STAR Review Workshop US EPA Endocrine Disruptors Program

Thyroid Toxicants: Developmental Outcomes and Chemical Mixtures

Mary Gilbert, PhD

Office of Research and Development MultiYear Plan for Endocrine Disruptors

- ***Focus Area A***

Development/standardization of protocols to identify endocrine disrupting chemicals in the environment

- ***Focus Area B***

Long-term consequences of developmental exposure to endocrine disrupting chemicals - gonadal steroids and *thyroid hormones*

- ***Focus Area C***

Cumulative risk/mixtures of endocrine disrupting chemicals

Extrapolation across species

NHEERL and STAR Thyroid Projects

Complex Mixtures of Thyroid Hormone Disruptors: Mechanisms and Predictive Modeling. Intramural Research in NTD and ETD

Low Dose Thyroid Hormone Insufficiencies and Neurological Outcomes in Rodent Models. Intramural Research in NTD

Endocrine Disrupting Chemicals and Thyroid Outcomes – Exposure-Effect Studies in Humans. STAR Grant to Dr. Henry Anderson, Wisconsin Dept Health and Family Services

Low Dose Effects of Thyroid Toxicants on Neurodevelopment – Mechanistic Studies. STAR COOP between NHEERL and Dr. Thomas Zoeller, U Massachusetts

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Thyroid Hormone Disruption & Neurological Dysfunction

- **TH critical for brain development**
  - **Iodine Deficiency, Congenital Hypothyroidism**

- **Treatment CH still leads to subtle cognitive deficits**

(Rovet, 2000)

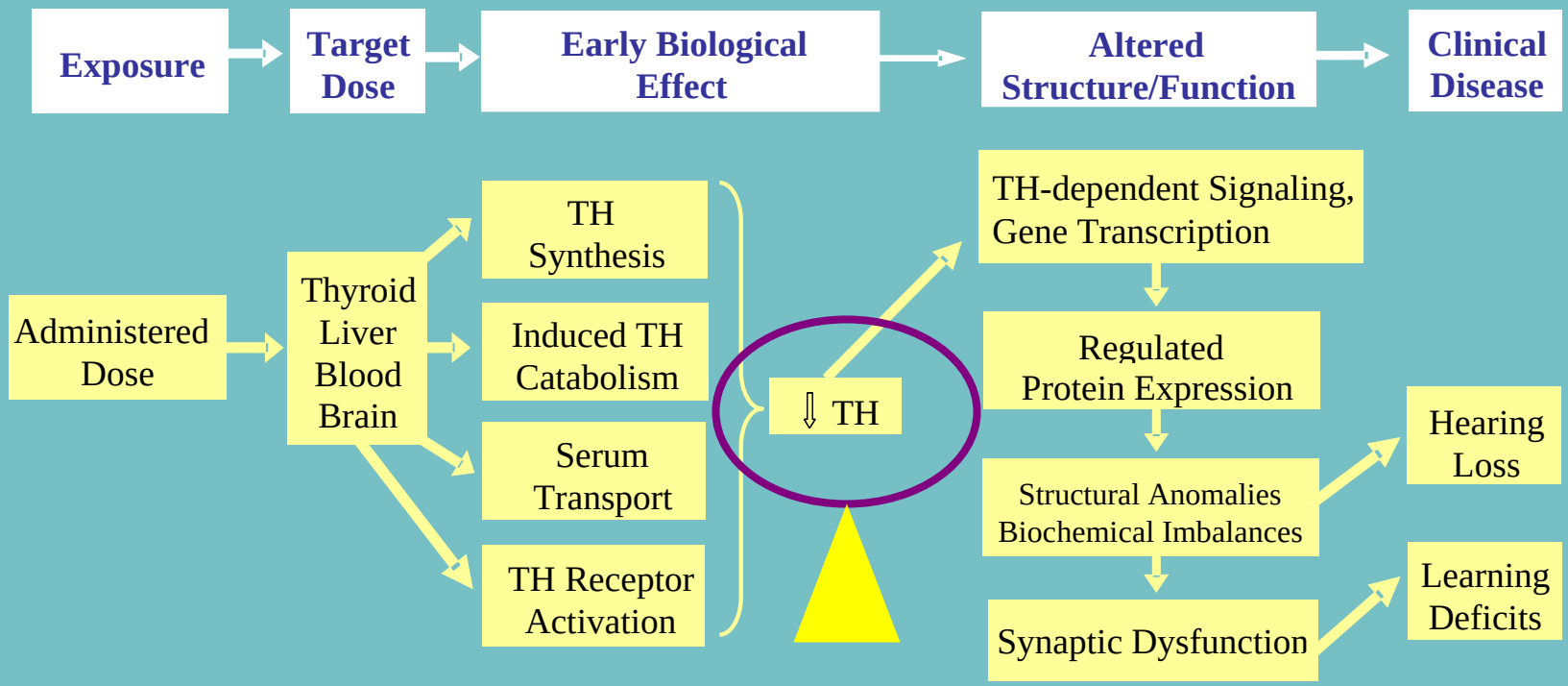
- **Hypothyroxinemia – pregnant women with low T4, children**
  - **↑ incidence attention deficit disorder**
  - **lower global IQ**

(Haddow et al., 1999; Allen et al., 2000)

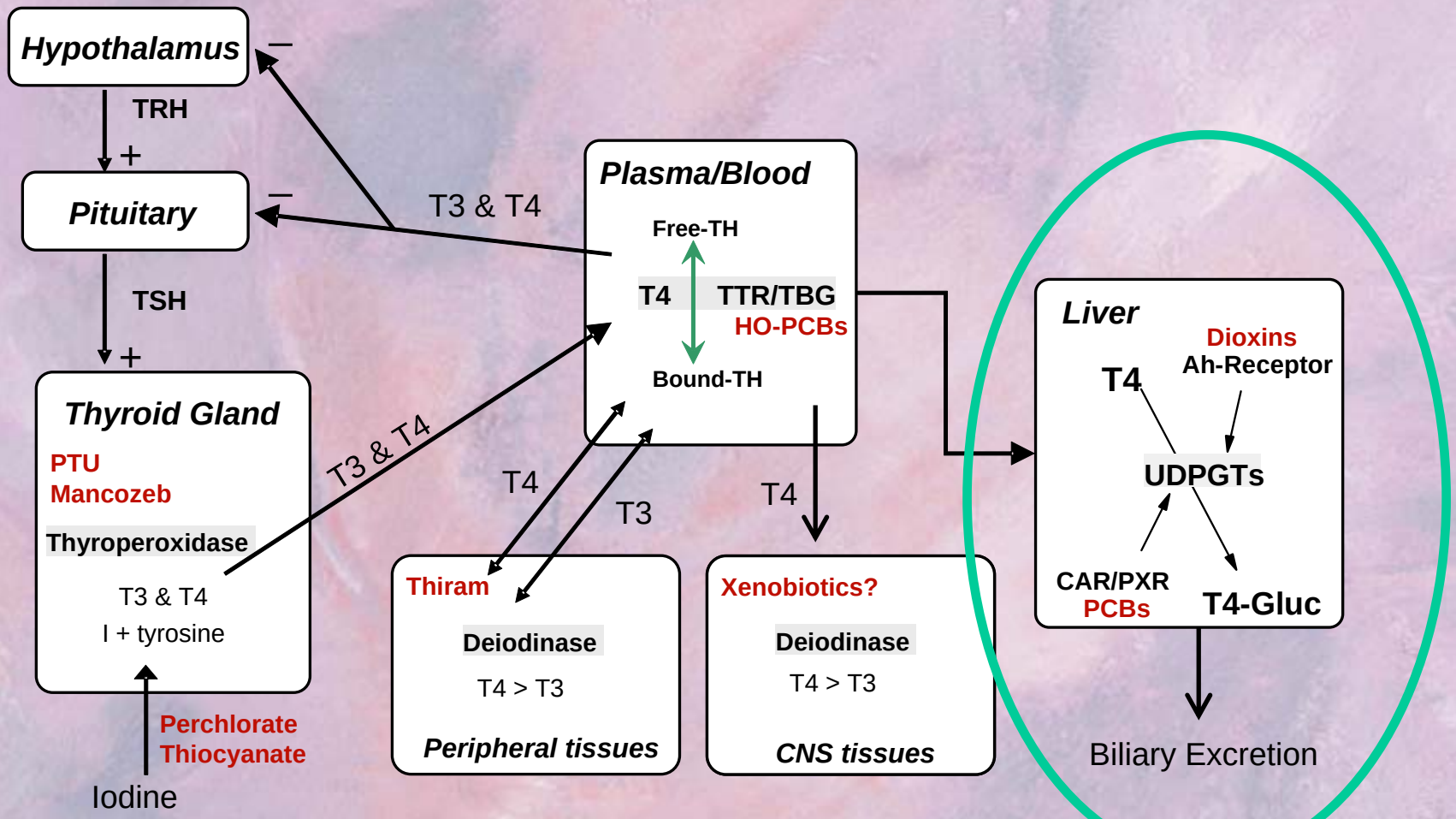
Research Challenges

- Interaction in brain development is complex: Thyroid hormone serves different roles in different cells at different times
- Many structurally diverse chemicals affect thyroid axis by interaction with a variety of targets
- Unclear how much change is adverse. We know little at the low end of the dose-response function
- Unclear which profiles of TH disturbance are predictive of adversity
- Extrapolation from animal models to humans
- Real world exposures are to complex mixtures of thyroid disrupting chemicals

BIOLOGICALLY-BASED DOSE-RESPONSE MODEL



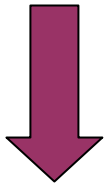
Target Sites and Early Biological Indicators
Structurally Diverse chemicals - Multiple Sites & Mechanisms



Induction of Liver Enzymes Reduces T4

Mixtures

A number of environmental contaminants induce liver glucuronidation of T4. These chemicals display distinct dose-response profiles



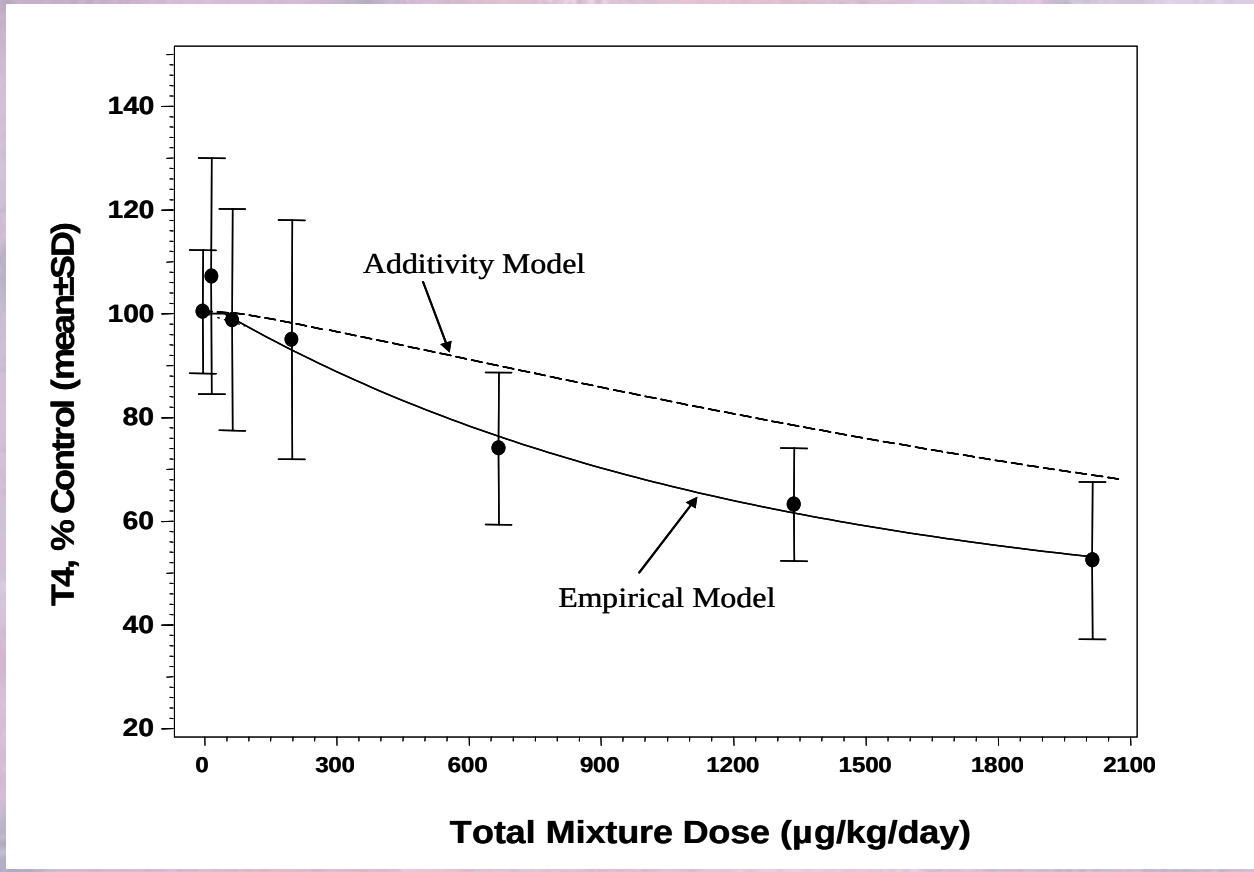
Does additivity theory predict the effects of complex mixtures that induce metabolism of T4?

Species Extrapolation

Glucuronidation of T4 is differentially induced in rats and mice following exposure chemicals

What is the most appropriate model for extrapolation to humans?

Additivity Model predicted effects on T4 of mixtures of chemicals with common MOA at low doses, but underestimated effects at high doses.



What of mixtures with different MOA?

How do these effects extrapolate to humans?

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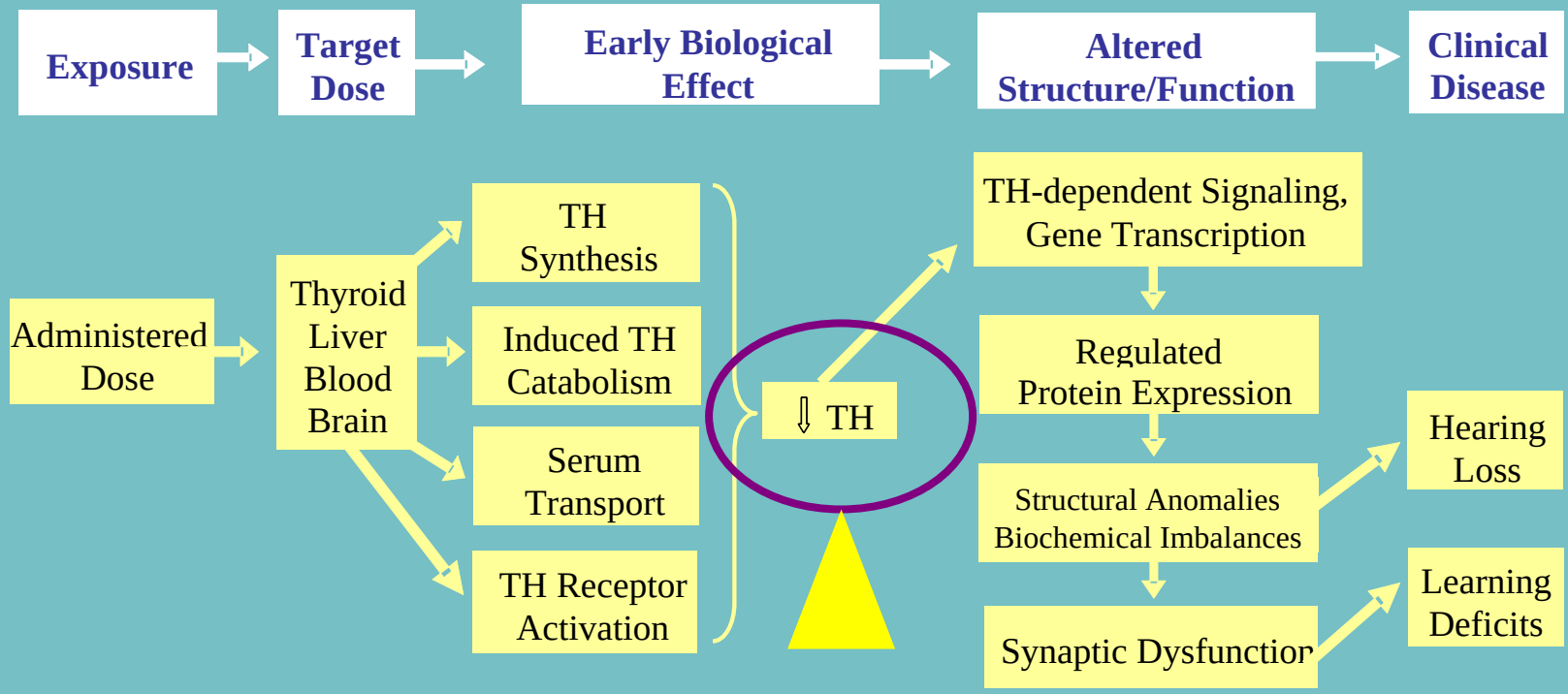
Species Extrapolation

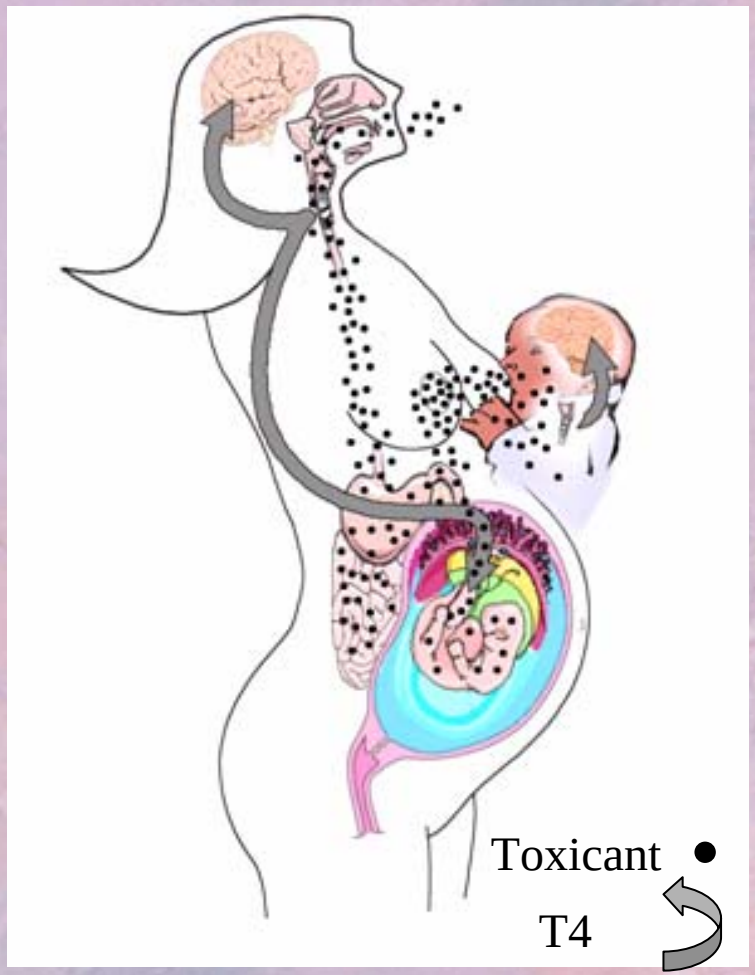
Glucuronidation of T4 is differentially induced in rats and mice following exposure chemicals

What is the most appropriate model for extrapolation to humans? Develop reporter gene assays in hepatocytes from mouse, rat, human

BIOLOGICALLY-BASED DOSE-RESPONSE MODEL

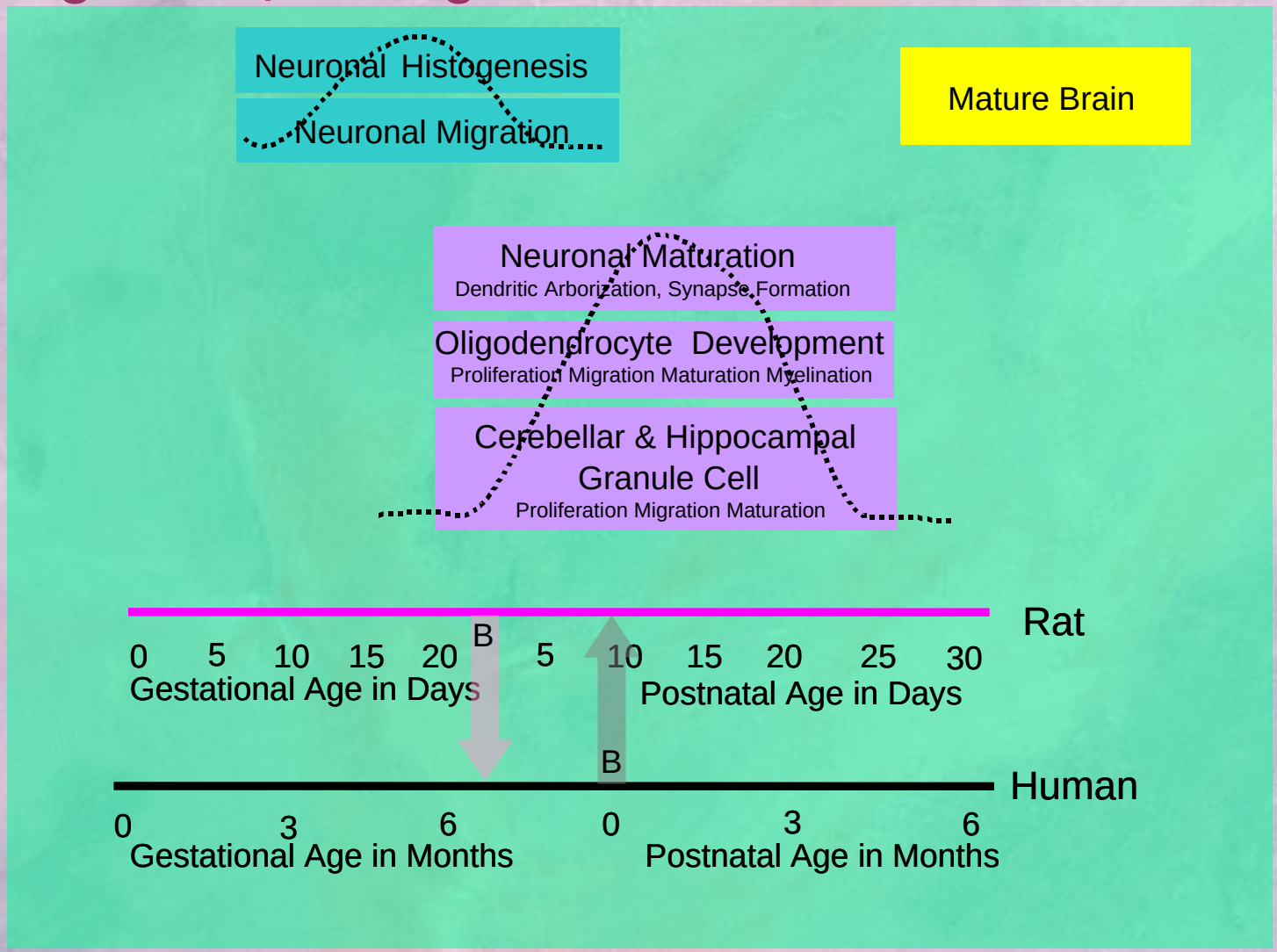


Low Level Thyroid Disruption and Neurodevelopment



- Subclinical hormone reductions in pregnant women leads to IQ deficits in offspring
- Developing fetus and newborn are populations of concern
- Cognitive function is endpoint of concern
- Evaluation at low levels of hormone disruption is needed

Critical Factors Impacting Outcome: Magnitude, Timing and Duration of TH Insufficiency

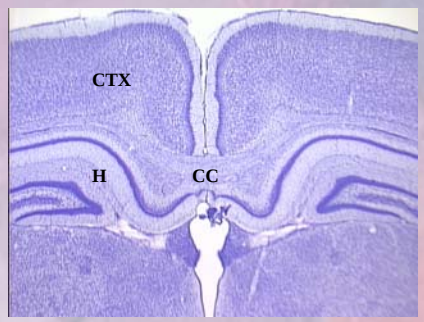


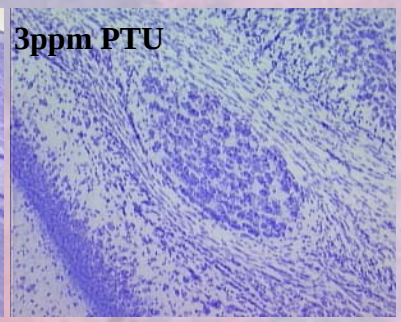
Adapted from Anderson et al. (2003) Thyroid, 13:1039-1056

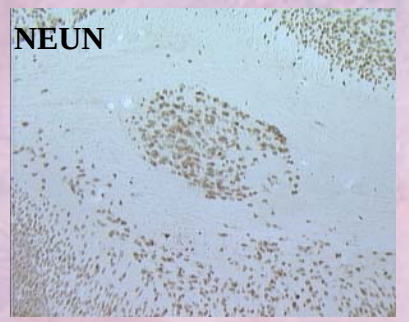
Timing and Duration are Important Elements for Consideration

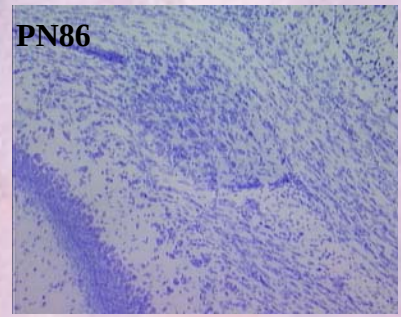
- **Prenatal** hypothyroidism – errors in migration?
  Functional Implications?
- **Postnatal** PV-Immunohistochemistry – altered neuronal phenotype?
  Functional Implications?
- **Postnatal** Cochlear Development – hair cell loss
  Functional Implications?

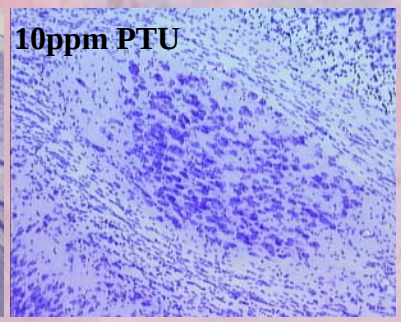
Prenatal : Cortical Malformations

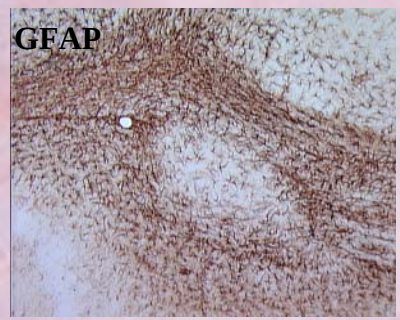












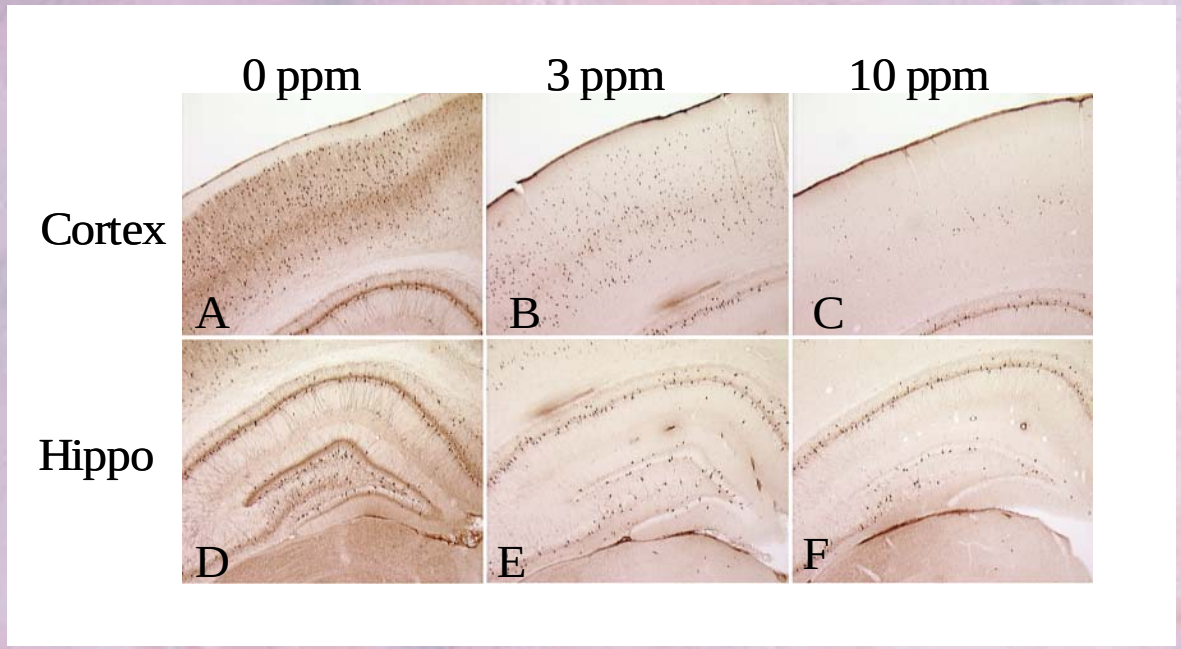
Cortical Malformation

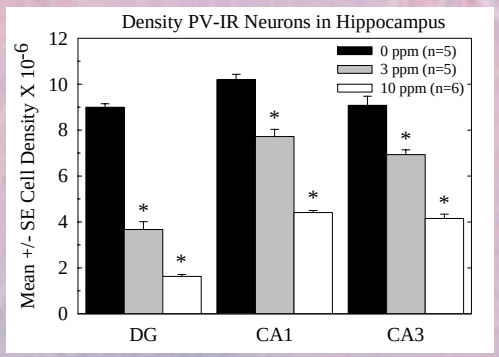
Dose-Dependent

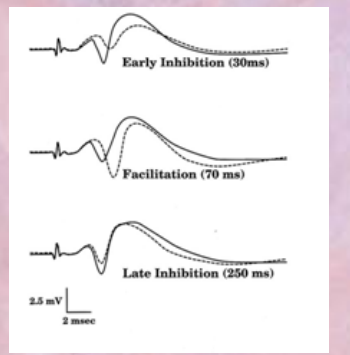
Neuronal

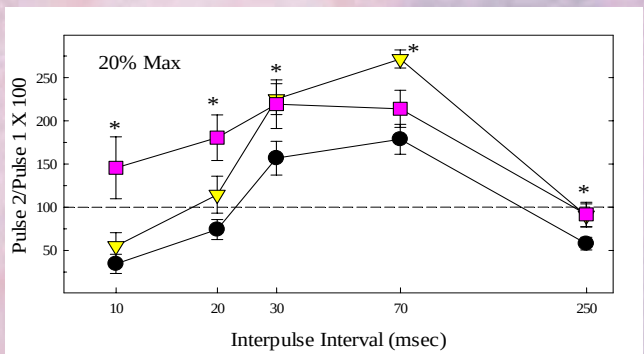
Persistent TH-Dependent

Postnatal: Parvalbumin Expression

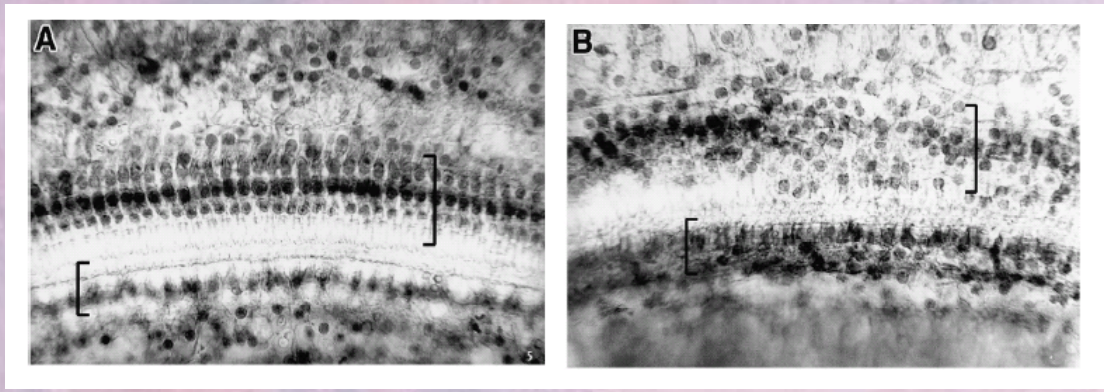




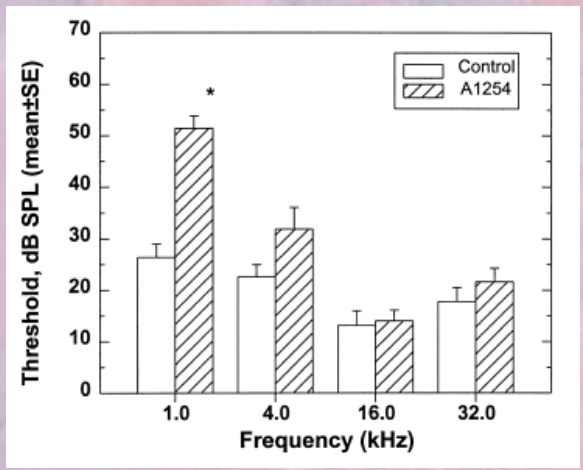




Postnatal: Cochlear Damage

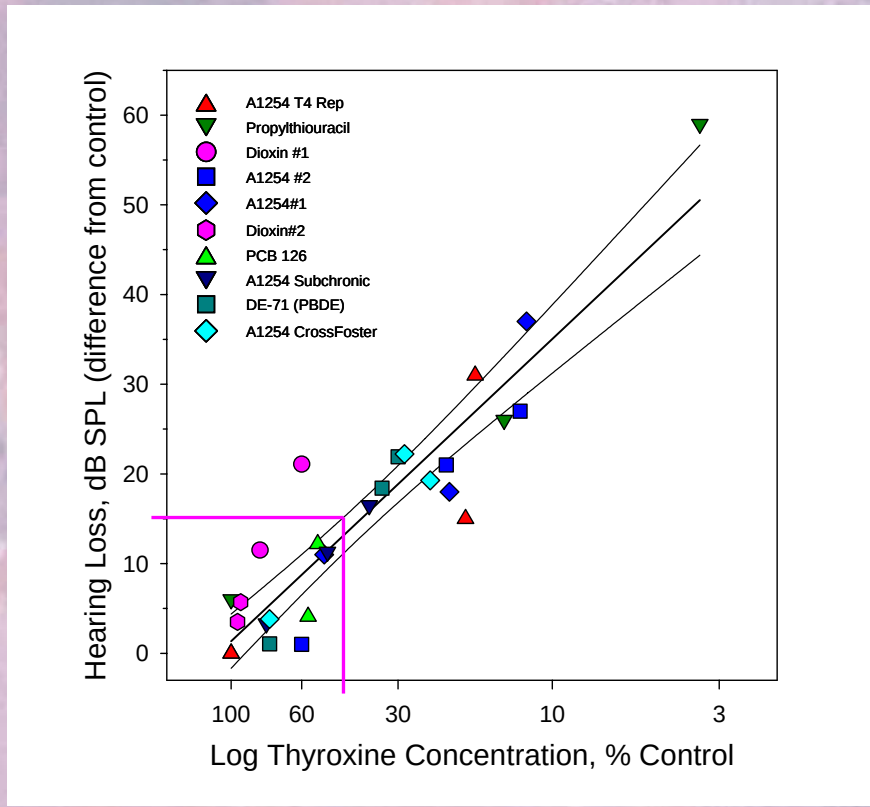


Postnatal PCB exposure reduces T4, induces hair cell loss in the basal turn of the cochlea



Low frequency hearing loss is evidenced by behavioral measures of acoustic startle reflex

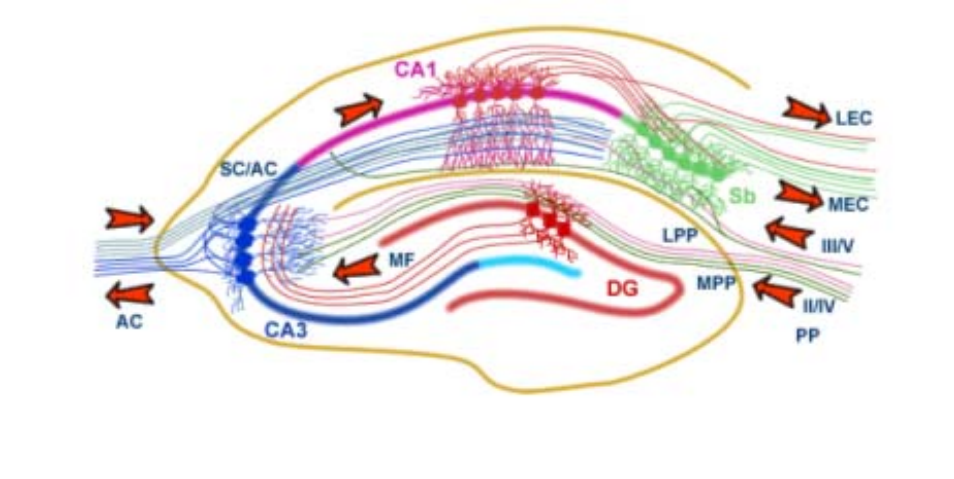
Dose-Response Relationships: Thyroid Hormones and Hearing Loss



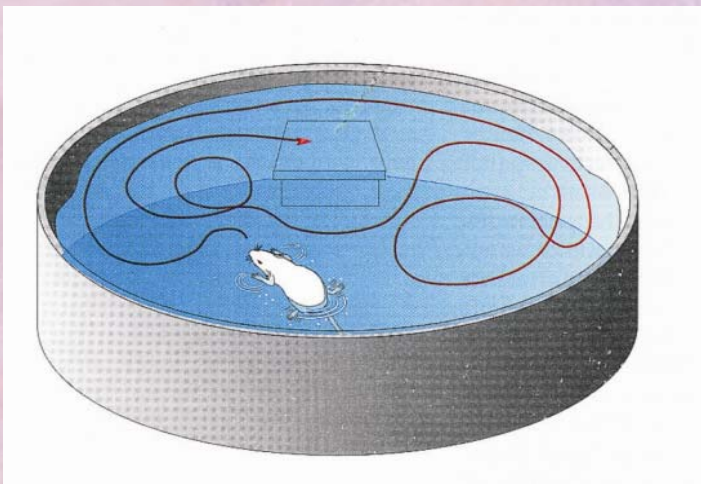
Developmentally-induced reductions in T4 on PN15 are predictive of hearing loss.

Sensitivity of Cognitive Endpoints?

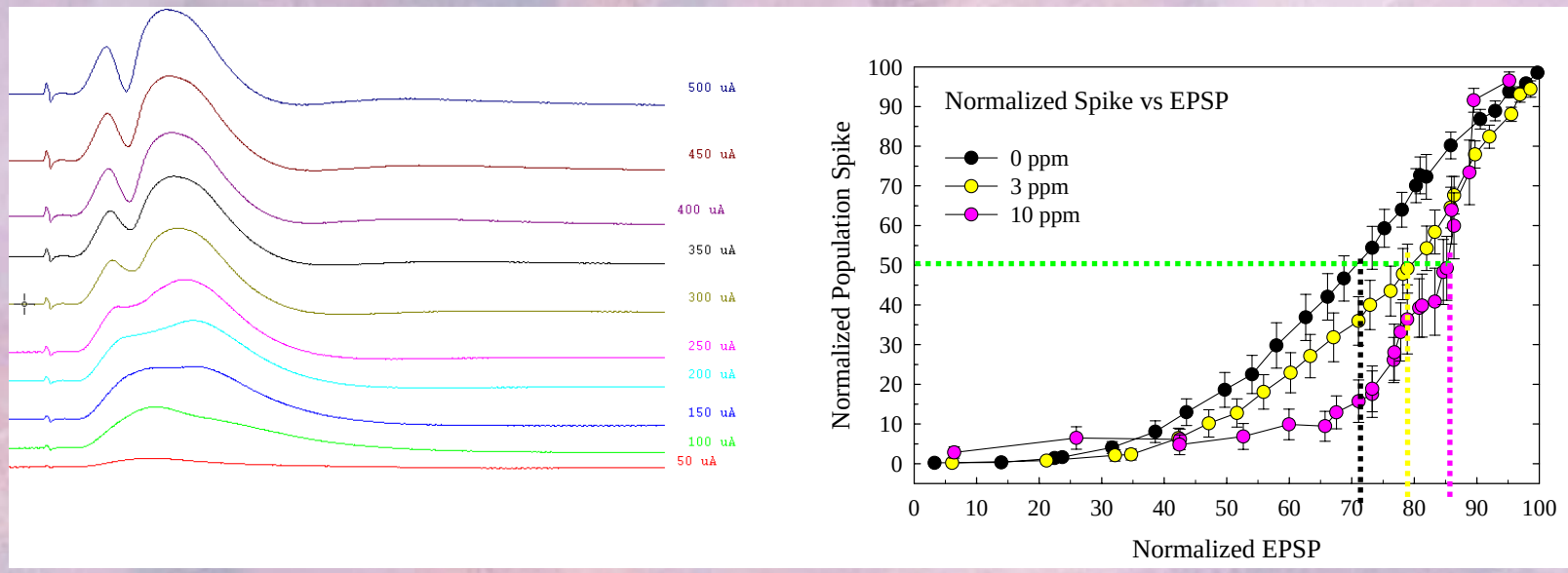
Cellular Models



Behavioral Models

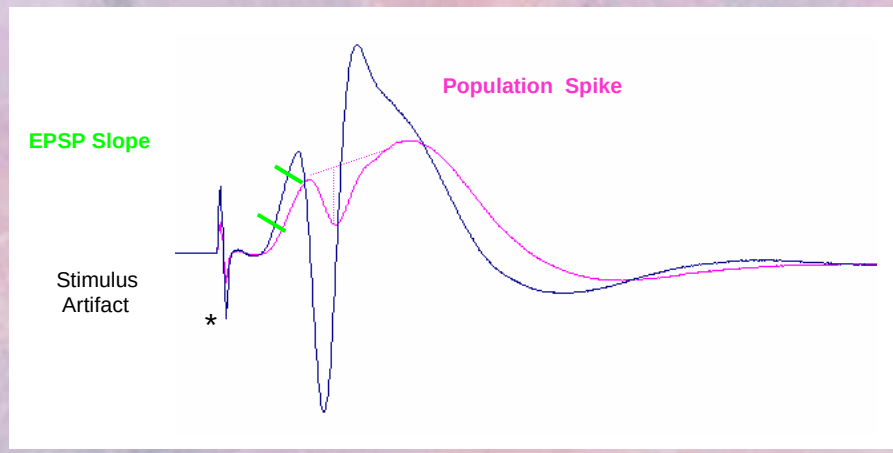


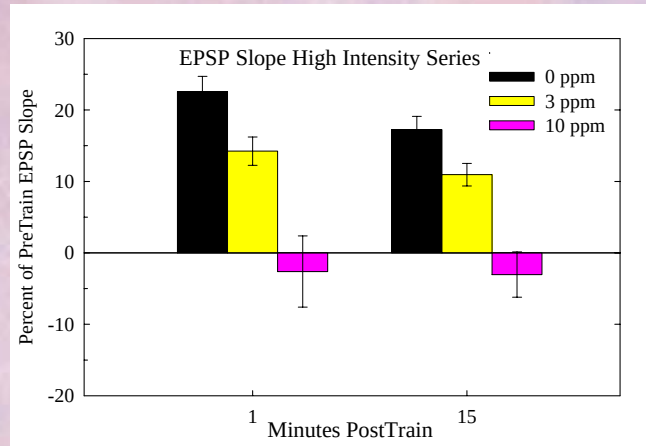
Hippocampal Synaptic Transmission is Impaired



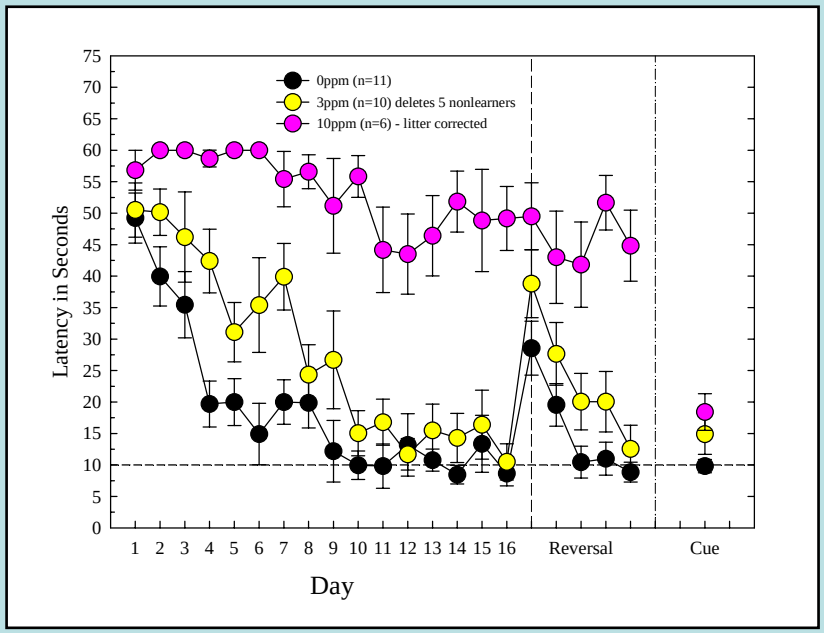
Synaptic Plasticity is Impaired

- Long term potentiation, a cellular model of learning and memory, is reduced in a dose-dependent manner

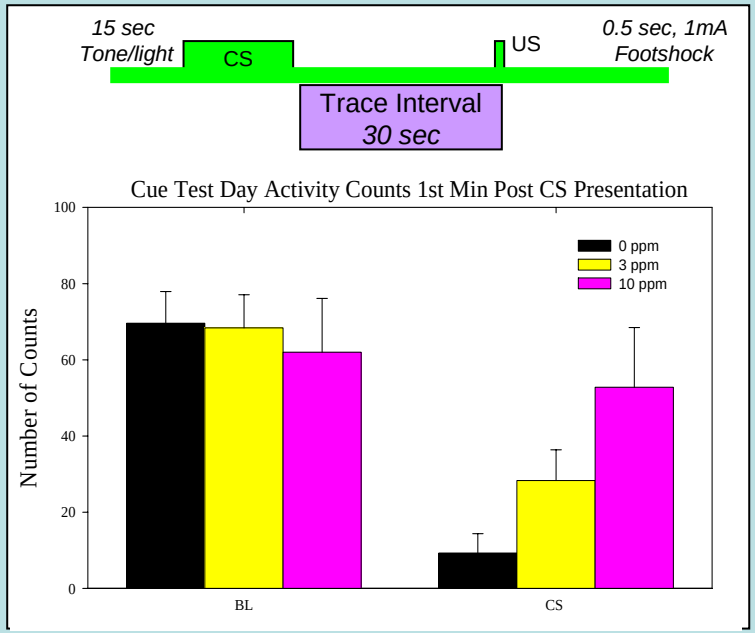




Hippocampal Learning is Impaired



Morris water maze acquisition and reversal learning are impaired in adult offspring



Trace fear conditioning is impaired in adult offspring.

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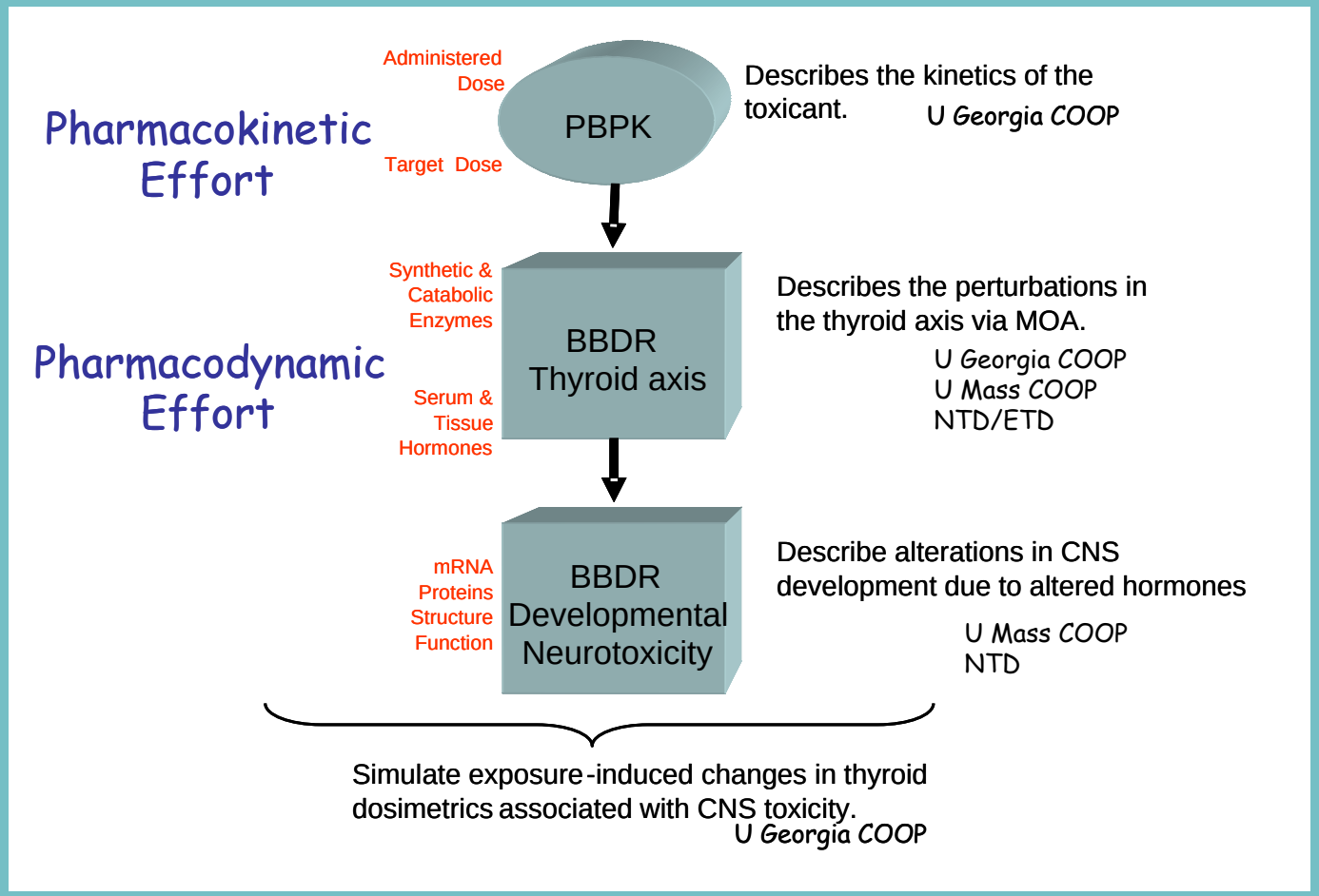
Exposure-Dose-Response Model




Neurotoxicology
Peer Review
Research Protecting the Nervous System in a Changing World

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