Physiologically-Based Quantitative System Toxicology Thyroid Hormones Modeling Platform

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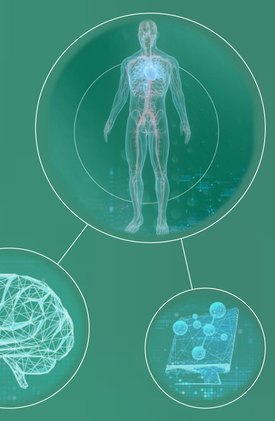

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Intro

Thyroid hormone (TH) disruption by endocrine-disrupting chemicals poses a substantial public health risk. Currently, toxicity assessment relies on preclinical studies in animals.

UGT induction is a common adverse outcome pathway that may lead to thyroid toxicity through increased TH clearance. However, due to species-specific differences in the TH regulation system, the relevance of preclinical results to humans is questionable.

We present a physiologically based kinetic quantitative systems toxicology (PBK-QST) platform for predicting TH levels after exposure to UGT inducers and other thyroid-disrupting chemical substances.

Methods

The platform is built using the OSP Suite Version 12 and integrates PBK models of thyroid disruptors with QST modules for TH regulation and quantitative adverse outcome pathways (qAOP) modules. The platform fully utilizes Version 12's modularization concept, allowing easy integration of new PBK models of potential thyroid active compounds or extension of the physiology to simulate, e.g., disturbance of TH levels during pregnancy and lactation.

Results

The standard PBPK physiology implemented in PK-Sim was extended by the thyroid organ[1] and the pituitary gland as part of the brain.

The QST modules include synthesis of thyroid-stimulating hormone (TSH), feedback-controlled Triiodothyronine (T3) and Thyroxine (T4) synthesis, DIO and UDPGT-mediated clearances of T4 and T3, and species-specific turnover and TH binding models for Albumin, Transthyretin (TTR), and Thyroxine-Binding Globulin (TBG) (Figure 1).

The model covers various scales of detail down to transporter-mediated TH uptake in tissues and receptor binding and activation (Figure 2).

A PBK model of phenobarbital, a known UGT inducer, has been included and describes the observed changes in T3/T4 levels in rats and humans.

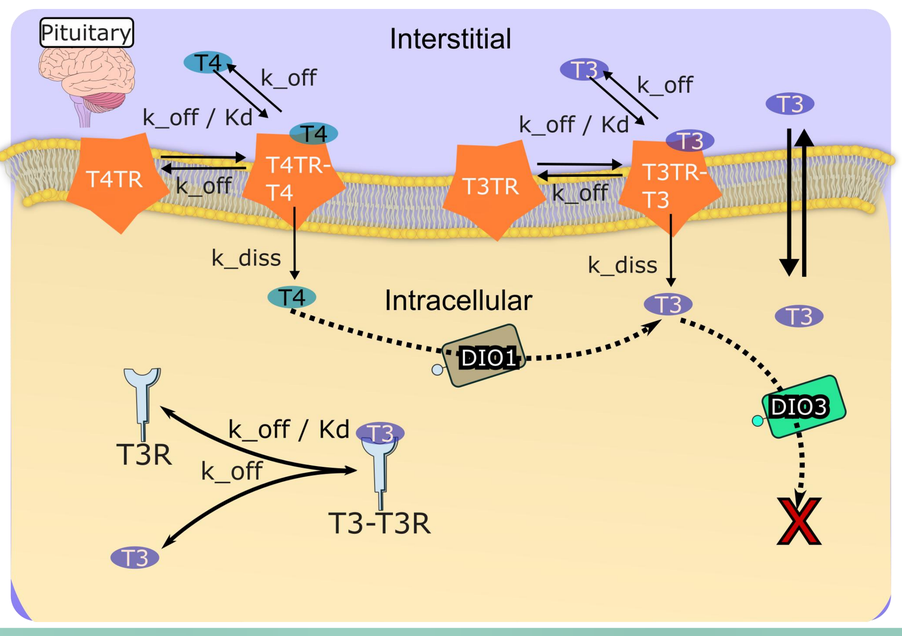


Figure 2: Overview of the implemented pathways of T3 and T4 metabolism in the pituitary gland. T3 and T4 bind to the transporter (T3TR and T4TR for T3 and T4, respectively) in the interstitial space and are transported into the cells. Intracellularly, T4 is converted to T3 by the enzyme DIO1. Both T3 and T4 are eliminated by DIO3. Free T3 reversibly binds to the T3 receptor (T3R), inhibiting the production of TSH. The pathways were parametrized using T3 concentration and T3R occupancy data from [2,3].

Conclusion

The developed platform covers the important processes relevant to predicting various thyroid toxicity molecular initiating events. It has been shown that the platform is capable of translating in vitro data into in vivo observations of changes in TH levels in rats and the absence of a pronounced effect in humans.

This PB-QST platform exemplifies how a modular approach can help to build a Next Generation Risk Assessment (NGRA) and Model Informed Drug Development (MIDD) ecosystems, with re-usable modules and extensibility for new process networks, medications, and chemicals.

PB QST Modeling Platform for Prediction of Thyroid Toxicity

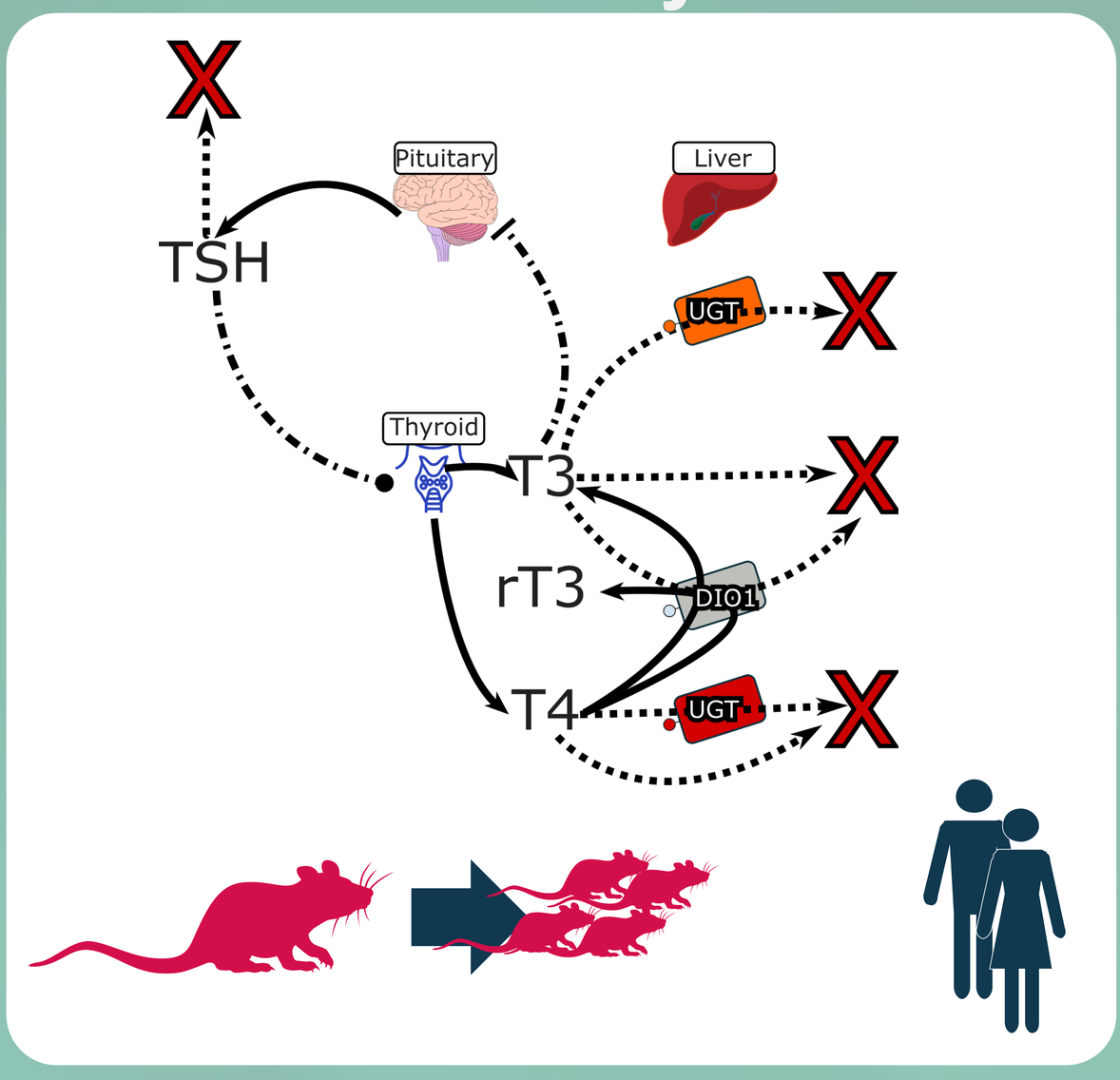
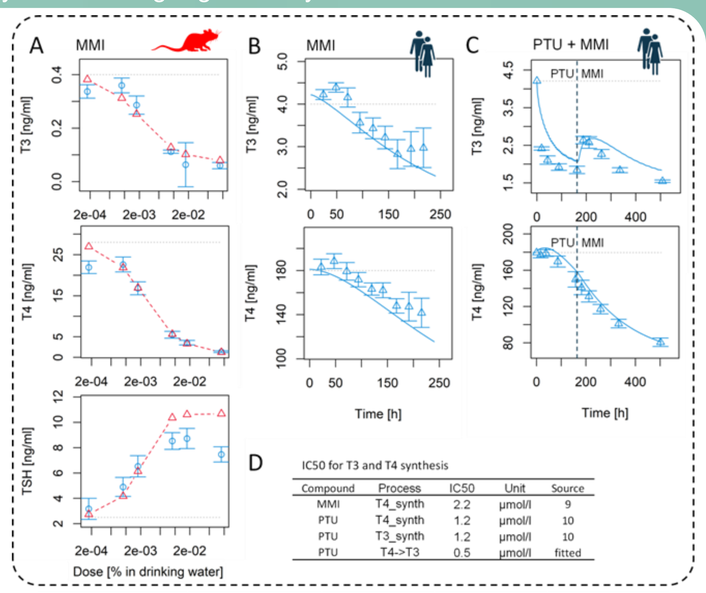


Figure 1: Overview of the implemented processes of TH homeostasis. T3 and T4 are synthesized in the thyroid gland, with the synthesis being regulated by TSH. T4 is converted to T3 and rT3 by DIO and metabolized by UGT in the liver and intestine. T3 is eliminated by DIO and UGT. TSH is secreted in the pituitary gland, with the synthesis being regulated by T3.

Toxicity modes of action

- TH synthesis inhibition
  Examples: Methimazole (MMI), Propylthiouracil (PTU)
- T4->T3 conversion inhibition
  Example: Propylthiouracil (PTU)
- UGT induction
  Example: Phenobarbital (PB)



E

	PB dose	% change T4	% change T3	% change TSH
Rat observed	179 mg/kg bw/ day	-43	-22	+76
	100 mg/kg bw/ day	[-60, -6]	[-24, +23]	[+3, +138]
Rat predicted	179 mg/kg bw/ day	-20	-22	+70
Human observed	100 mg/day	+5	+6	+16
Human predicted	100 mg/day	0	0	+3

Figure 3: Implemented Modes of Action of various thyroid-disrupting chemicals. For Table E, the range of observed TH concentration changes is given as [min, max]

References

1. Pilari S, Gaub T, Block M, Görlitz L. Development of Physiologically Based Organ Models to Evaluate the Pharmacokinetics of Drugs in the Testes and the Thyroid Gland. CPT: Pharmacometrics & Systems Pharmacology. 2017;6(8):532–42.
2. Silva JE, Larsen PR. Pituitary nuclear 3,5,3'-triiodothyronine and thyrotropin secretion: an explanation for the effect of thyroxine. Science. 1977 Nov 11;198(4317):617–20.
3. Silva JE, Larsen PR. Contributions of plasma triiodothyronine and local thyroxine monodeiodination to triiodothyronine to nuclear triiodothyronine receptor saturation in pituitary, liver, and kidney of hypothyroid rats. Further evidence relating saturation of pituitary nuclear triiodothyronine receptors and the acute inhibition of thyroid-stimulating hormone release. J Clin Invest. 1978 May;61(5):1247–59.

Modeling

Coding

Supporting the open-source development of:
PK-Sim® MoBi® OSP OPEN SYSTEMS PHARMACOLOGY Software Suite
www.Open-Systems-Pharmacology.org

Presented at OSP CC 2025, Paris, France

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