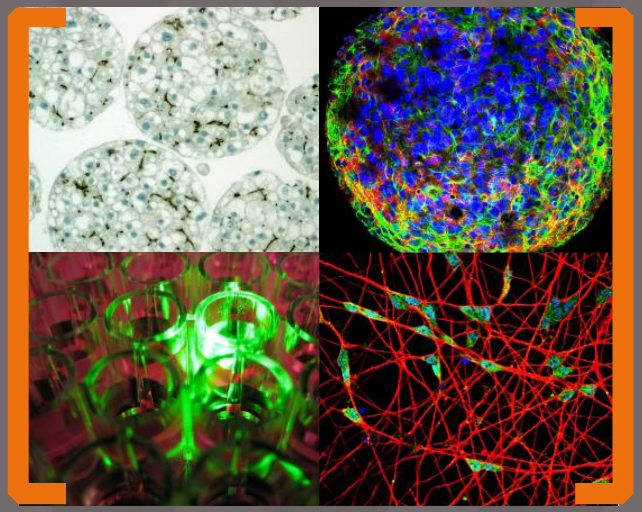
Technical University of Denmark

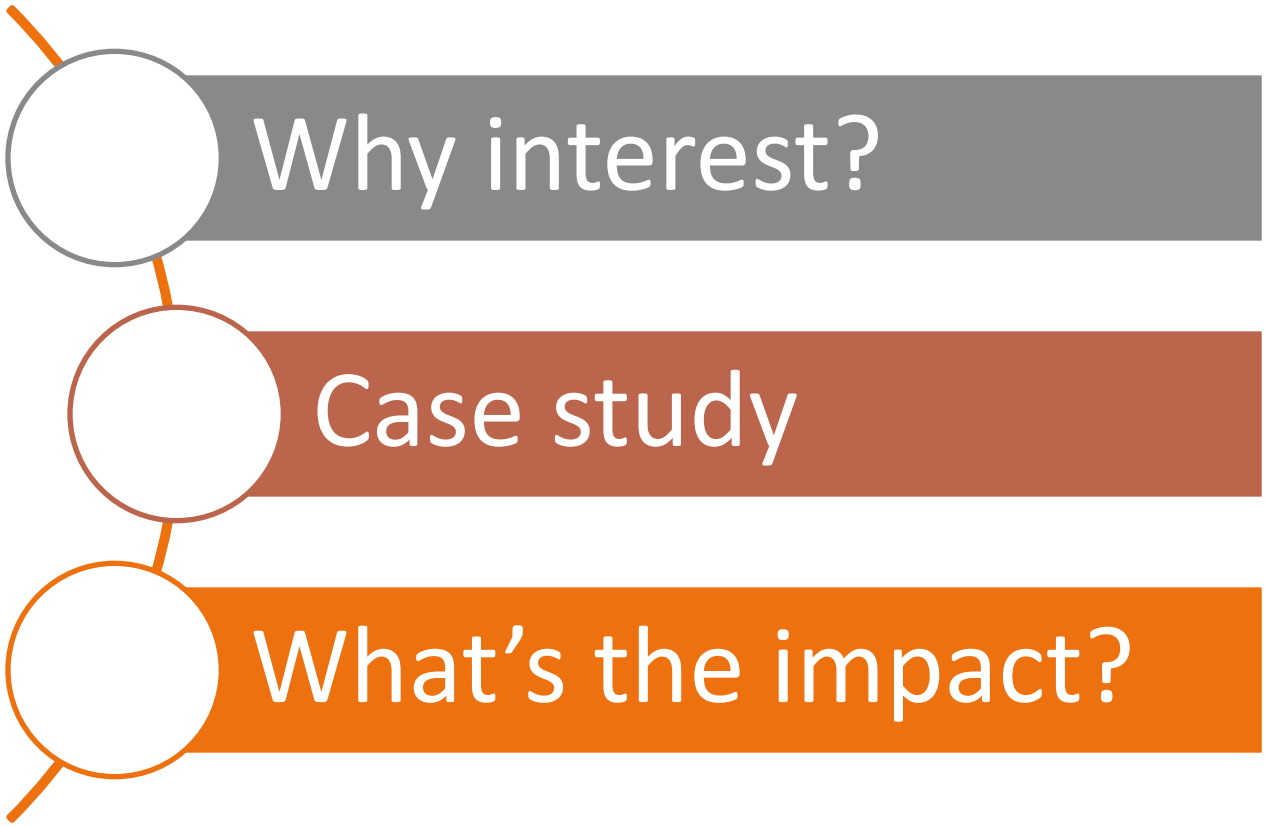
DTU

EUTOXRISK

NGRA of developmental neurotoxicity liabilities of neonicotinoids insecticides

Susanne Hougaard Bennekou
EU-ToxRisk Final symposium
4th. November 2021





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Neonicotinoid pesticides

Designed to target insect nicotine acethylcholine receptors (nAChR). Less affinity to mammalian nAChRs

Use in EU declining due to conecern for pollinators

Systemic uptake by plants – found as residue in food

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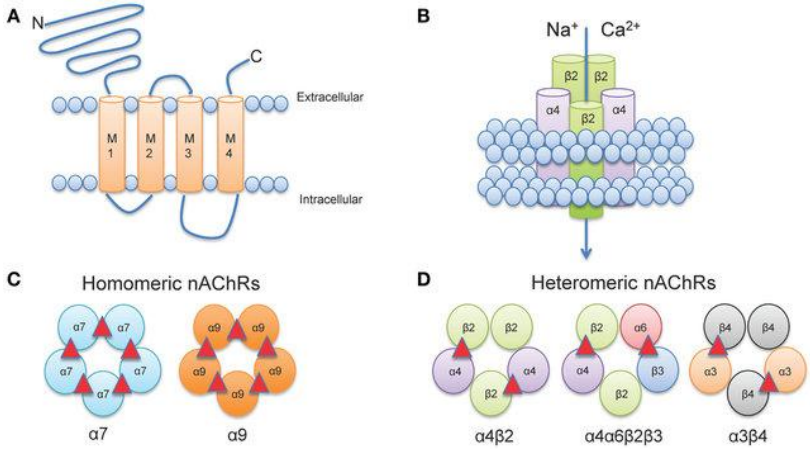
Neonicotinoids: risks to bees confirmed

Published: 28 February 2018

Most uses of neonicotinoid pesticides represent a risk to wild bees and honeybees, according to assessments published today by EFSA. The Authority has updated its risk assessments of three neonicotinoids – clothianidin, imidacloprid and thiamethoxam – that are currently subject to restrictions in the EU because of the threat the pose to bees.



Hendrikson et al 2013

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Regulatory concern?

Nicotine-Like Effects of the Neonicotinoid Insecticides Acetamiprid and Imidacloprid on Cerebellar Neurons from Neonatal Rats

Junko Kimura-Kuroda*, Yukari Komuta, Yoichiro Kuroda, Masaharu Hayashi, Hitoshi Kawano

Department of Brain Development and Neural Regeneration, Tokyo Metropolitan Institute of Medical Science, Setagaya-city, Tokyo, Japan

Acetamiprid & imidaclorprid similar to nicotine - exert excitatory effects on nAChRs of rat neo-natal cerebellar granular cells in culture at low concentrations (from 1µM). ->May adversely affect the developing human brain

efsa
European Food Safety Authority

EFSA Journal 2013;11(12):3471

SCIENTIFIC OPINION

Scientific Opinion on the developmental neurotoxicity potential of acetamiprid and imidacloprid[1]

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EFSA 2013

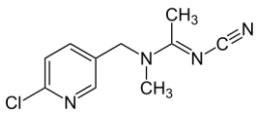
Regulatory developmental neurotoxicity (DNT)studies (TG426):

Imidacloprid: Effectson offspring, however the data was not be sufficient for a robust characterisation of dose-response. There were neuropathological finding at the top-dose.

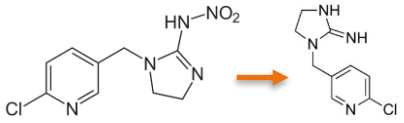
Acetamiprid: Motor activity and learning & memory could not be adequately assessed. The study can only provide supportive evidence, but is inadequate for a robust characterisation of effects and dose-response.

Consequence: Both studies had limitations -> Reference values were revised

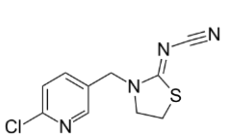
Case study: Neonicotinoid pesticides



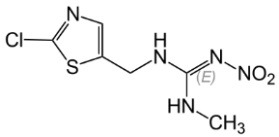
Acetamiprid



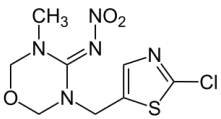
Imidacloprid -> desnitro-IMI



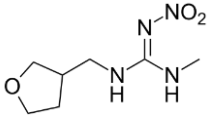
Thiacloprid



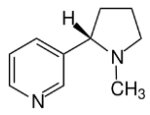
Clothianidin



Thiamethoxam



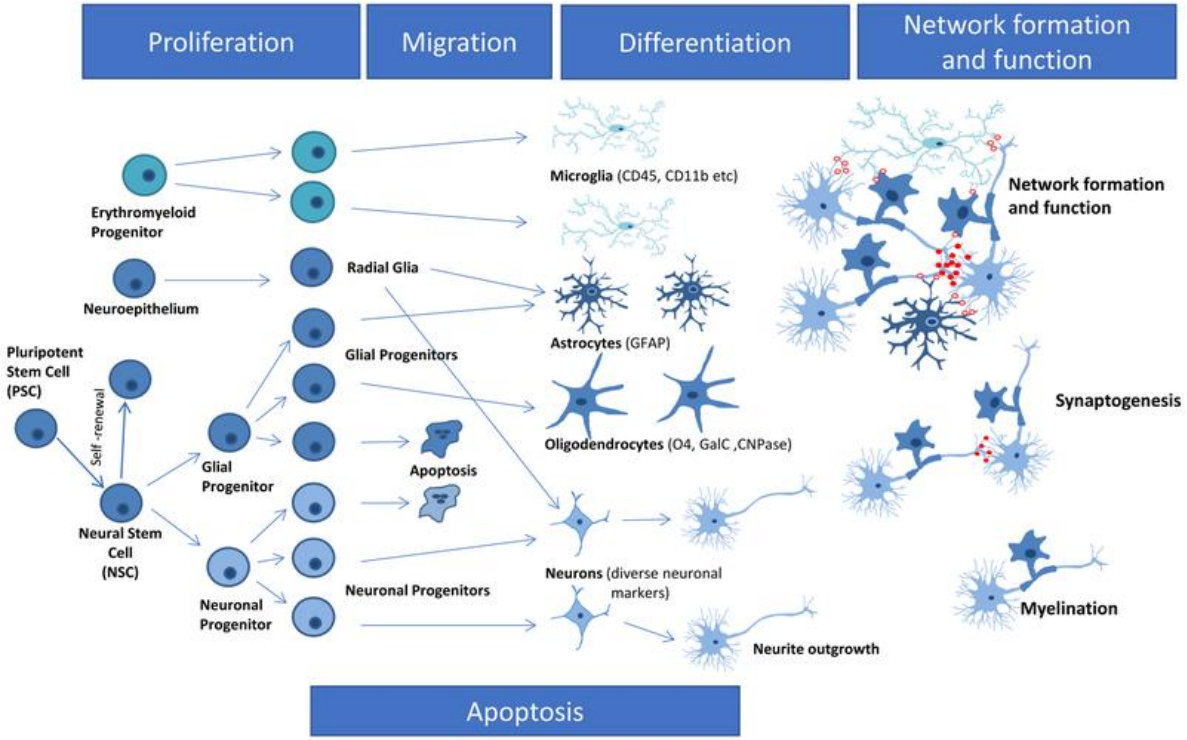
Dinotefuran



Nicotine

Fundamental neurodevelopmental processes relevant for DNT

It is assumed that DNT toxicants exert their toxicity by disturbing at least one of these processes



Bal-Price et al. ALTEX 2018

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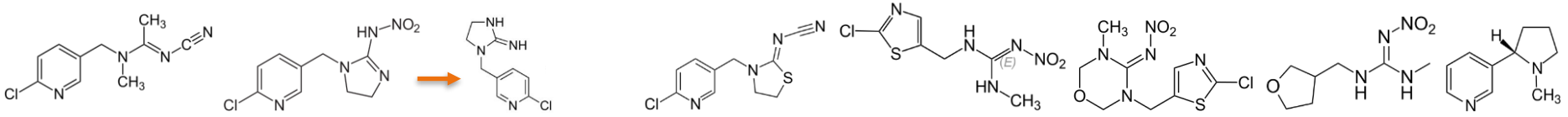
Case study: Neonicotinoid pesticides



Acetamiprid | Imidacloprid -> desnitro-IMI | Thiacloprid | Clothianidin | Thiamethoxam | Dinotefuran | Nicotine

	Key neurodevelopmental processes and cell survival					
Test Method	**UKN2**	**UKN4**	**UKN5**	**RoFA**	**TD42 iPSCs**	**SHSY5Y cells**
Test System	neural crest cells	LUHMES (CNS neurons)	hiPSC neurons (PNS neurons)	hiPSC differentiation into neuronal		
Endpoint 1	cytotoxicity	cytotoxicity	cytotoxicity	cytotoxicity	cytotoxicity	cytotoxicity
Endpoint 2	migration	neurite outgrowth	neurite outgrowth	rosette formation	-	-

	Biochemical/Signalling			Zebrafish	In silico	
Test Method	**CALUX assays**	**Calcium measurements**		**FET (OECD 236)**	**Docking**	**PBTK/QIVIVE**
Test System	reporter gene assays in U2OS	LUHMES	SHSY5Y	Fish embryos	IFD; Schrödinger Release 2020-2	in silico
Endpoint 1	cytotoxicity	Ca^{2+} whole well and single cell	Ca^{2+} whole well	Lethality	representative docking poses	Internal exposure
Endpoint 2	receptor- or stress pathway	patch clamp	-	developmental alterations	-	-

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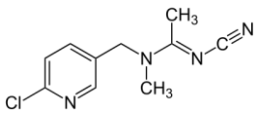
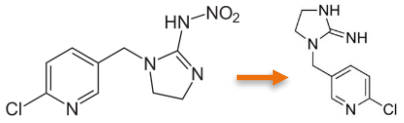
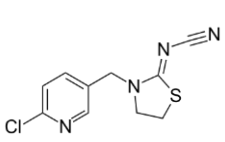
Case study: Neonicotinoid pesticides



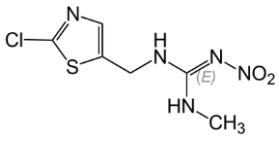
Acetamiprid



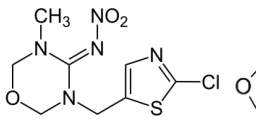
Imidacloprid -> desnitro-IMI



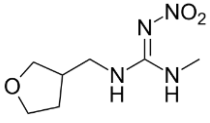
Thiacloprid



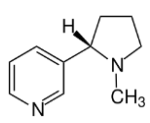
Clothianidin



Thiamethoxam



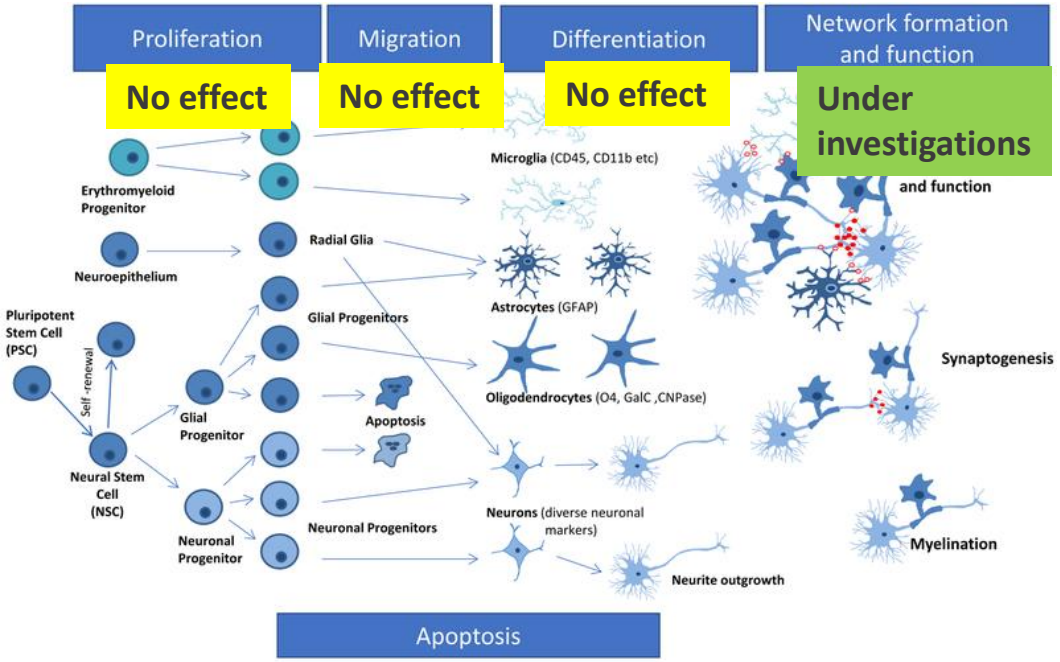
Dinotefuran



Nicotine

- **Neuronal signaling is altered by the neonicotinoids in a similar manner to nicotine**
- **Interactions with human receptors**

Nicotine	Active
Desnitro- Imidacloprid	Active
Imidacloprid	**Active**
Acetamiprid	**Active**
Thiacloprid	**Active**
Clothianidin	**Active**
Thiamethoxam	Inactive
Dinetefuran	Inactive



Loser et al. 2021a. Arch. Tox. doi.org/10.1007/s00204-021-03031-1
Loser et al. 2021b. Arch. Tox. doi.org/10.1007/s00204-021-03168-z

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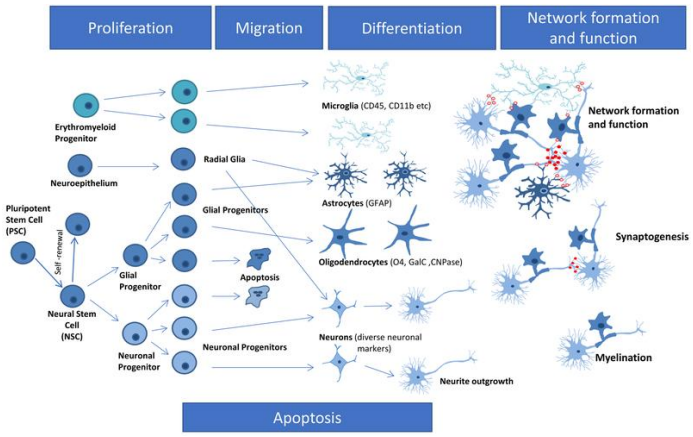
Regulatory impact?

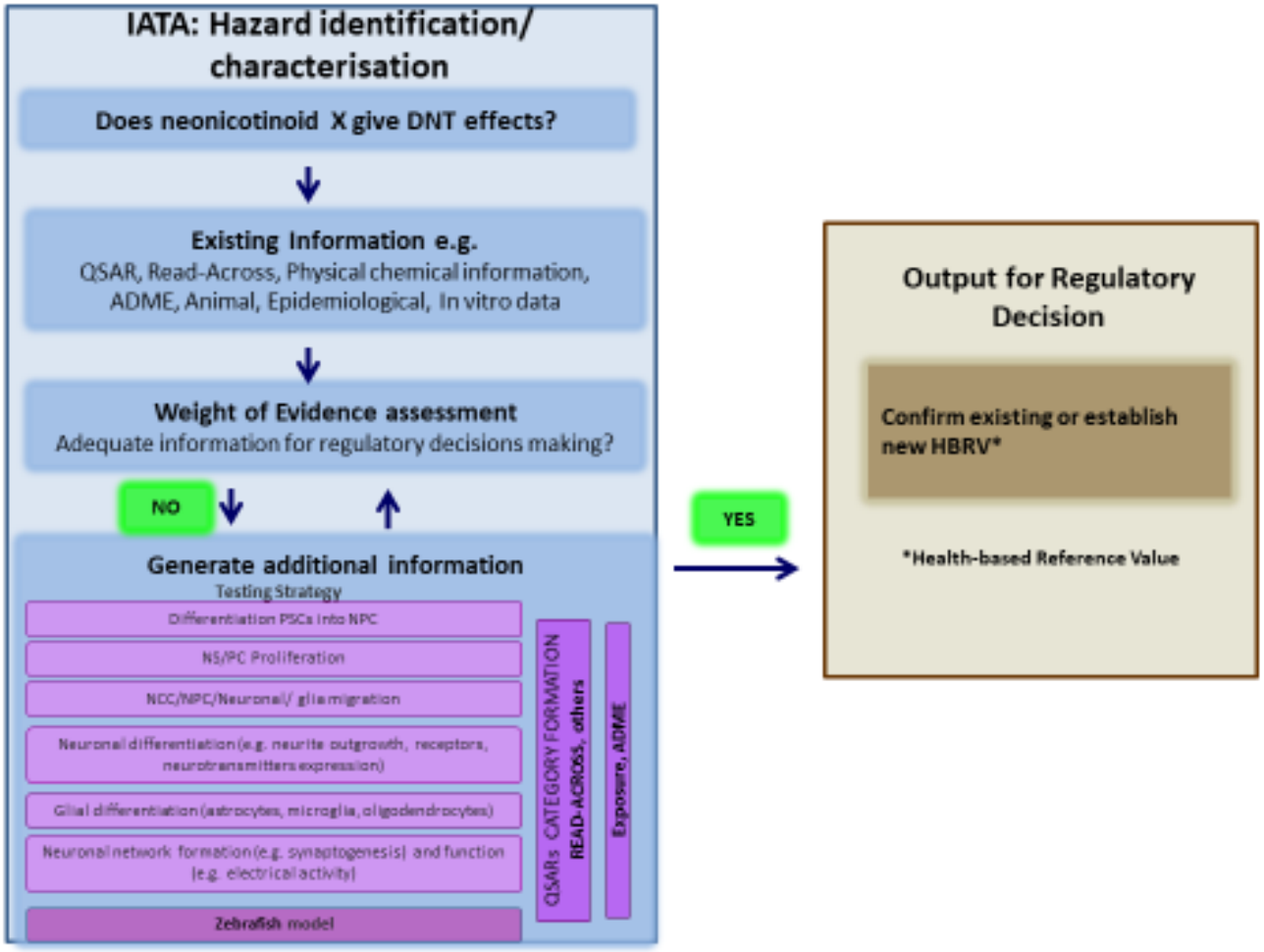
OECD Test guideline program: The DNT project

- Develop a **guidance** on application and interpretation of in vitro DNT assays
- Provide a flexible and tailored DNT **testing battery** to address different regulatory needs, identify the current suitability of different assays and provide elements for an Integrated approach to testing and assessment (IATA) of DNT modalities not related to the endocrine system
- Applicable to **all chemicals**



Regulatory Impact: Case Studies for OECD IATA project

Problem formulation: Can new approach methods data in an IATA context (integrating existing information) on a neonicotinoid, sufficiently characterize DNT hazard?



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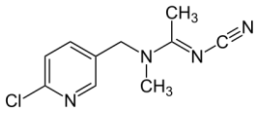
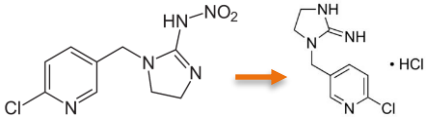
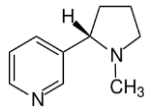
IATA case studies



Acetamiprid

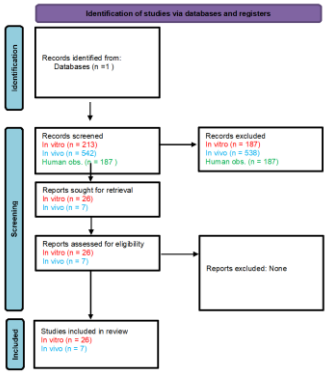


Imidacloprid -> desnitro-IMI

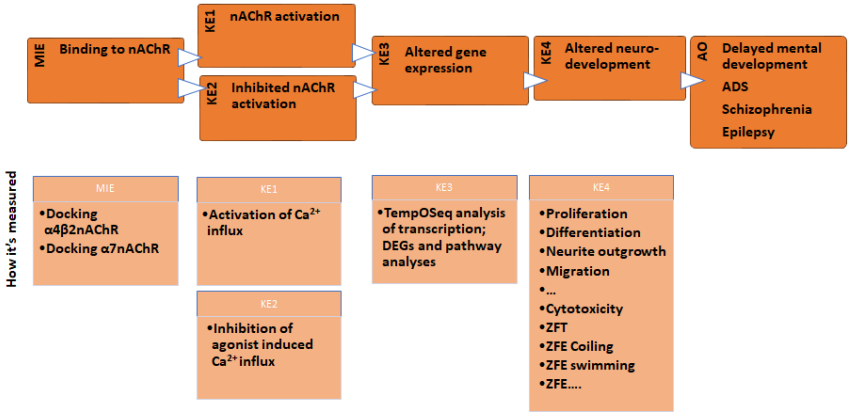


Nicotine

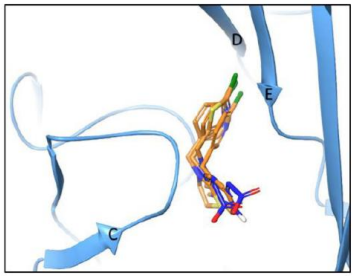
Literature review



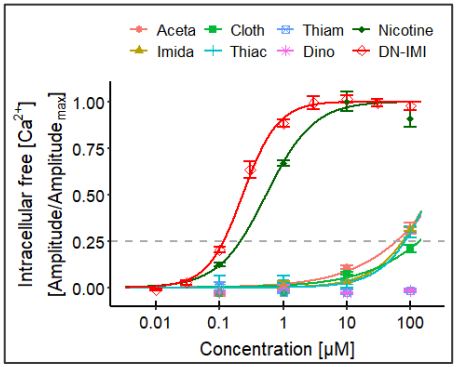
AOP



In silico – receptor docking

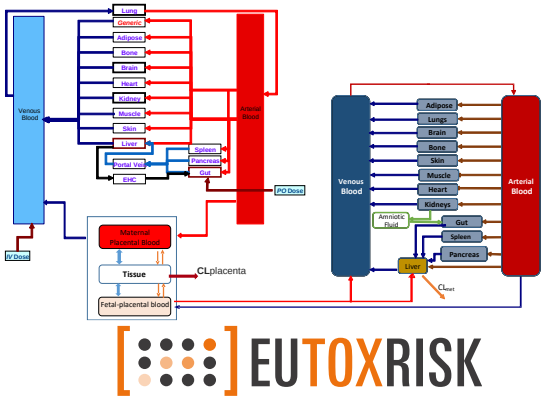


In vitro testing - battery



Human exposure

IVIVE-PBK



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Case study

IATA Case Study on the use of Integrated Approaches for Testing and Assessment for developmental neurotoxicity hazard characterisation of imidacloprid and the metabolite desnitro-imidacloprid

Jonathan Blum, Ylva Johansson, Rebecca von Hellfeld, Thomas Braunbeck, María Hinojosa, Melinda Zana, Andras Dinnyes, Dominik Loser, Marcel Leist, Karin Grillberger, Gerhard Ecker, Barbara M.A. van Vugt-Lussenburg, Bart van der Burg, Iain Gardner, Anna Forsby, Susanne Hougaard Bennekou

IATA Case Study on the use of Integrated Approaches for Testing and Assessment for developmental neurotoxicity hazard characterisation of acetamiprid

Ylva Johansson, Jonathan Blum, Rebecca von Hellfeld, Thomas Braunbeck, María Hinojosa, Melinda Zana, Andras Dinnyes, Dominik Loser, Marcel Leist, Karin Grillberger, Gerhard Ecker, Barbara M.A. van Vugt-Lussenburg, Bart van der Burg, Iain Gardner, Anna Forsby, Susanne Hougaard Bennekou

Coming soon

Universität Konstanz

Stockholms universitet

BDS BioDetection Systems

CERTARA Implementing Translational Science

Technical University of Denmark DTU

BioTalentum

universität wien

cyprotex

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Thank you