zones



Quotes

- Any genes with repeats are targets for miRNAs...and repeats are conserved across species
- There can be changes in immune function without changes in cellularity
- At the next EED GC we need to have a Hawaiian shirt day...



THE END....

Or is it just the beginning?????