



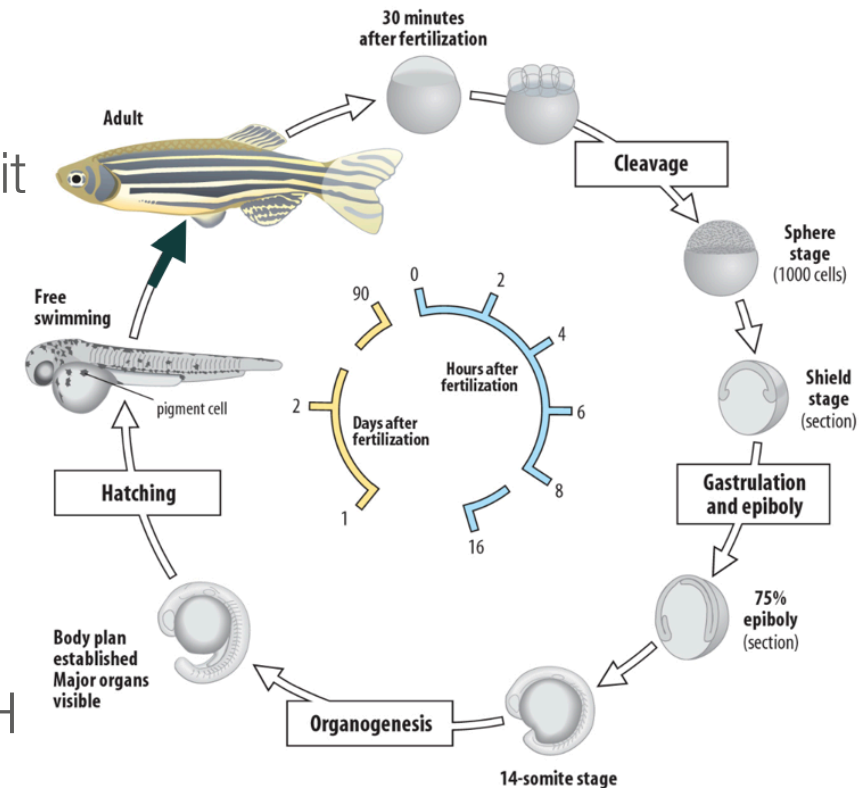
© 2017 Zebrafishlab - UAntwerpen

Het voorspellen van acute en chronische
schildkliertoxiciteit in vroege levensstadia van de zebravis

Dries Knapen

Fish Early Life Stage Test

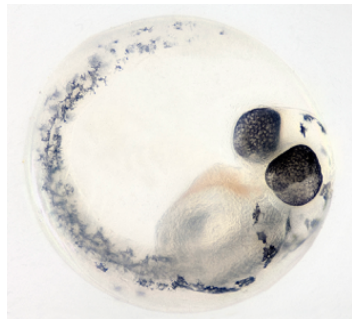
- OESO-testrichtlijn 210
- Test voor het inschatten van chronische toxiciteit
- Duur van de test: 1 tot 3 maanden
- Minstens 360 vissen per test, meestal > 700
- Typische CRO-kost per test: 50-125 kEUR
- Vandaag zeer relevant in de context van REACH



Vervangen van de FELS-test



In vitro
In chemico



Embryo



Larve



Adult

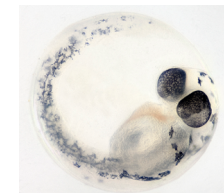
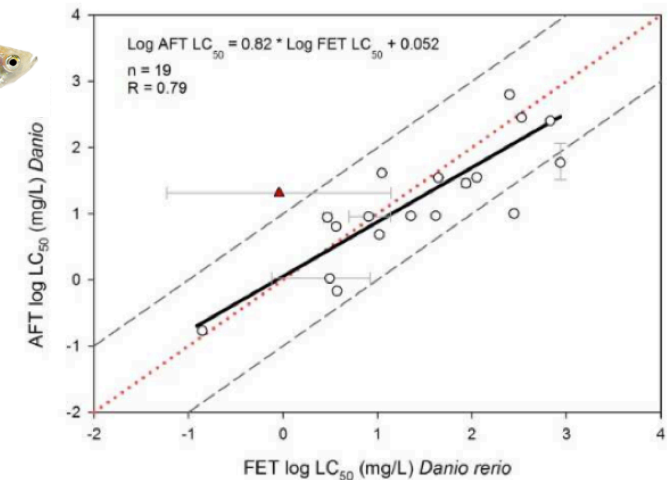
Proefdiervrij

Relevantie

Tot 120 uur na bevruchting: geen proefdier

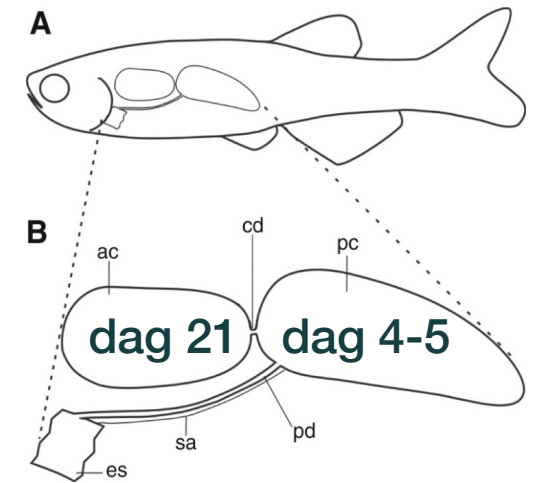
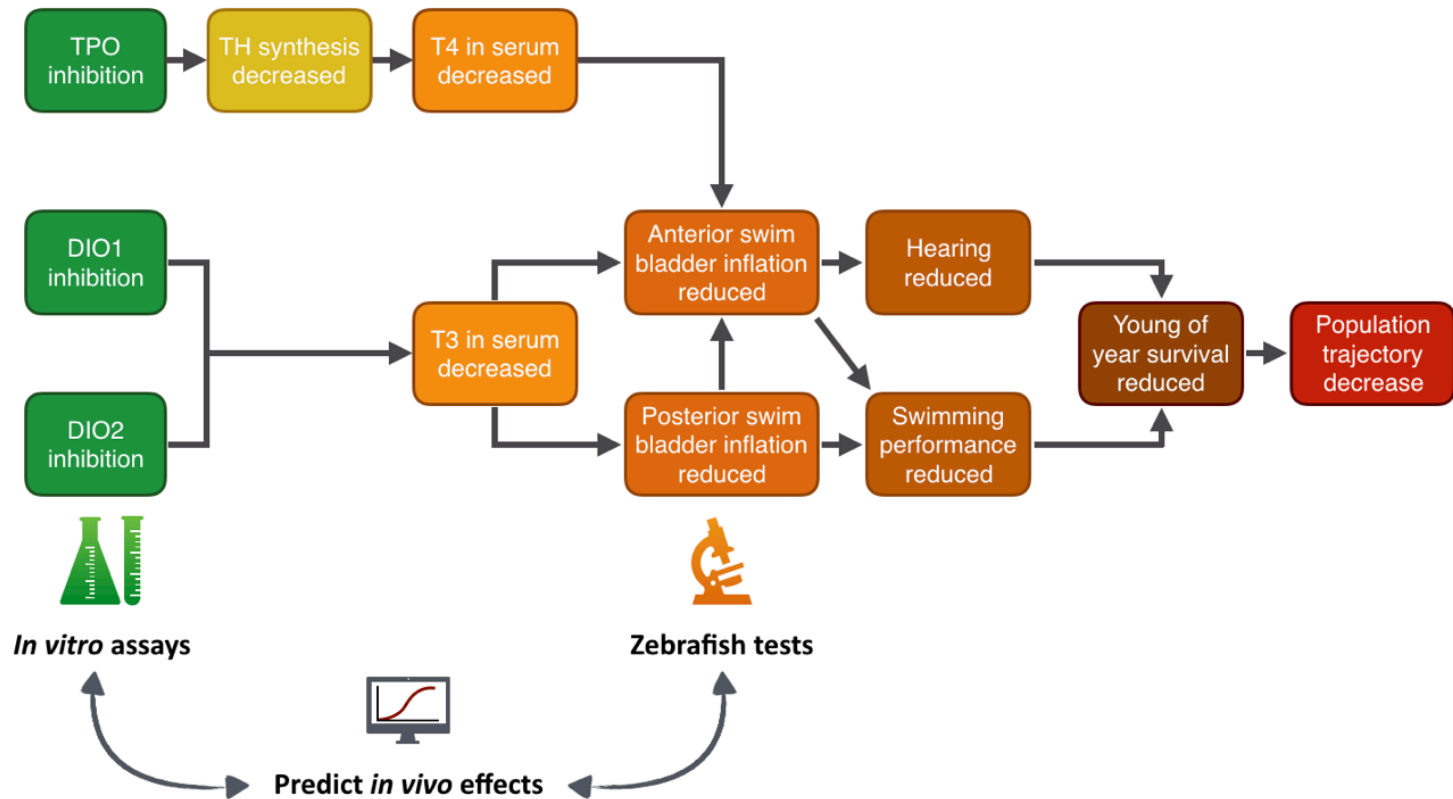
Vervangen van de FELS-test

- Niet enkel mortaliteit voorspellen
- Vraag naar mechanistische informatie:
 - Kankerverwekkend?
 - Onvruchtbaarheid?
 - Hormoonhuishouding?



Case-study: verstoring schildklierhormonen

Strategie gebaseerd op Adverse Outcome Pathways



Strategie gebaseerd op Adverse Outcome Pathways

Stap 1: *in vitro*

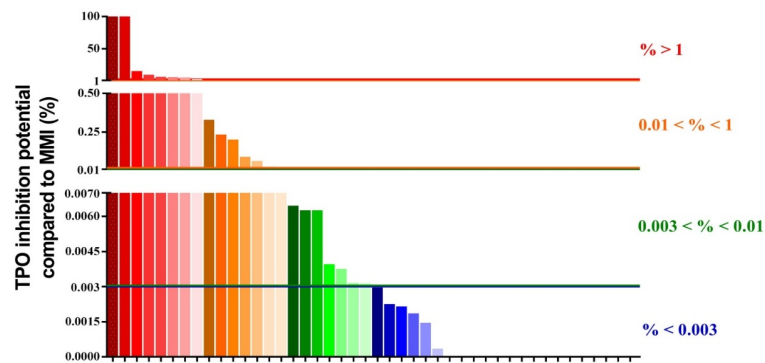
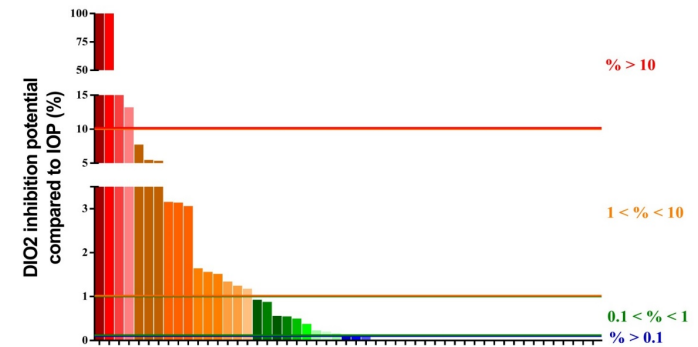
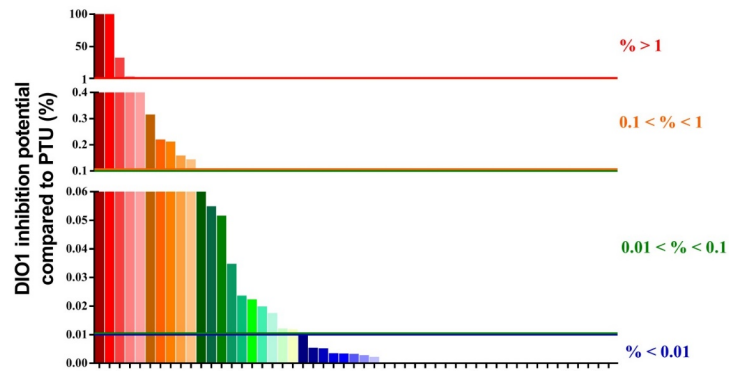
TPO inhibition

DIO1 inhibition

DIO2 inhibition



In vitro assays



- 50 stoffen gemeten
- Effecten ingeschat

Strategie gebaseerd op Adverse Outcome Pathways

Stap 2: *in vivo*

Anterior swim bladder inflation reduced

Posterior swim bladder inflation reduced



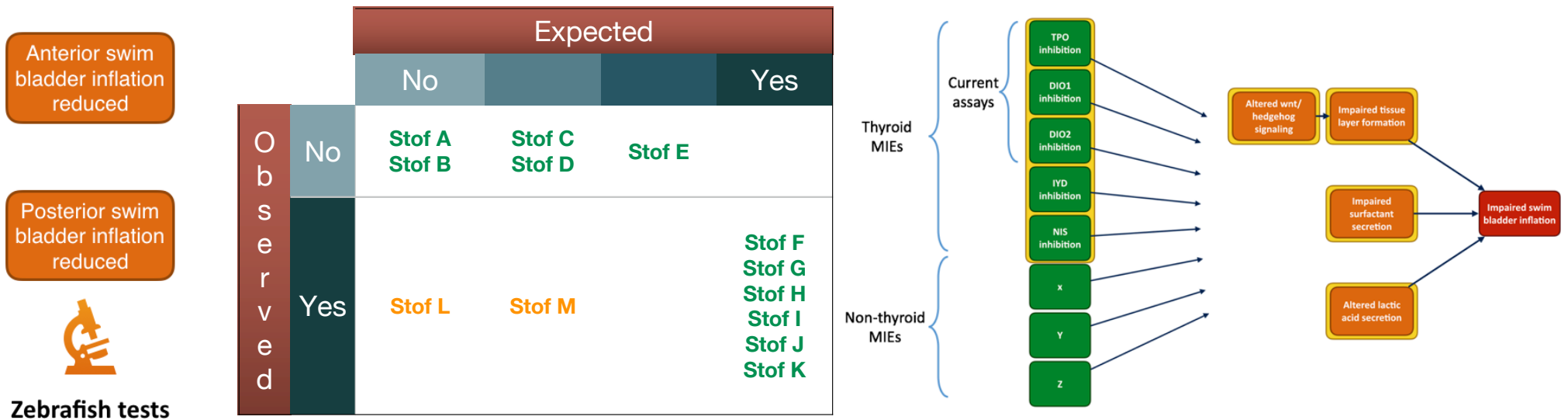
Zebrafish tests



dag 21

Strategie gebaseerd op Adverse Outcome Pathways

Stap 2: *in vivo*



Strategie gebaseerd op Adverse Outcome Pathways

- *In vivo*-effecten kunnen goed voorspeld worden
- Veelbelovende alternatieve test
- Enkel reëel gebruikt indien **regulatorisch aanvaard / vereist**
 - Geformaliseerde wetenschappelijke onderbouwing
 - Case-studies, screening
 - Breder toepasbaar



Regulatorische aanvaarding

Geformaliseerde wetenschappelijke onderbouwing: AOPs



OECD Series on Adverse Outcome Pathways No. 1

**Users' Handbook
supplement to the Guidance
Document for developing
and assessing Adverse
Outcome Pathways**

Project 1.35: The AOP on Thyroperoxidase and/or deiodinase inhibition leading to impaired swim bladder inflation in fish during early life stages

Lead:

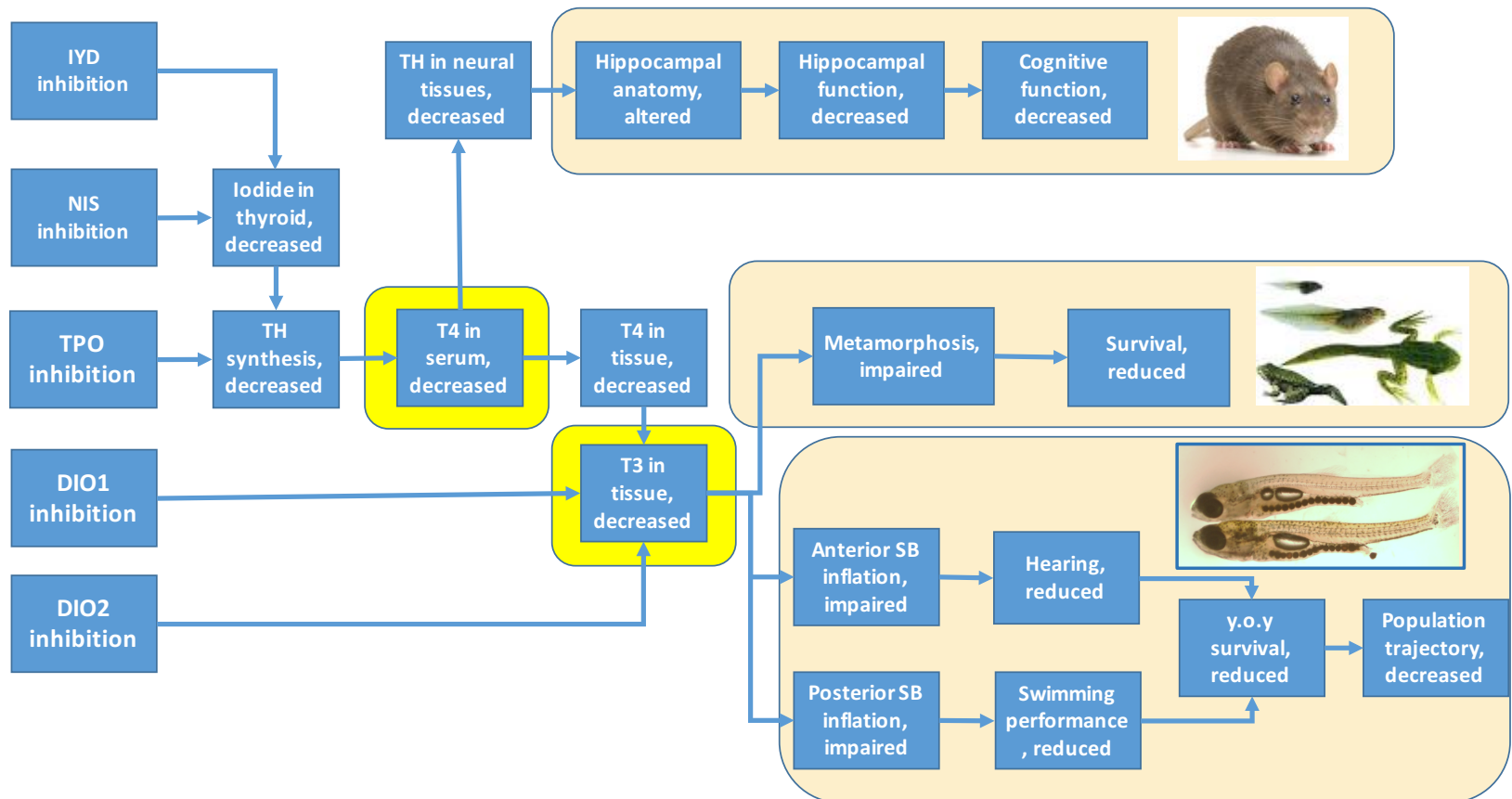
[Belgium](#)

Inclusion in work plan:

2015

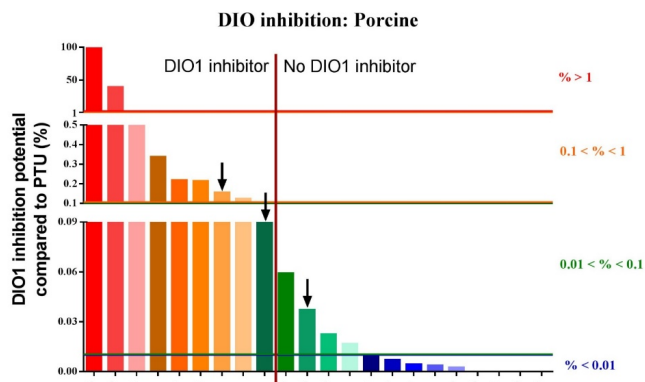
Regulatorische aanvaarding

Breder kader

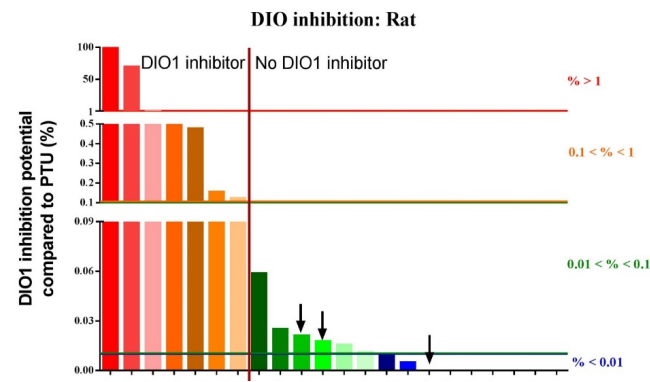


Regulatorische aanvaarding

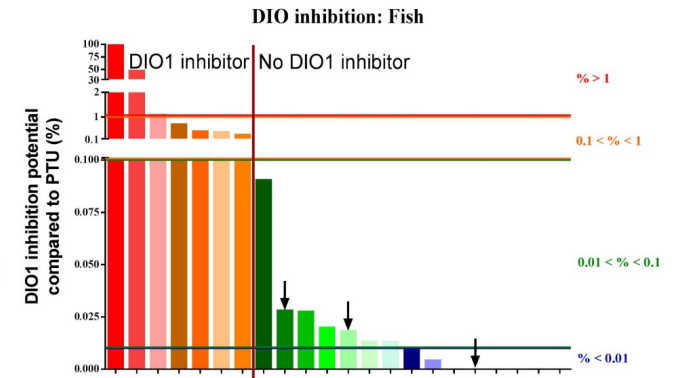
Toepasbaarheid tussen soorten



Varken



Rat



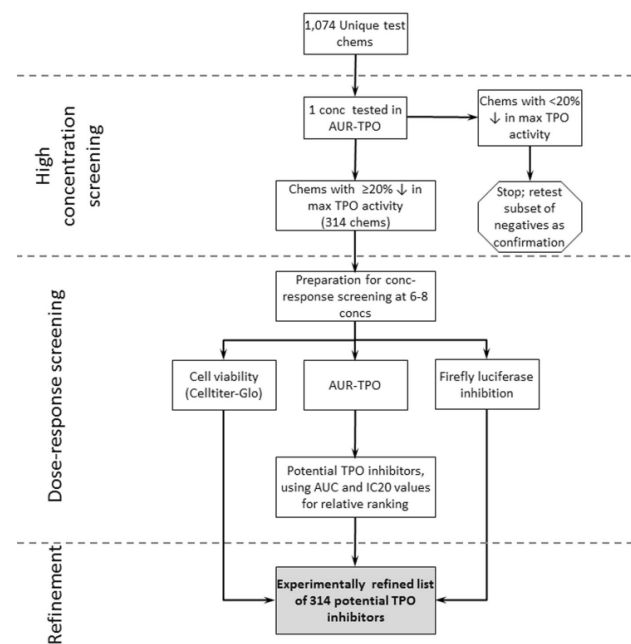
Zebravis

Regulatorische aanvaarding

Screening van grote aantallen stoffen



IYD inhibition	HT assay under development
NIS inhibition	HT assay under development
TPO inhibition	HT assay developed >1000 chemicals screened
DIO1 inhibition	HT assay developed >100 chemicals screened
DIO2 inhibition	HT assay developed >100 chemicals screened



Friedman et al., 2016. Tiered High-Throughput Screening Approach to Identify Thyroperoxidase Inhibitors Within the **ToxCast Phase I and II** Chemical Libraries. *Toxicol Sci* 151 (1): 160-180

Regulatorische aanvaarding OESO-testrichtlijn 236



Based on current knowledge, ECHA considers that OECD TG 236 might be used within a weight of evidence approach together with other independent, adequate, relevant and reliable sources of information leading to the conclusion that the substance has or does not have a particular dangerous property (for further information see Annex XI, 1.2 to the REACH Regulation and the considerations below).

Dankwoord



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