Integrative Biologically Based Model for Thyroid Hormones Disruption in Fetal and Neonate Serum and Developing Brain
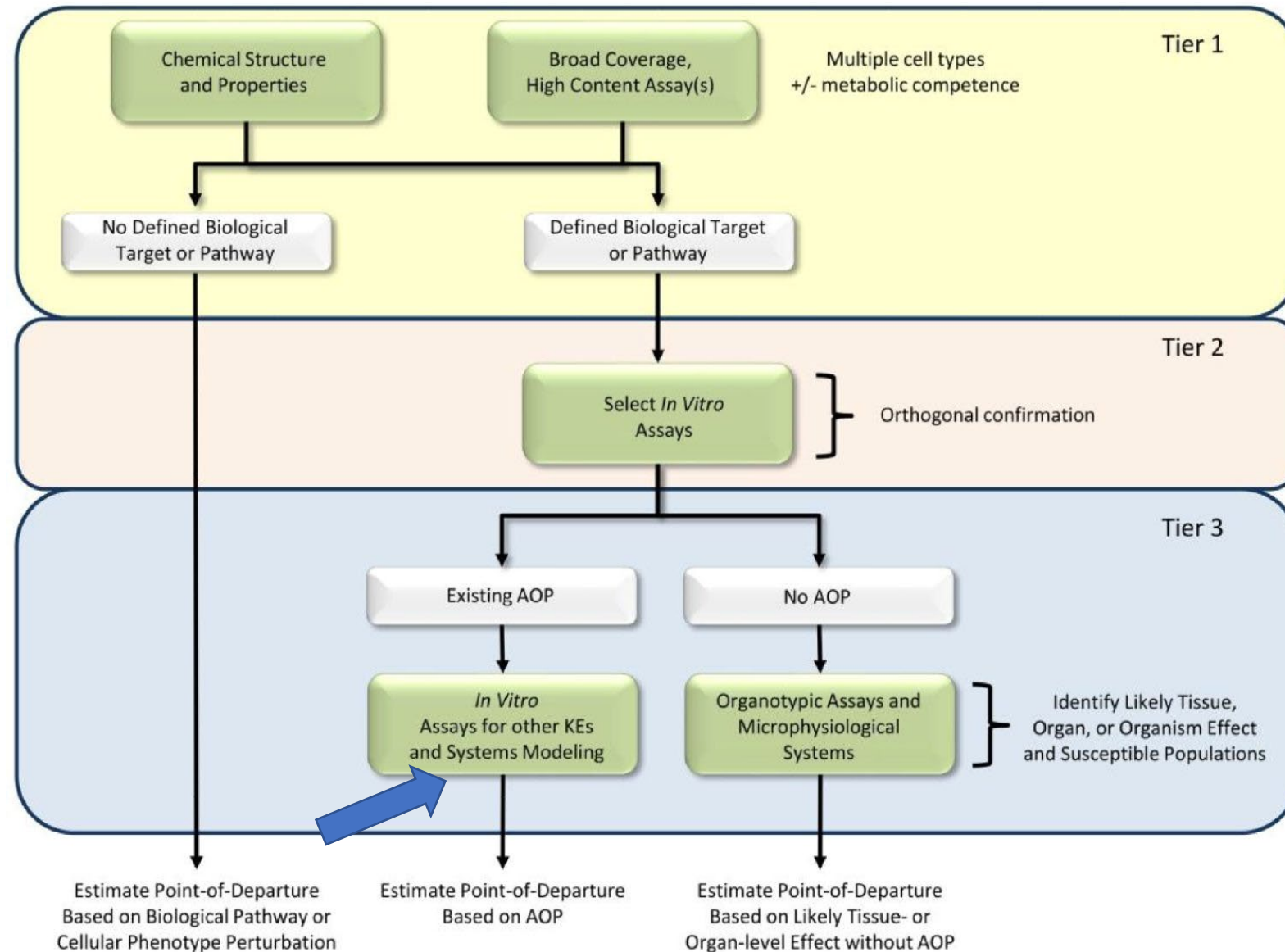
Hisham El-Masri, Ph.D.
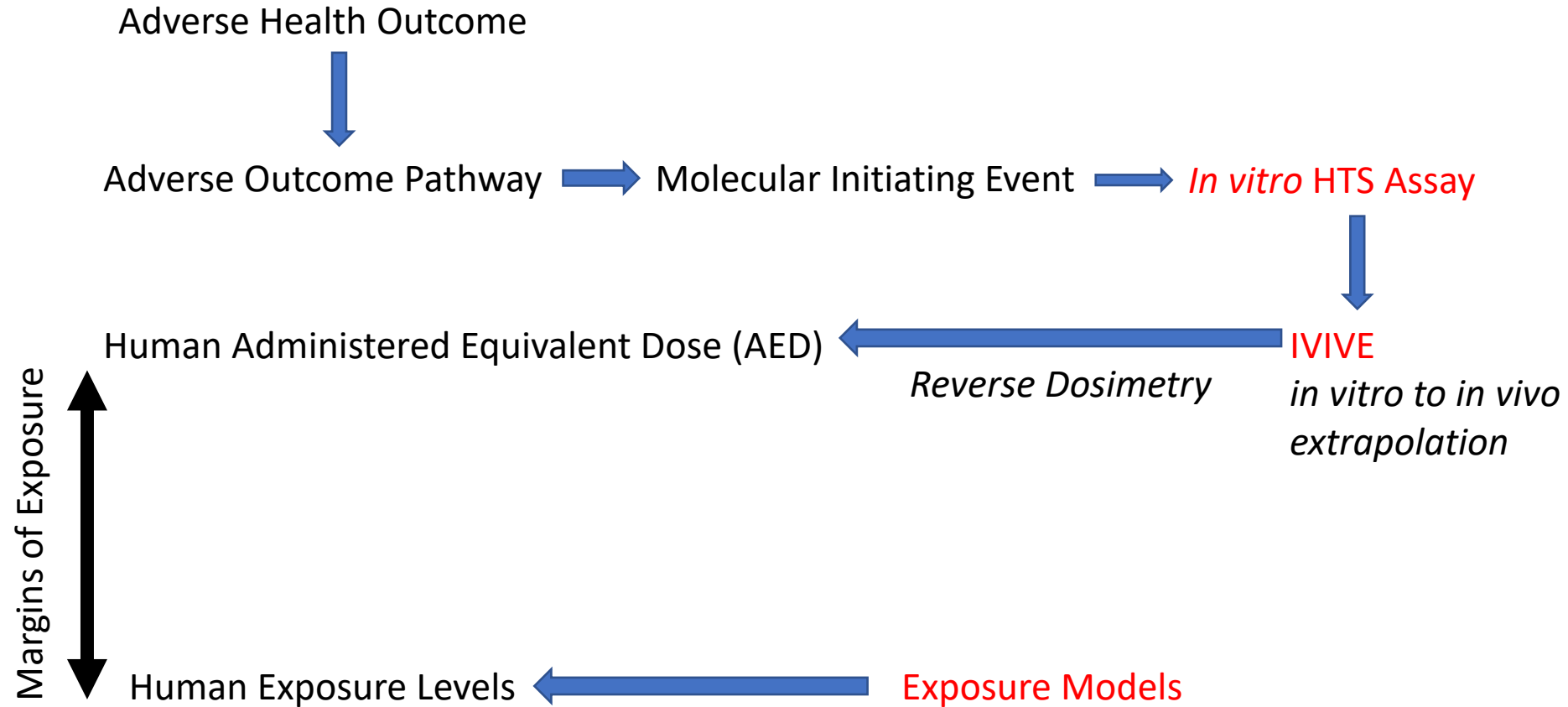U.S. Environmental Protection Agency
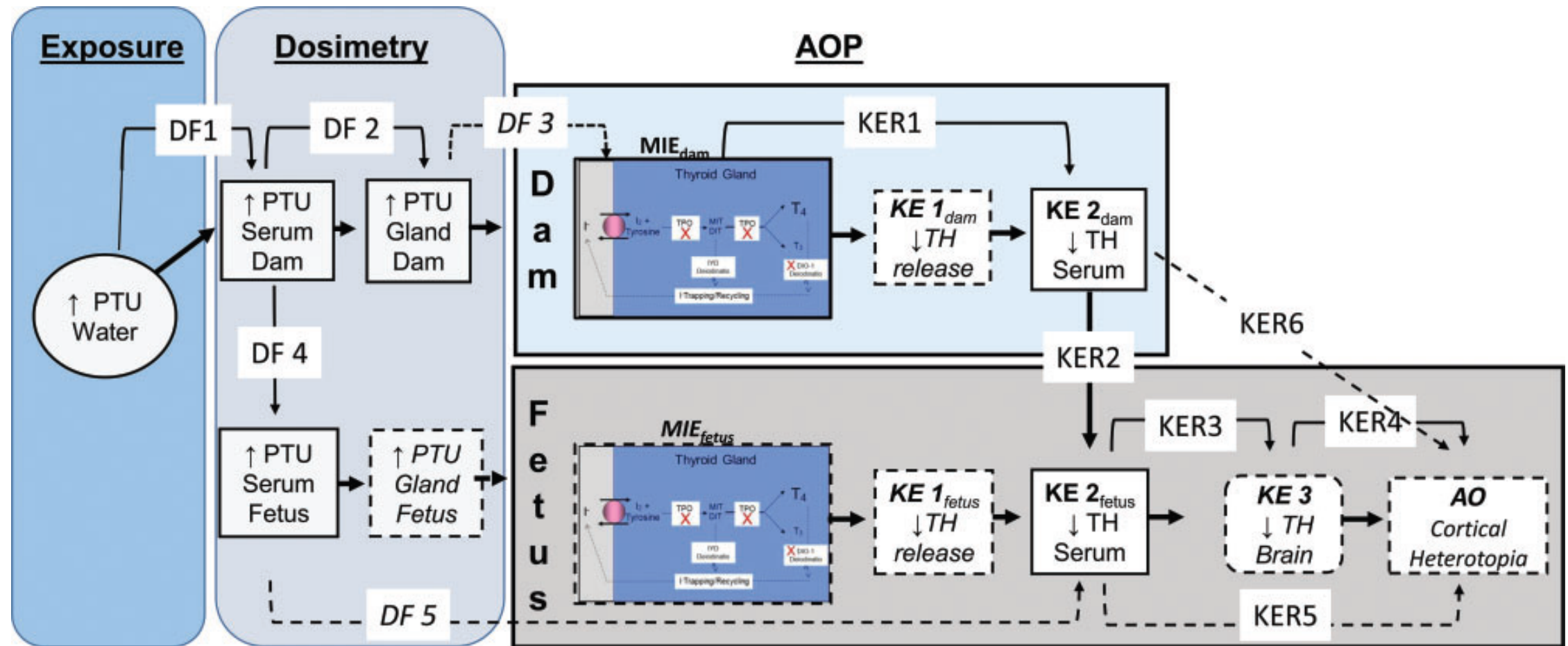ORD/CCTE/CCED/CETB

The next generation blueprint of computational toxicology at the U.S. Environmental Protection Agency. *Thomas et al. 2019*
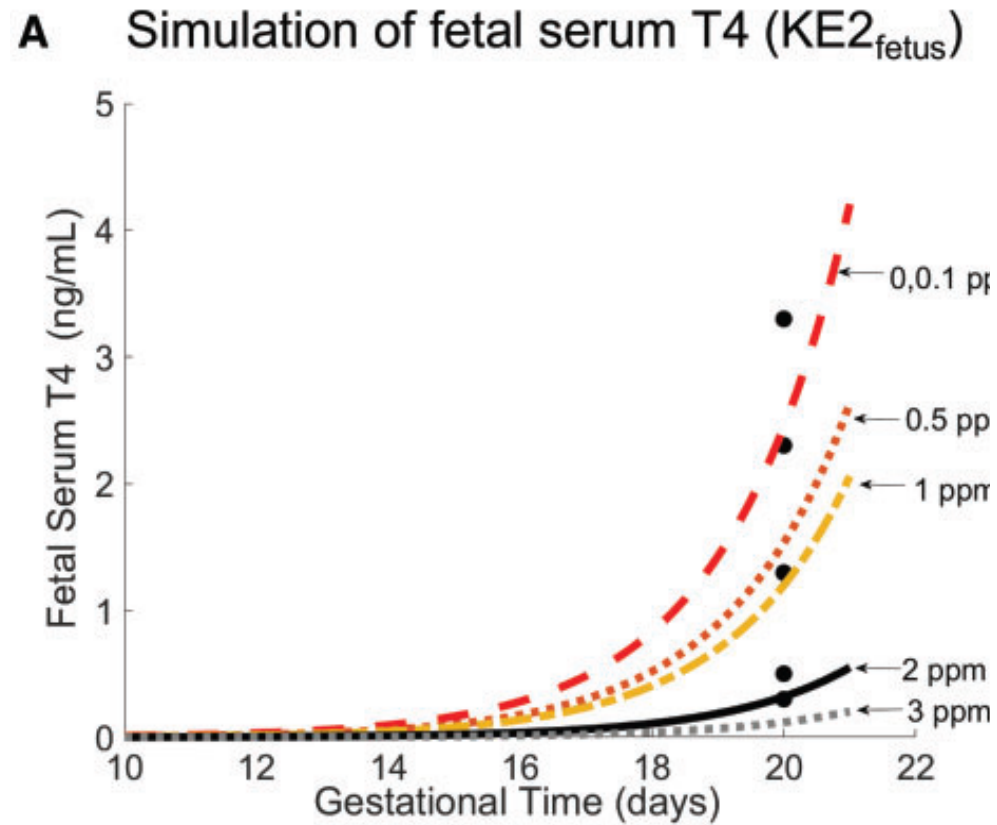
Systems Modeling for Estimations of AOP-Based Margin of Exposures. *El-Masri et al. 2022*
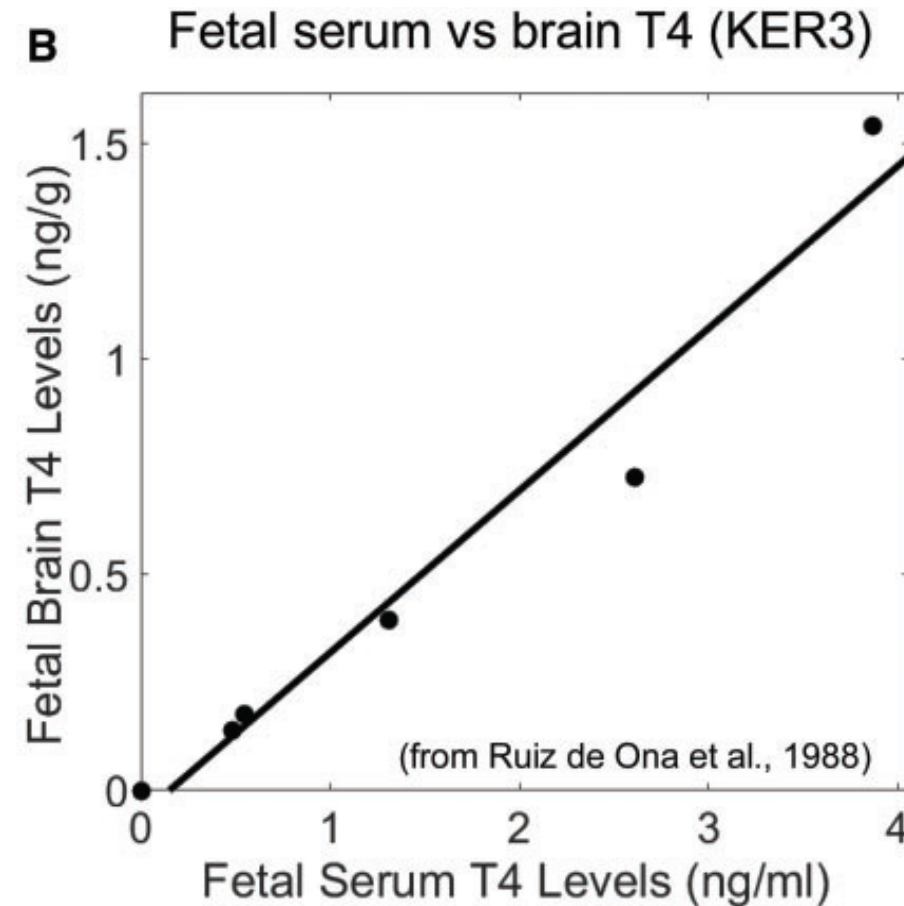
Neurodevelopment and Thyroid Hormone Synthesis Inhibition in the Rat: Quantitative Adverse Outcome Pathway (qAOP) *Hassan et al. 2017*

Neurodevelopment and Thyroid Hormone Synthesis Inhibition in the Rat: Quantitative Adverse Outcome Pathway (qAOP) *Hassan et al. 2017*

A Simulation of fetal serum T4 (KE2$_{fetus}$)

Neurodevelopment and Thyroid Hormone Synthesis Inhibition in the Rat: Quantitative Adverse Outcome Pathway (qAOP) *Hassan et al. 2017*

B Fetal serum vs brain T4 (KER3)

(from Ruiz de Ona et al., 1988)

Neurodevelopment and Thyroid Hormone Synthesis Inhibition in the Rat: Quantitative Adverse Outcome Pathway (qAOP) *Hassan et al. 2017*
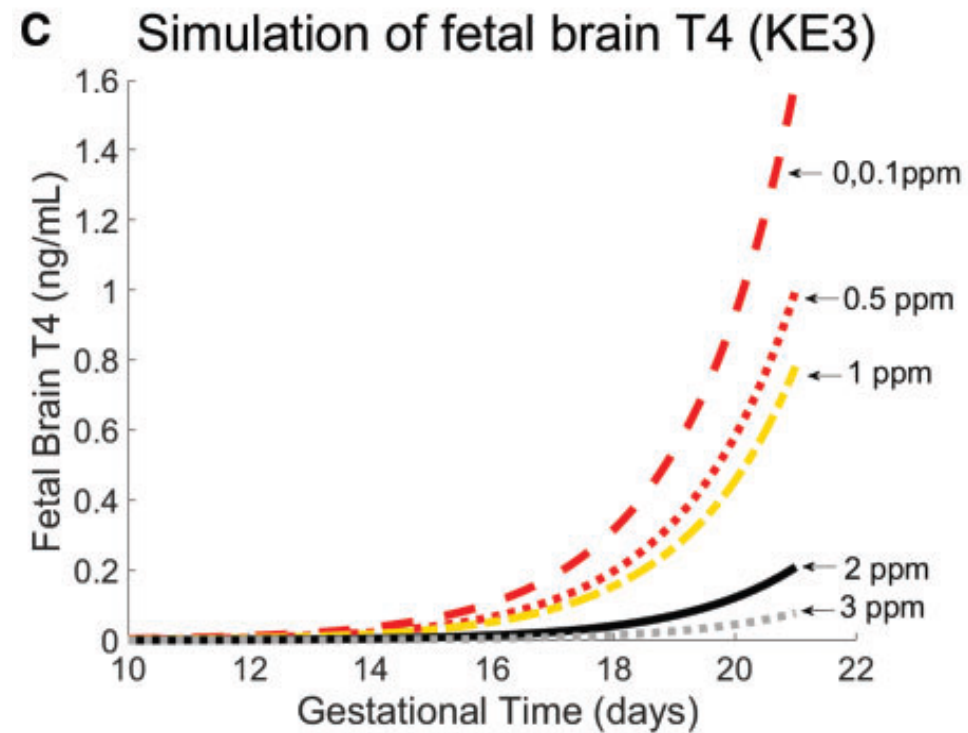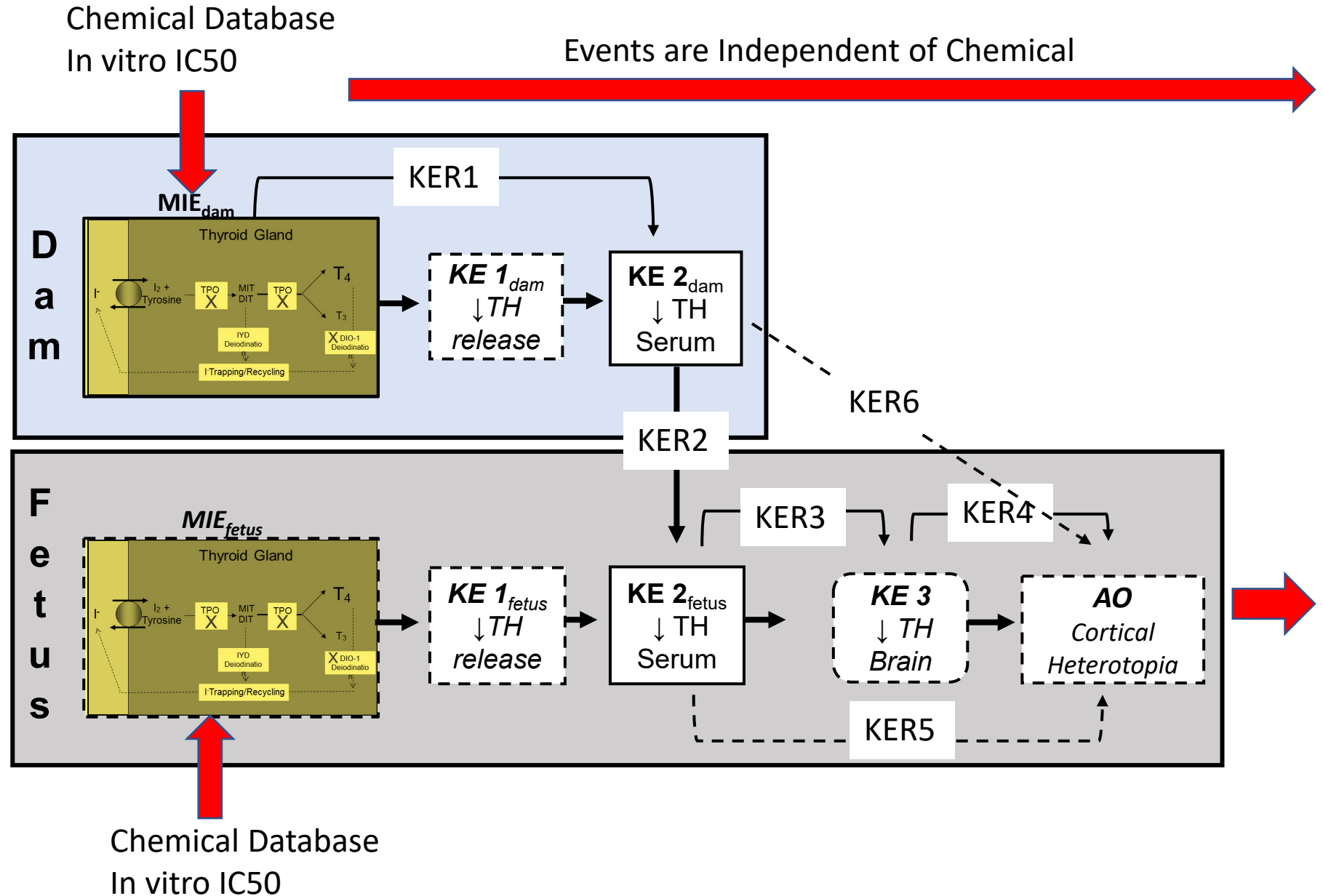
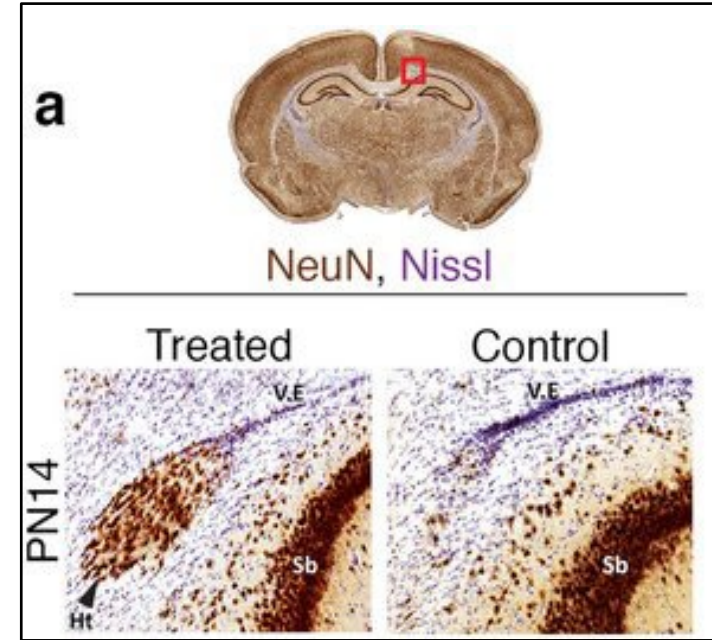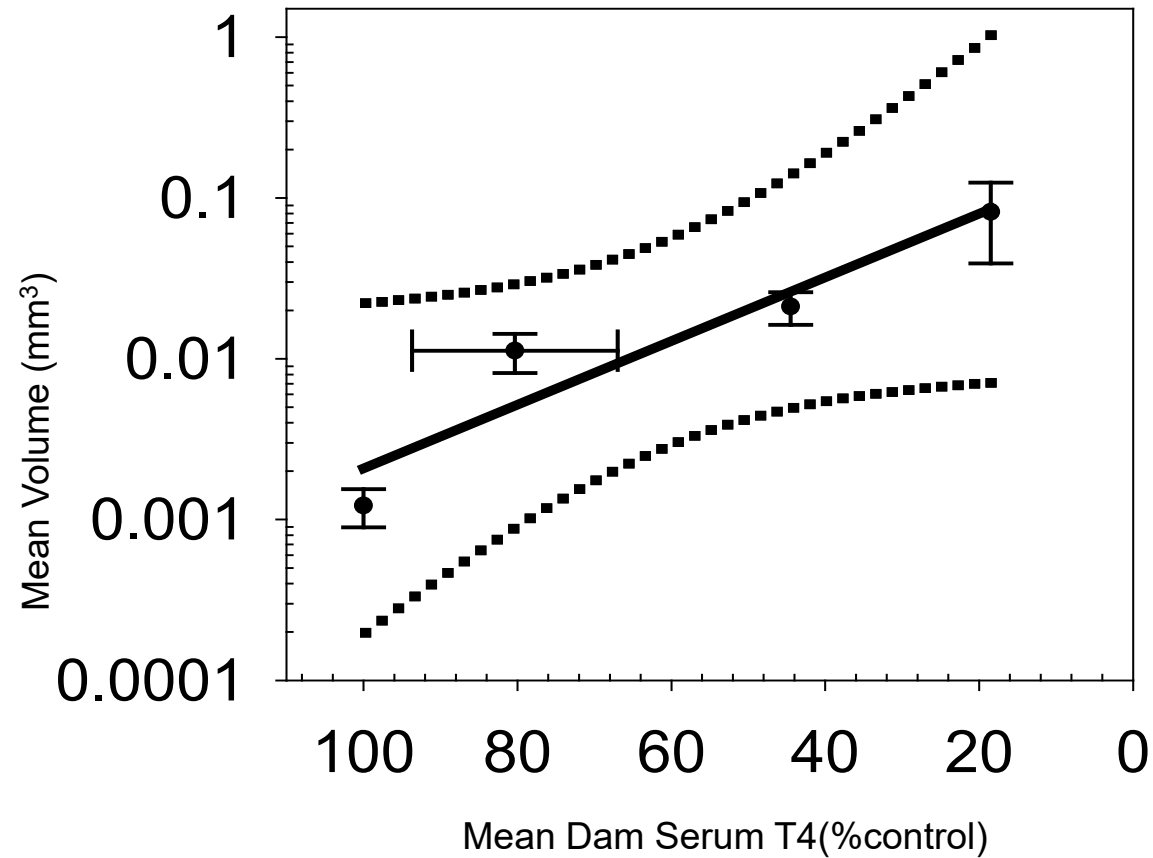

C Simulation of fetal brain T4 (KE3)

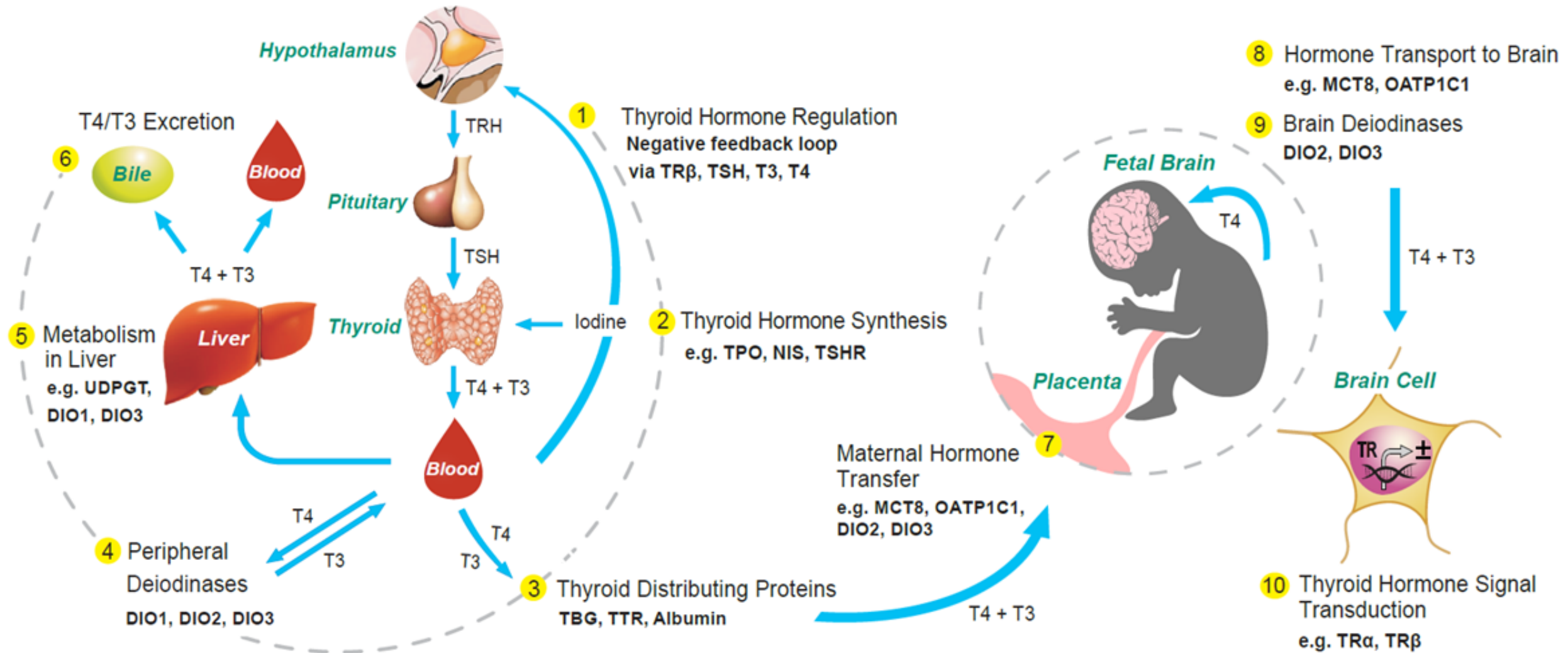# Application of qAOP to Screen Chemicals

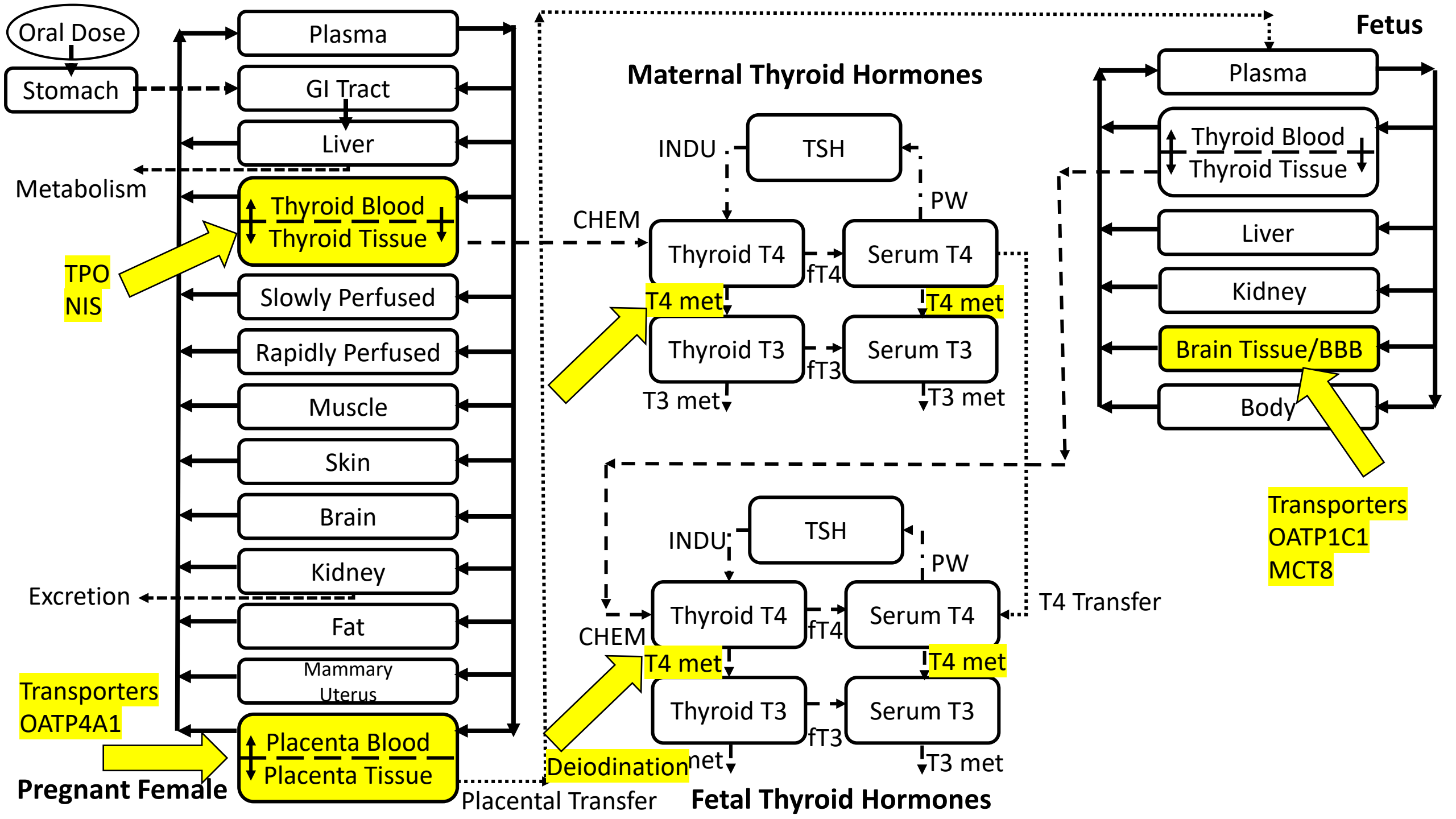# Application of qAOP to Screen Chemicals
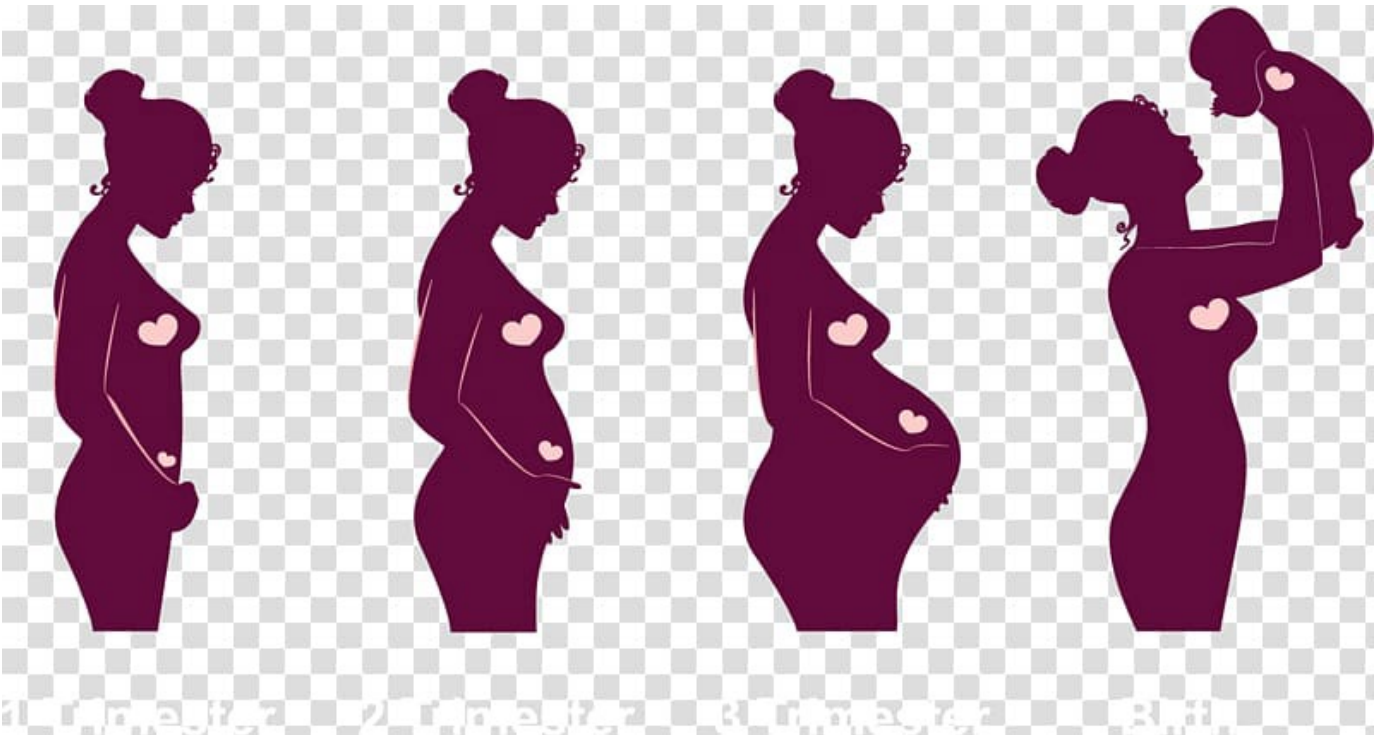
Brain Heterotopia Volume vs. Dam Serum Levels

O'Shaughnessy et al. (2019)

Sites of Interference for Thyroid Disrupting Chemicals

Gilbert et al., 2020, Endocrinology

Fetus

Maternal Thyroid Hormones

Fetal Thyroid Hormones

Pregnant Female

Oral Dose

Stomach

Plasma

GI Tract

Liver

Metabolism

Thyroid Blood / Thyroid Tissue

Slowly Perfused

Rapidly Perfused

Muscle

Skin

Brain

Kidney

Excretion

Fat

Mammary Uterus

Placenta Blood / Placenta Tissue

TPO NIS

Transporters OATP4A1

Placental Transfer

INDU — TSH

CHEM

Thyroid T4 — fT4 → Serum T4

T4 met

Thyroid T3 — fT3 → Serum T3

T3 met

PW

T4 met

T3 met

Deiodination

INDU — TSH

CHEM

Thyroid T4 — fT4 → Serum T4

T4 met

Thyroid T3 — fT3 → Serum T3

T3 met

PW

T4 met

T3 met

T4 Transfer

Plasma

Thyroid Blood / Thyroid Tissue

Liver

Kidney

Brain Tissue/BBB

Body

Transporters OATP1C1 MCT8

Physiological Differences Between Humans and Rats


hCG (*Human Chorionic Gonadotropin*)

hCG levels during pregnancy (in weeks sincelast menstrual period)	
3 weeks LMP	5 - 50 mIU/ml
4 weeks LMP	5 - 426 mIU/ml
5 weeks LMP	18 - 7,340 mIU/ml
6 weeks LMP	1,080 - 56,500 mIU/ml
7 - 8 weeks LMP	7, 650 - 229,000 mIU/ml
9 - 12 weeks LMP	25,700 - 288,000 mIU/ml
13 - 16 weeks LMP	13,300 - 254,000 mIU/ml
17 - 24 weeks LMP	4,060 - 165,400 mIU/ml
25 - 40 weeks LMP	3,640 - 117,000 mIU/ml

Model Simulations – Plasma TSH
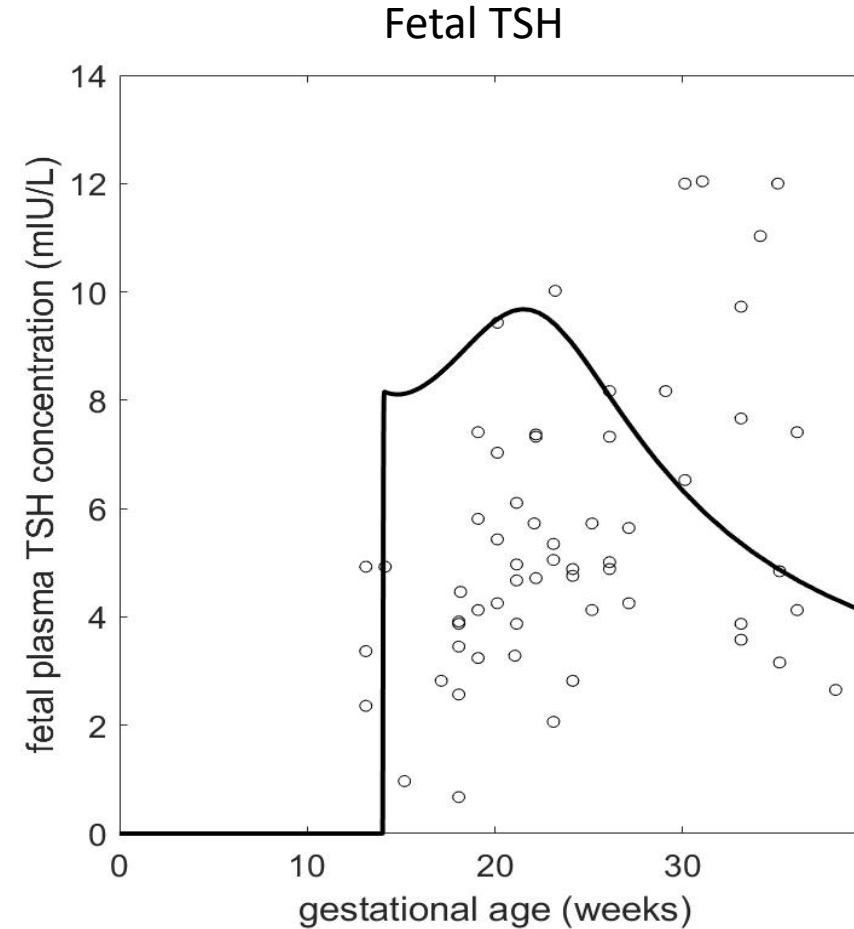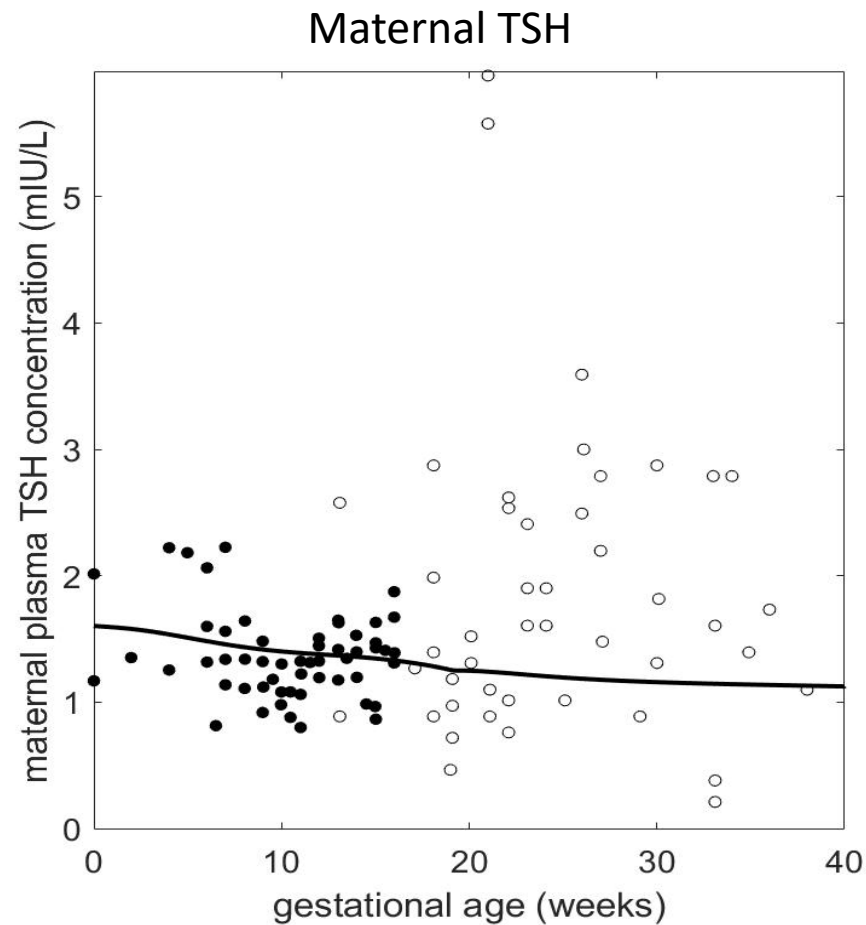
Maternal (left) and fetal (right) plasma TSH concentrations.
Closed circles represent data from Schlosser et al. 2017 and
open circles are data digitized from Thorpe-Beeston et al. 1991

Model Simulations – Plasma Thyroid Hormones
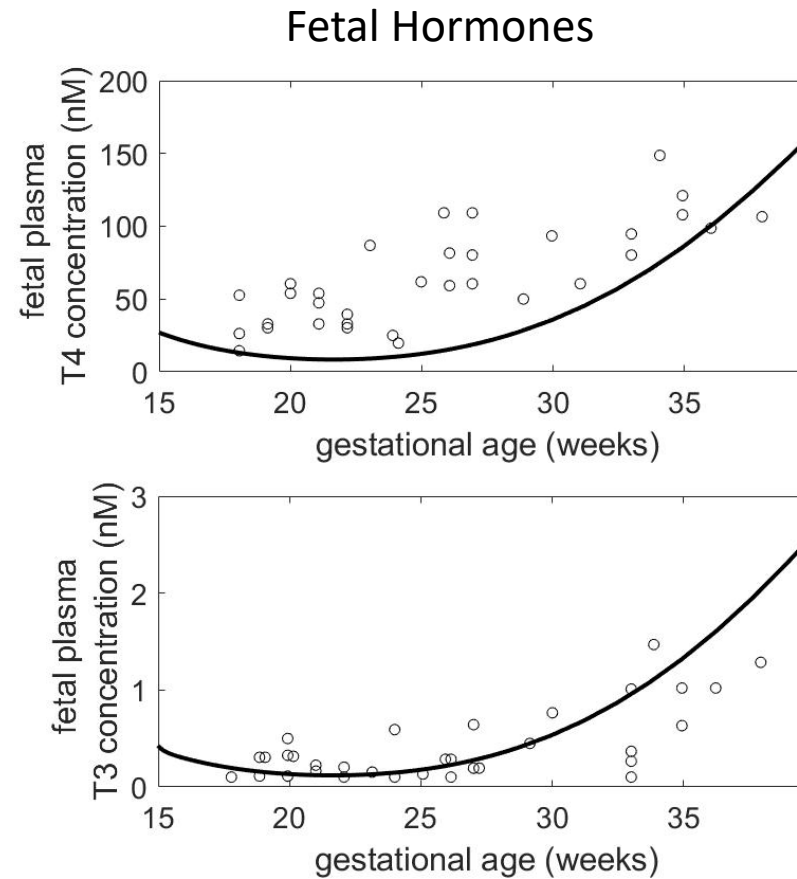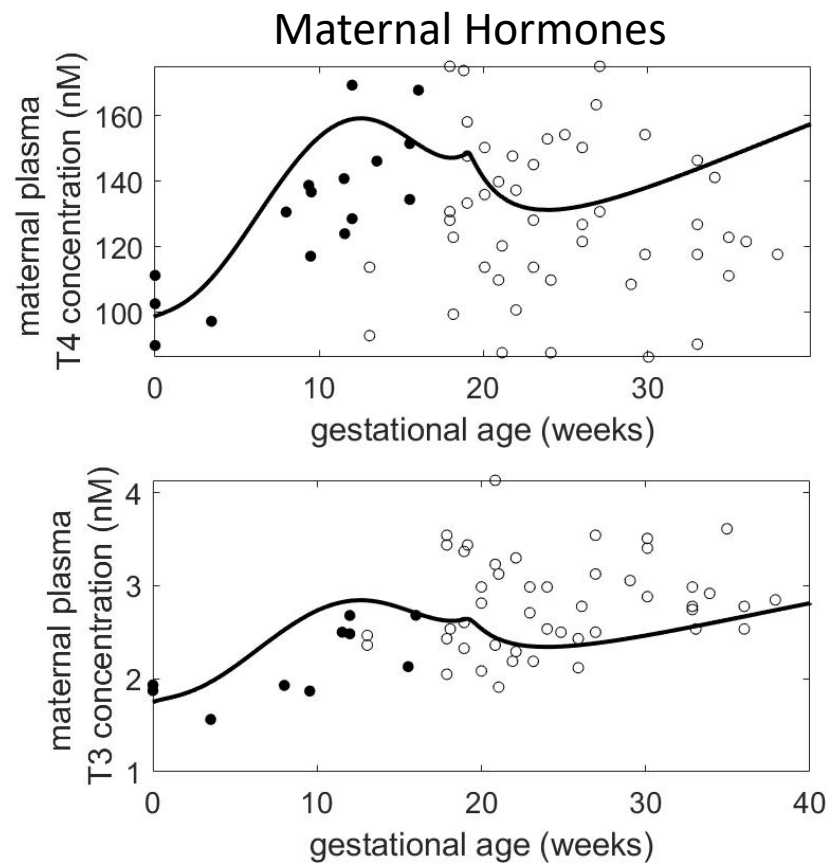
Maternal (top) and fetal (bottom) plasma TH concentrations. T4
(left) and T3 (right). Closed circles represent data from
Schlosser et al. 2017 and open circles are data digitized from
Thorpe-Beeston et al. 1991.

Acknowledgment