Development of computer models to predict chemicals interference with thyroid hormones

3R symposium 2017

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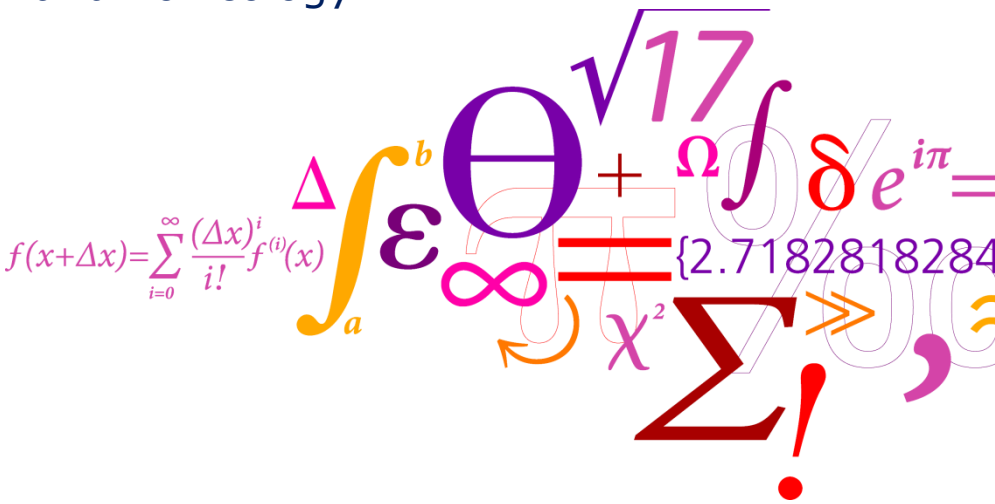


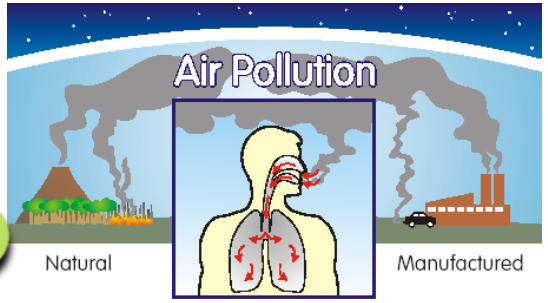
DTU Food
National Food Institute

The aim of the project

- The aim of the present project was to develop **computer models** for some of the most important mechanisms known to disturb the **thyroid hormone** balance.

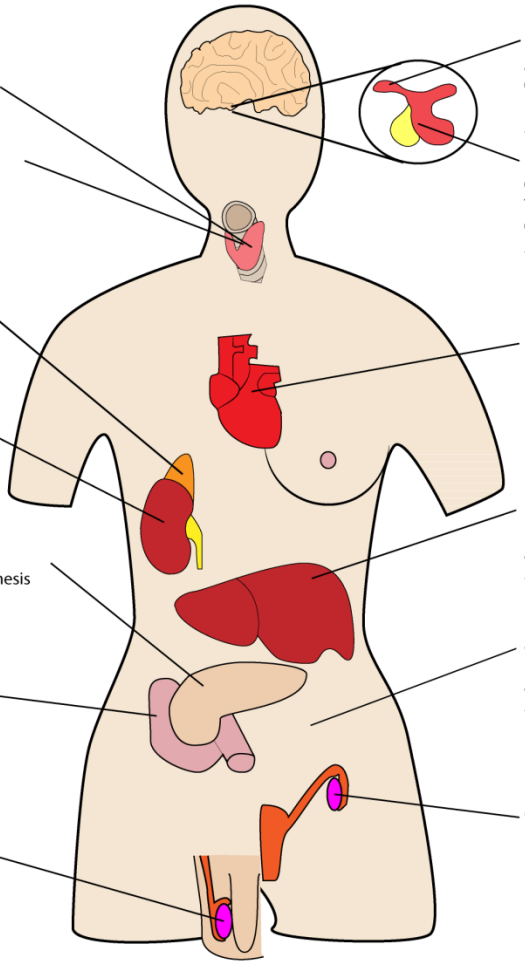
- The models are so-called **QSARs** (quantitative structure-activity relationships), that can predict effects of chemicals based on their **molecular structure**.

Background


Air Pollution
Natural
Manufactured


Pampers
Feel n Learn
Febreze
Pringles
DAWN
Tide

The hormone (or endocrine) system



Thyroid gland
T3/T4: involved in e.g. metabolism and development
Calcotonin: regulates blood calcium levels

Parathyroid gland
Parathyroid hormone: regulates blood calcium levels

Adrenal glands
Cortisol: e.g. stimulates gluconeogenesis
Dopamine: regulates heart rate and blood pressure
Adrenaline: e.g. increase oxygen and glucose in brain
...

Kidneys
Renin: regulates blood pressure
Erythropoietin: stimulates red blood cell production

Pancreas
Insulin: regulates glucose uptake and glycolyses
Glucagon: regulates glucuse release and gluconeogenesis
...

Gastro-intestinal tract
Gastrin: stimulates gastric acid secretion
Ghrelin: stimulates appetite
...

Testes
Androgens: e.g. male secundary sex characteristics
Inhibin and activin: regulate gonadotropin release

Hypothalamus
Anti-diuretic hormone: regulates body water levels
Oxytocin: contraction of uterus and mammary gland
Releasing hormones: Contol hypophysis hormone release
...

Hypophysis (adeno- and neuro-)
Growth hormone: stimulates growth
Thyrotropin TSH: stimulates thyroid gland T3/T4 secretion
Gonadotropins FSH and LH: affect the gonads
...

Heart
Natriuretic peptides: e.g. inhibit renin secretion

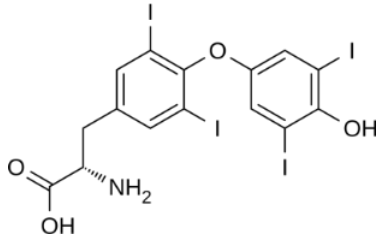
Liver
Insuline-like growth factor-1: regulates cell growth
Angiotensinogen: angiotensin precursor, vasoconstriction
...

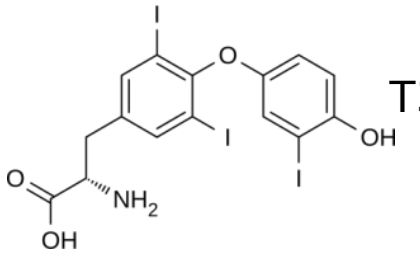
Adipose tissue
Leptin: decreases appetite and increases metabolism
Adiponectin: regulates glucose levels and fatty acid breakdown
...

Ovaries
Estrogens: e.g. female secundary sex characteristics
Progestarone: prepares uterus for a fertilized egg
Inhibin and activin: regulate gonadotropin release

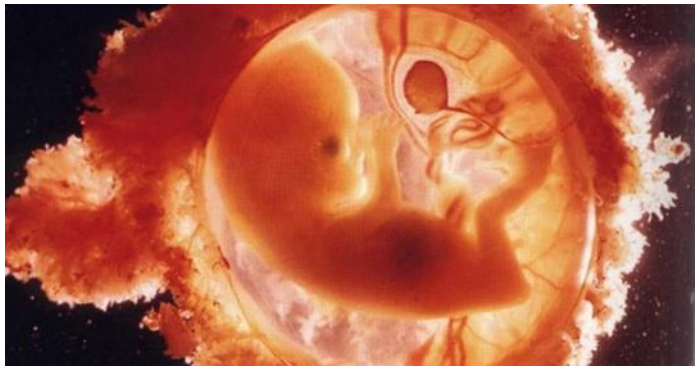
Thyroid hormones

T4 (thyroxine)

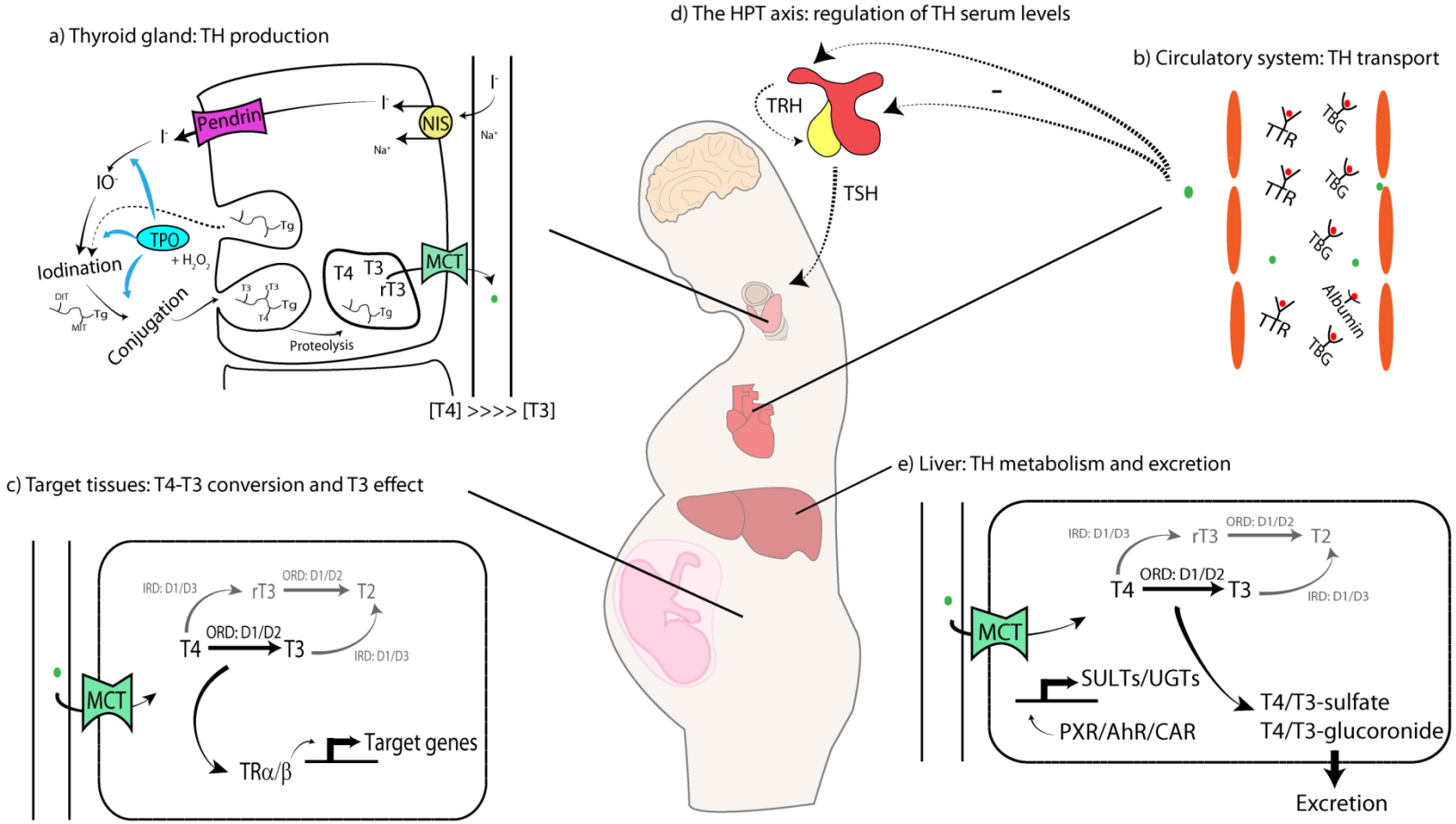




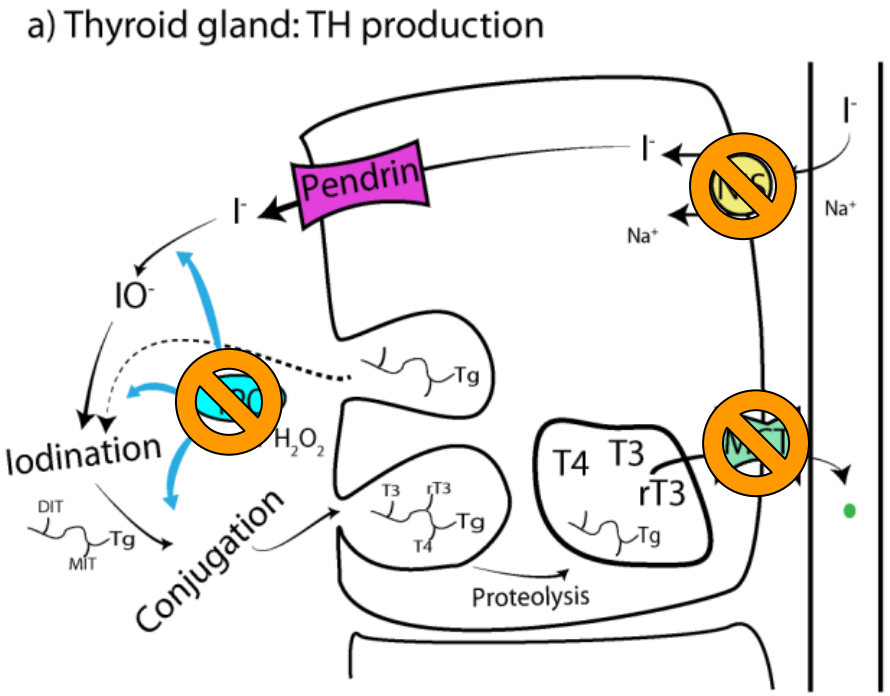
T3 (triiodothyronine)

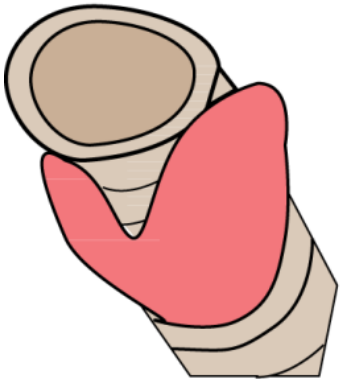


The thyroid hormone system

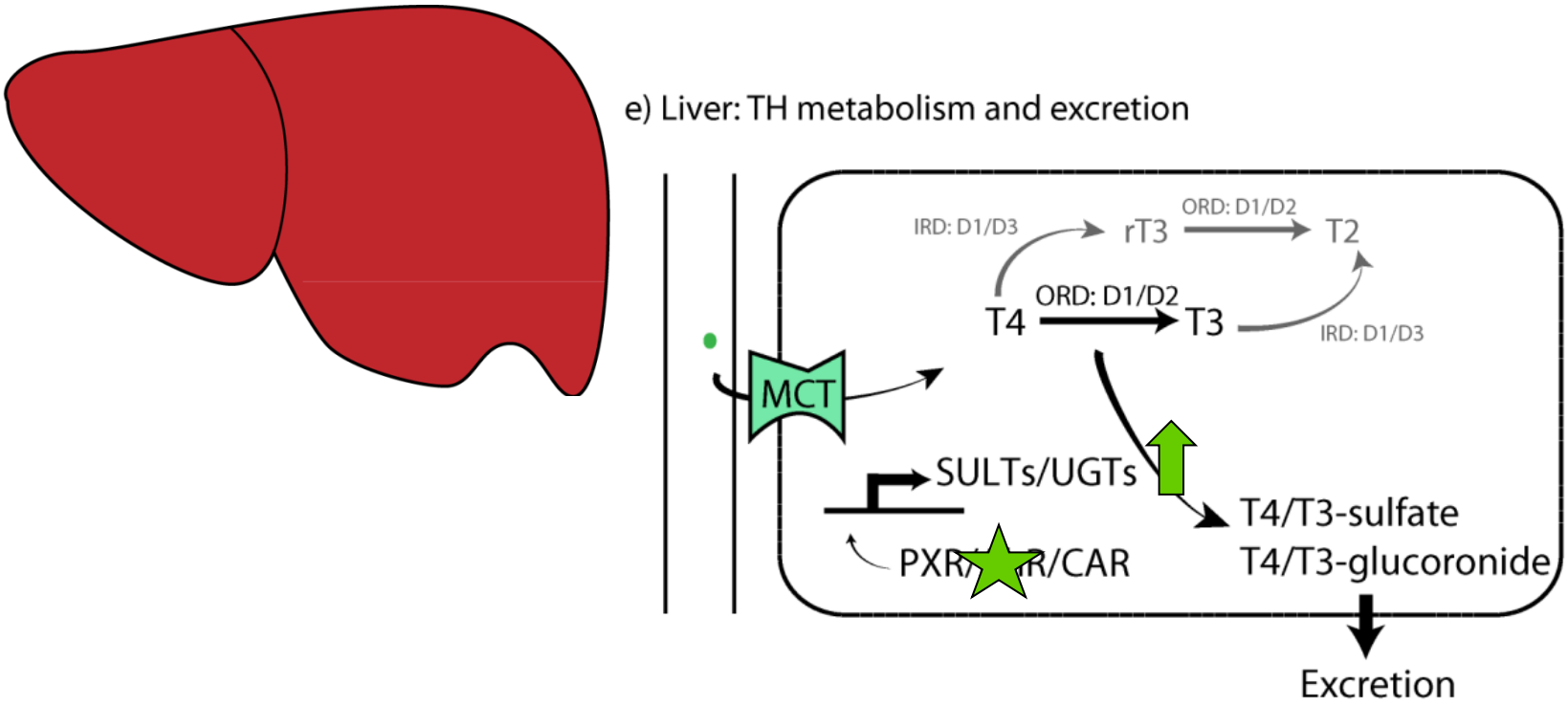


Thyroid disrupting chemicals





Thyroid disrupting chemicals



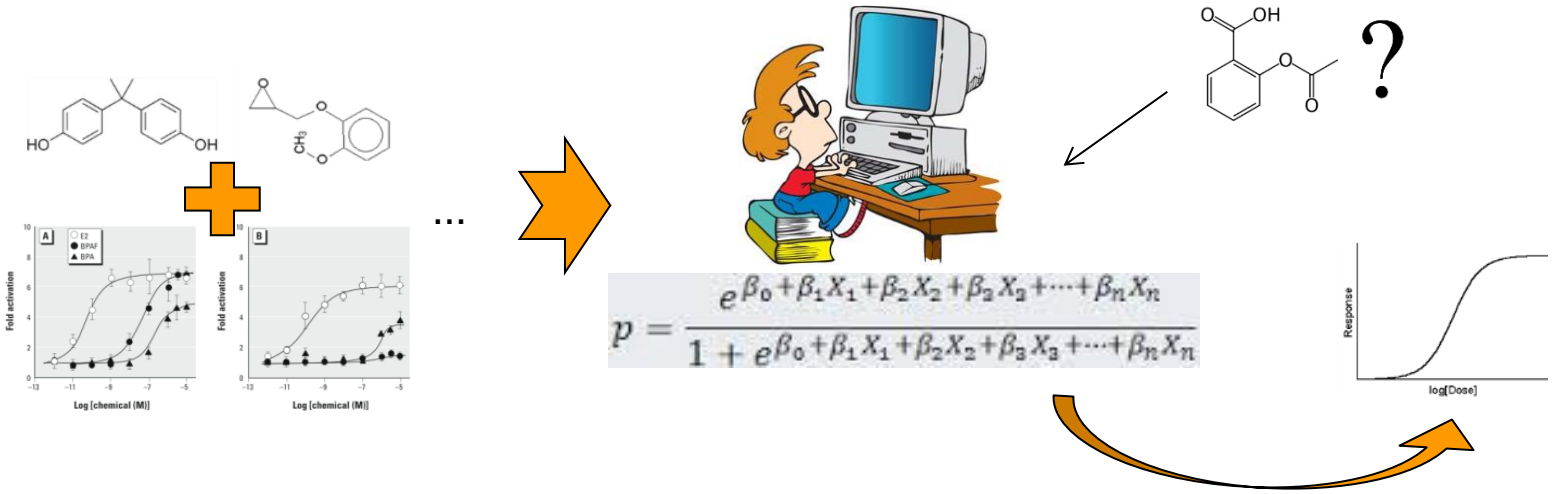
A role for computer models

- Chemicals may interfere with the thyroid hormones in **many different ways** (hormone production, metabolism etc).

- A **battery** of test methods is therefore needed to cover all mechanisms, and this is a very resource-consuming task for the **many 1000s of untested chemicals**.

- To facilitate this task, computer models have become an important tool to **screen and prioritize chemicals** for further experimental testing, thereby reducing costs and number of test animals.

QSAR:
Quantitative Structure-Activity Relationship



Assumption: the **structural similarity principle**, i.e. structurally similar chemicals exert similar properties

A **mathematical model** based on existing experimental data (training set), which relates **chemical structures** and a property →

It can **predict** the property of an **untested chemical** based on its structure information

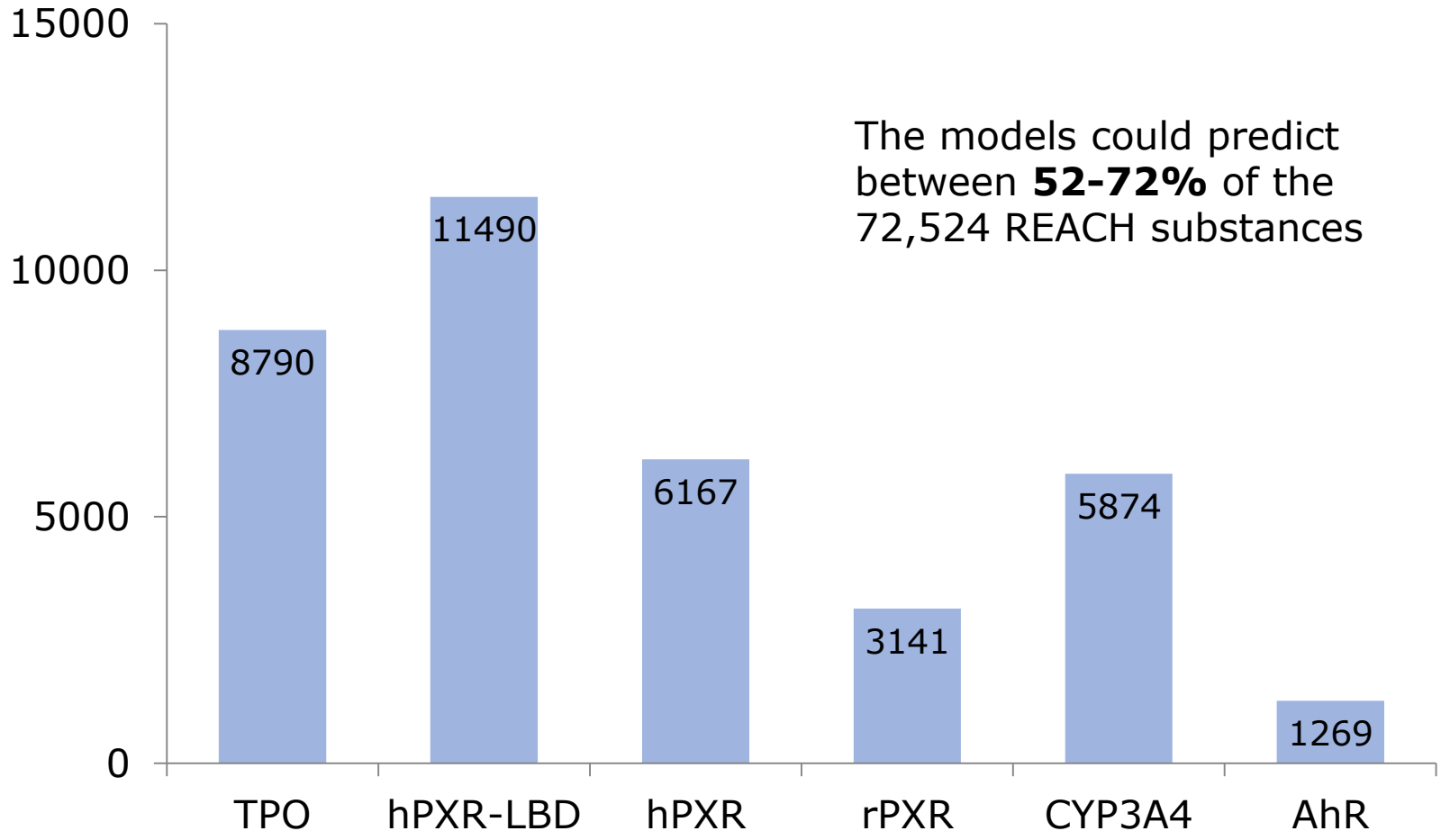
This project

Experimental data used to make the models (training sets)

Model	Total	Active	Inactive	Source
TPO inhibition	1519	230	1289	US-EPA
hPXR binding	1537	143	1394	NIH
hPXR activation	1644	207	1437	NIH
rPXR activation	1671	97	1574	NIH
CYP3A4 induction	1676	179	1497	NIH
AhR activation	4160	832	3328	PubChem

The accuracy of the QSAR models were between 75-93%, which means that the models are highly predictive

Number of REACH compounds predicted active



http://qsar.food.dtu.dk

Free online database

Predictions for > 600,000 compounds

>200 QSAR predictions (e.g. phys.-chem. properties, health effects)

Danish (Q)SAR Models – coming soon

- On-the-fly predictions for user-defined chemical substances in >20 models from the Danish (Q)SAR database

Danish (Q)SAR Models

powered by Leadscope Predictive Data Miner

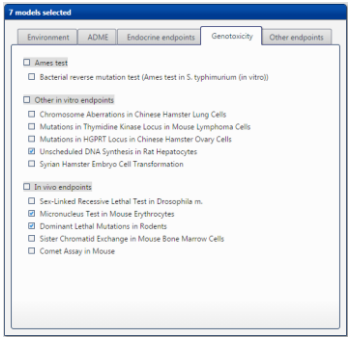
Ministry of Environment and Food of Denmark

Leadscope®

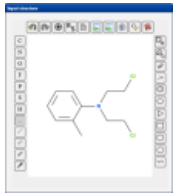
DTU Food National Food Institute

New query | User manual | Model documentation | About | Contact | Danish (Q)SAR Database

Select models



Input structure



Predict and download report

QSAR Results

Model	Probability	Prediction	Report
ER alpha binding (human in vitro), all	0.155	NEG_IN	
ER alpha activation (human in vitro)	0.0186	NEG_IN	
Androgen receptor antagonism (human in vitro)	0.138	NEG_IN	
Unscheduled DNA Synthesis in Rat Hepatocytes	0.308	NEG_OUT	
Micronucleus Test in Mouse Erythrocytes	0.96	POS_IN	
Dominant Lethal Mutations in Rodents	0.979	POS_IN	
Maximum recommended daily dose (MRDD) in Humans	0.51	POS_OUT	

Publication will be announced

on the Danish (Q)SAR Database homepage: http://qsar.food.dtu.dk

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Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox

QSAR development and profiling of 72,524 REACH substances for PXR activation and CYP3A4 induction

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QSAR models for thyroperoxidase inhibition and screening of U.S. and EU chemical inventories☆

S.A. Rosenberg[a], E.D. Watt[b,2], R.S. Judson[b], S.O. Simmons[b], K. Paul Friedman[b], M. Dybdahl[a,1], N.G. Nikolov[a,1], E.B. Wedebye[a,*,1]

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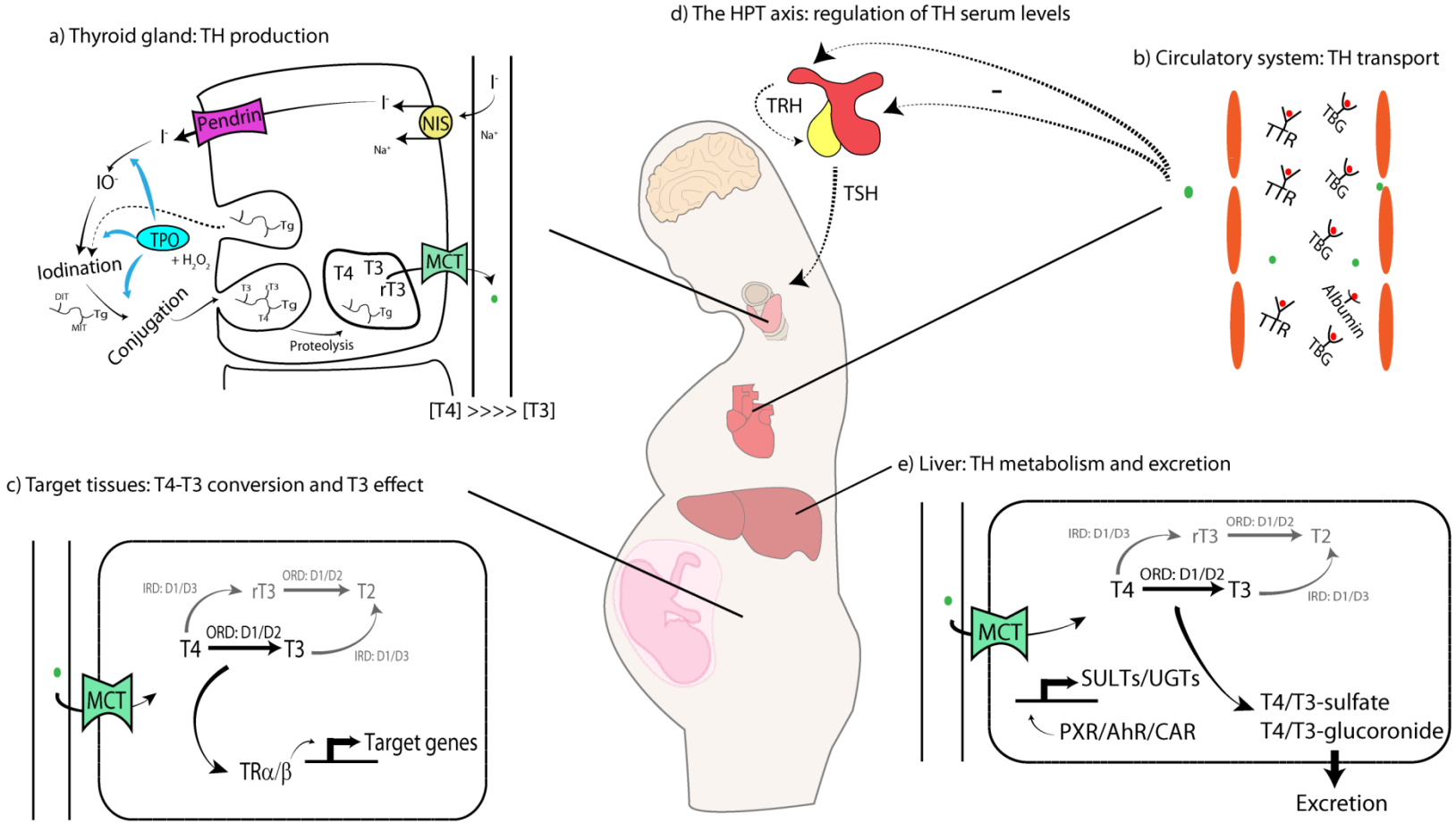
Future research



In summary

- A number of **QSAR models** covering different mechanisms have been developed and validated. The models can predict if chemicals can interfere with the production and metabolism of thyroid hormones.

- The developed models have been used to screen around 70,000 REACH chemicals, i.e. chemicals potentially available at the European market.

- In this way, knowledge from experimental data on a limited number of chemicals was used to **generate information for 10,000s of untested chemicals**.

Conclusion

- The models can in a **fast and cost-efficient** way identify potential hormone disrupting chemicals in our food, environment and consumer products. The new models can also contribute to **future design of safer chemicals and drugs**.

- Results from the project was published recently in *Computational Toxicology* 2017; 1:39-48 and *Computational Toxicology* 2017; 4:11-21. The results are also included in a PhD report by Sine Rosenberg.

Thank you for listening