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FÜR UMWELT-
MEDIZINISCHE
FORSCHUNG

ENTWICKLUNGSNEUROTOXIZITÄT (DNT)

Ellen Fritsche

Ulm, GPTS, Advanced Course in Toxicology ‚Moderne Ansätze in der Risikoabschätzung: Weight of Evidence und Unsicherheitsanalyse und -quantifizierung‘

6. März 2023

Mitglied der Leibniz-Gemeinschaft

Tests auf DNT sind derzeit in der EU oder den USA nicht vorgeschrieben, es sei denn, sie werden durch adulte Neuro-toxizität oder eine endokrine Aktivität von Chemikalien ausgelöst.

DNT in vivo Studien:

- **OECD TG426**
- **OECD TG443 mit**

Daten-lücke

110-140 Substanzen wurden durch Guideline Studien auf ihr DNT Potential getestet

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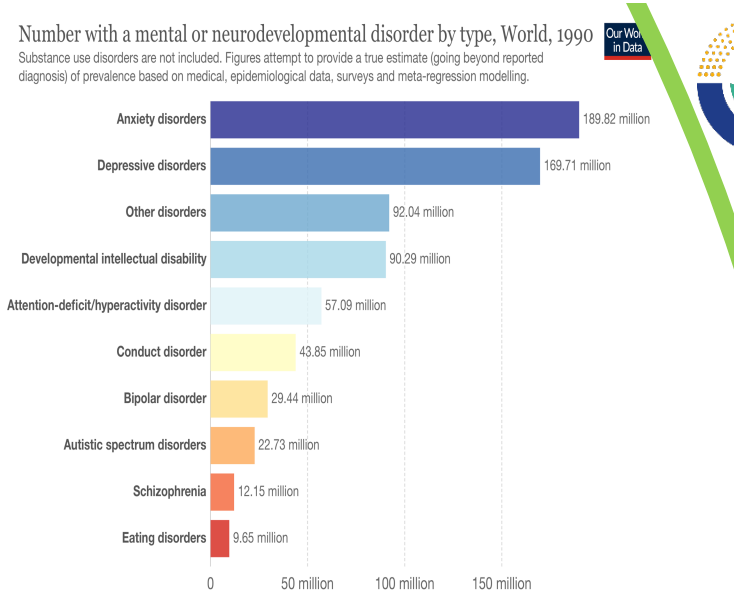
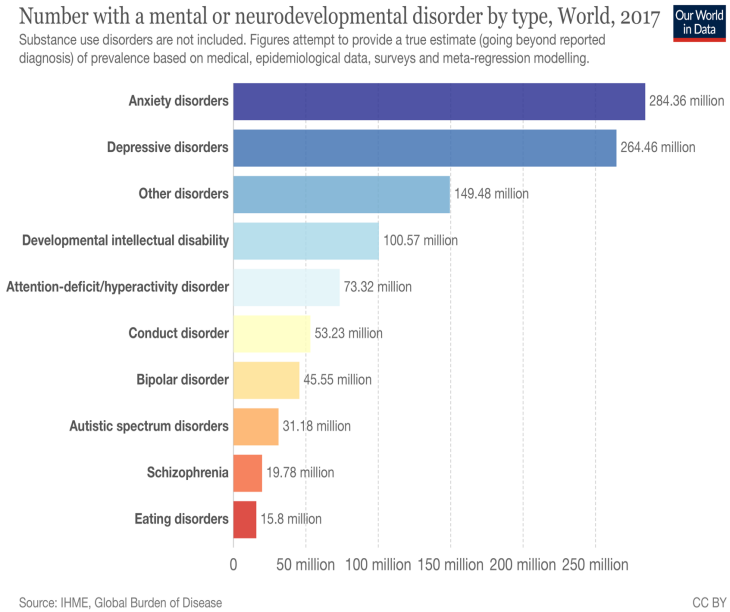


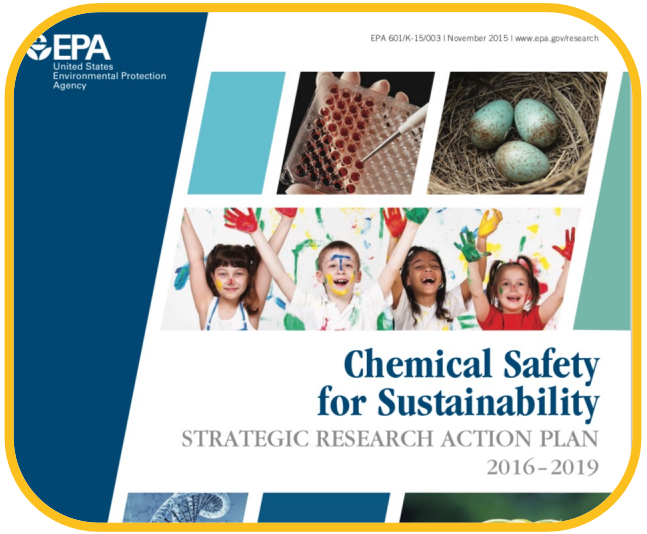


efsa

Annex II of the Regulation No 1107/2009 (concerning the placing of plant protection products on the market): **DNT** is considered **“a critical effect of particular significance”.**

http://www.efsa.europa.eu/de/efsajournal/pub/3471.htm

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



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Bridging the Gap

Category	Size of Category	Estimate Mean Percent In the Select Universe
Pesticides and Inert Ingredients of Pesticides Formulations	3,350	10 24 2 26 38
Cosmetic Ingredients	3,410	2 14 10 18 56
Drugs and Excipients Used in Drug Formulations	1,815	18 18 3 36 25
Food Additives	8,627	5 14 1 34 46
Chemicals in Commerce: At Least 1 Million Pounds/Year	12,860	11 11 78
Chemicals in Commerce: Less than 1 Million Pounds/Year	13,911	12 12 76
Chemicals in Commerce: Production Unknown or Inaccessible	21,752	10 8 82

Complete Health Hazard Assessment Possible | Partial Health Hazard Assessment Possible | Minimal Toxicity Information Available | Some Toxicity Information Available (But Below Minimal) | No Toxicity Information Available

Crofton et al. Congenit Anom 2012

Roadmap für DNT Daten Lückenschluss

ch Toxicol (2015) 89:269–287
DOI 10.1007/s00204-015-1464-2

MEETING REPORT

International STakeholder NETwork (ISTNET): creating a developmental neurotoxicity (DNT) testing road map for regulatory purposes

Anna Bal-Price · Kevin M. Crofton · Marcel Leist · Sandra Allen · Michael Arand · Timo Buetler · Nathalie Delrue · Rex E. FitzGerald · Thomas Hartung · Tuula Heinonen · Helena Hogberg · Susanne Hougaard Bennekou · Walter Lichtensteiger · Daniela Oggier · Martin Paparella · Marta Axelstad · Aldert Piersma · Eva Rached · Benoît Schilter · Gabriele Schmuck · Luc Stoppini · Enrico Tongiorgi · Manuela Tiramani · Florianne Monnet-Tschudi · Martin F. Wilks · Timo Ylikomi · Ellen Fritsche

Received: 6 November 2014 / Accepted: 4 December 2014 / Published online: 25 January 2015
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Meeting report

OECD/EFSA Workshop on Developmental Neurotoxicity (DNT): The Use of Non-Animal Test Methods for Regulatory Purposes

https://doi.org/10.14573/altex.1701171

Fritsche et al. ALTEX 2017

Resultate des OECD/EFSA DNT Workshops

Wissenschaftler aus 15 Ländern, Interessenvertreter von Regulierungsbehörden, Nichtregierungsorganisationen (NGOs), Hochschulen und der Industrie, erzielten folgenden Konsens:

- Die derzeitigen Datenanforderungen für in vivo Tests zur Entwicklungsneurotoxizität (DNT) reichen nicht aus, um potenziell gefährliche Substanzen zu prüfen und zu charakterisieren.
- Es besteht die Notwendigkeit, eine standardisierte in vitro Testbatterie zu entwickeln, um zusätzliche Daten über die Auswirkungen von Chemikalien auf das sich entwickelnde Nervensystem zu gewinnen.

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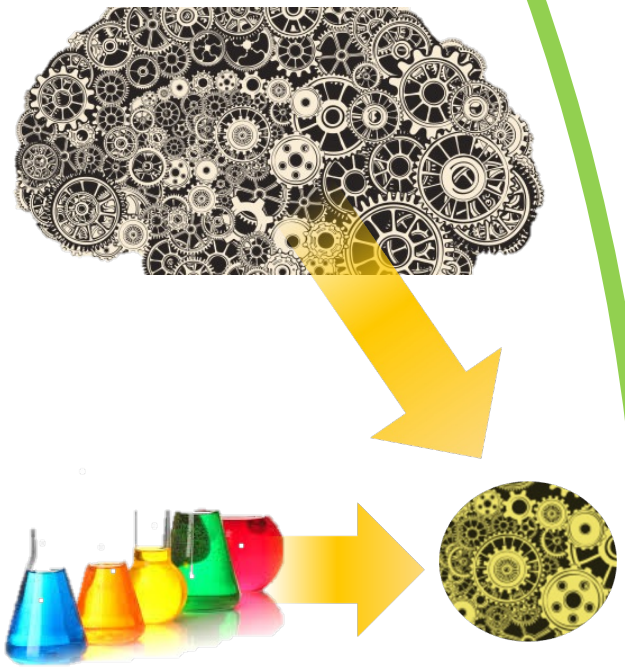
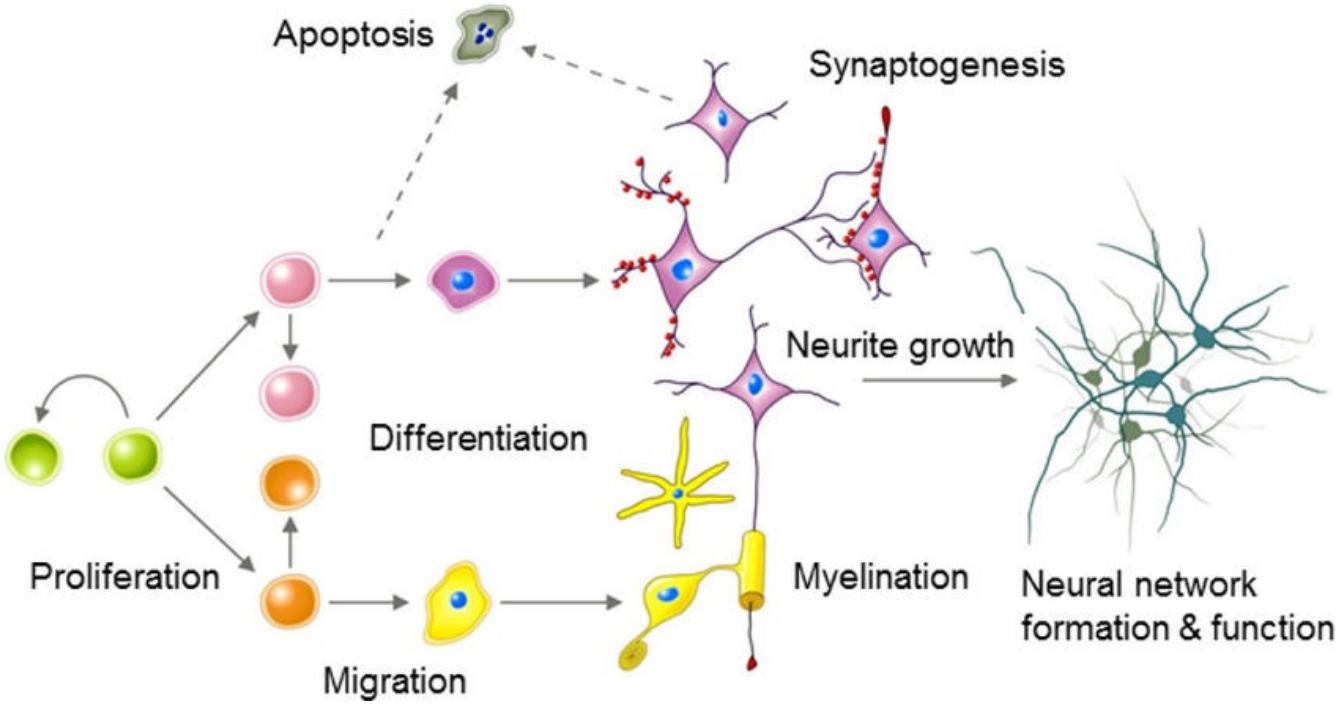
Das Prinzip der DNT in vitro Batterie (IVB)





Kindly provided by **William Mundy, U.S. Environmental Protection Agency** and **John Havel, SRA International, Inc.**

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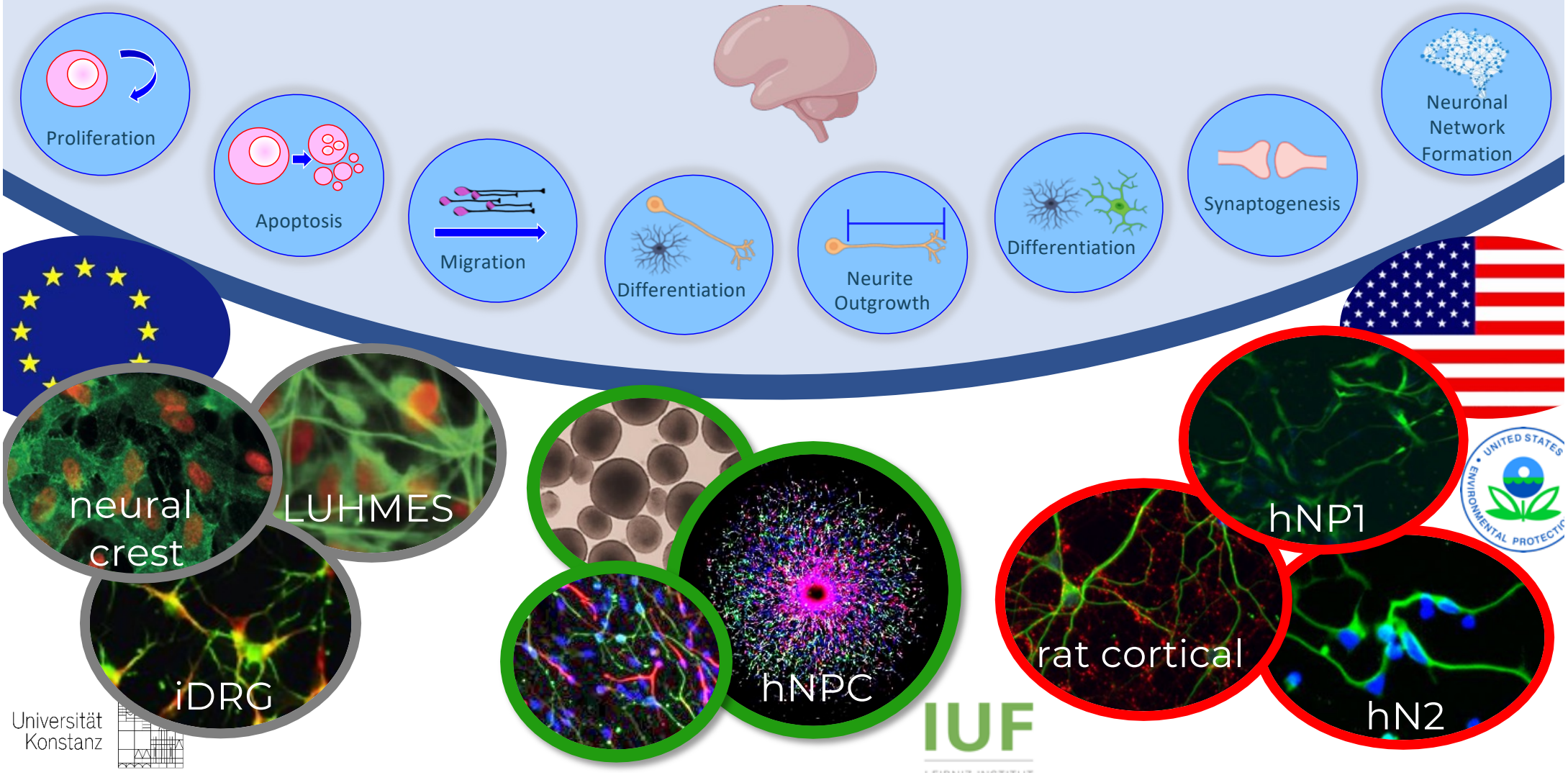
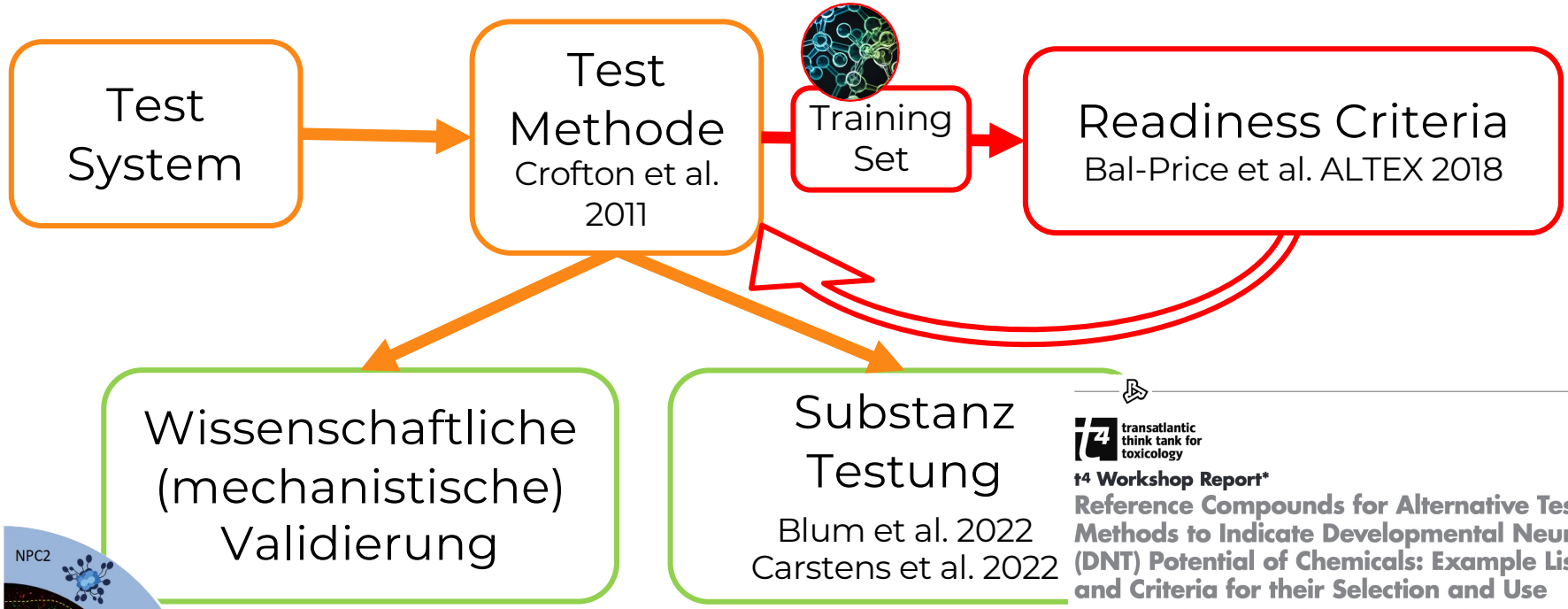
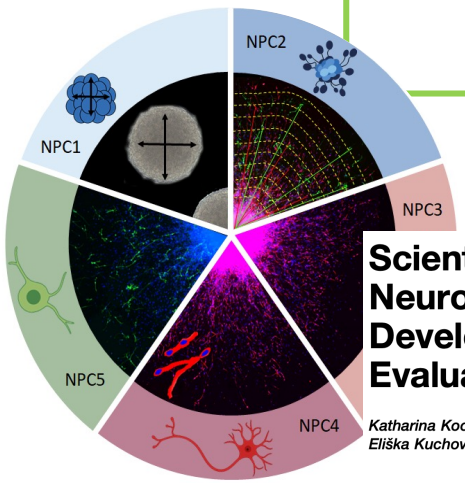
Test Systeme der DNT in vitro Batterie



Vom akademischen Zellmodell zur regulatorischen Anwendung





Scientific Validation of Human Neurosphere Assays for Developmental Neurotoxicity Evaluation

*Katharina Koch[1], Kristina Bartmann[1], Julia Hartmann[1], Julia Kapr[1], Jördis Klose[1], Eliška Kuchovská[1], Melanie Pahl[1], Kevin Schlüppmann[1], Etta Zühr[1] and Ellen Fritsche[1,2]**

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European Food Safety Authority

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

transatlantic think tank for toxicology

t4 Workshop Report*

Reference Compounds for Alternative Test Methods to Indicate Developmental Neurotoxicity (DNT) Potential of Chemicals: Example Lists and Criteria for their Selection and Use

Michael Aschner[1], Sandra Casati[2], Magdalini Daneshian[3], Ellen Fritsche[4]

Neurotoxicology and Teratology 52 (2015) 25–35

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

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

Review article

Expanding the test set: Chemicals with potential to disrupt mammalian brain development

William R. Mundy [a,*], Stephanie Padilla [a], Joseph M. Breier [a,1], Kevin M. Crofton [b], Mary E. Gilbe
David W. Herr [a], Karl F. Jensen [a], Nicholas M. Radio [a,2], Kathleen C. Raffaele [c], Kelly Schumacher
Timothy J. Shafer [a], John Cowden [b]

Vom akademischen Zellmodell zur regulatorischen Anwendung

The 15 Principles of DNT Test Method Development

P1 “Key Event of Neurodevelopment”

P2 “Endpoint Measurement”

P3 “Dynamic Range”

P4 “Parametric Controls”

P5 “Response Characterization”

P6 “Concentration range/concentration-response“

P7 “Endpoint Selectivity”

P8 “Endpoint-specific controls”

P9 “Training Set Chemicals”

P10 “Testing Set Chemicals”

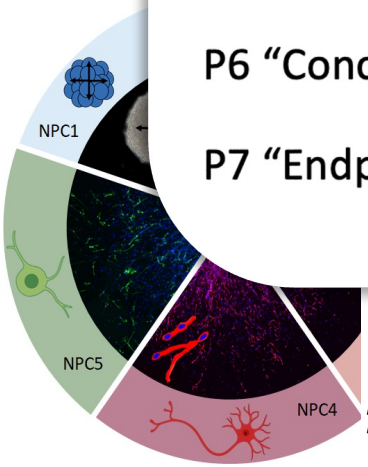
P11 “Specificity and Sensitivity”

P12 “HighThroughput”

P13 “Documentation”

P14 “Transferability”

P15 “Data Sharing”



Developmental Neurotoxicity Evaluation

*Katharina Koch[1], Kristina Bartmann[1], Julia Hartmann[1], Julia Kapr[1], Jördis Klose[1], Eliška Kuchovská[1], Melanie Pahl[1], Kevin Schlüppmann[1], Etta Zühr[1] and Ellen Fritsche[1,2]**

Review article

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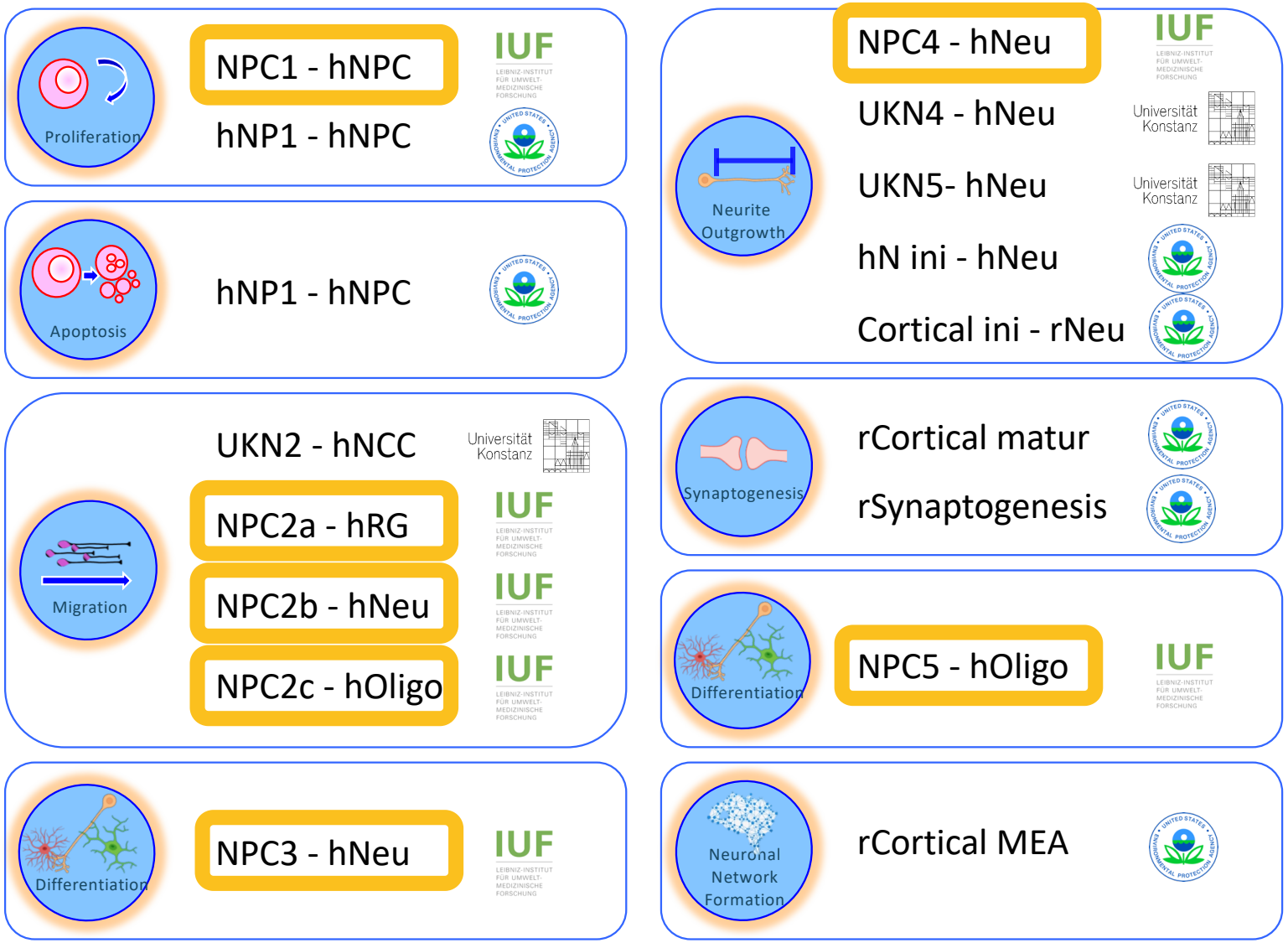
Timothy J. Shafer [a], John Cowden [b]

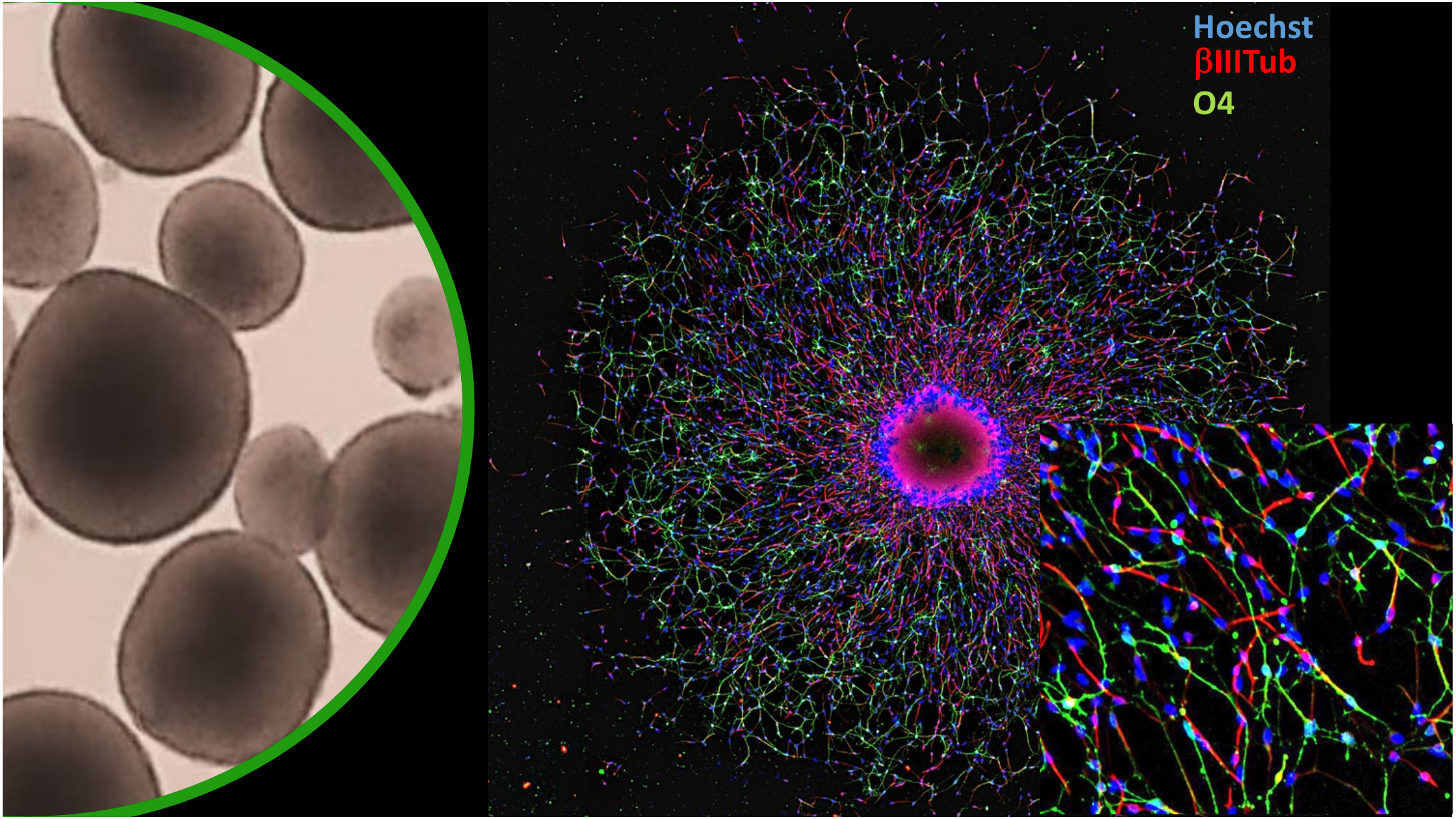
Test Methoden der **DNT IVB** basierend auf **‚Readiness Kriterien' in 2018**

Bal-Price et al. ALTEX 2018



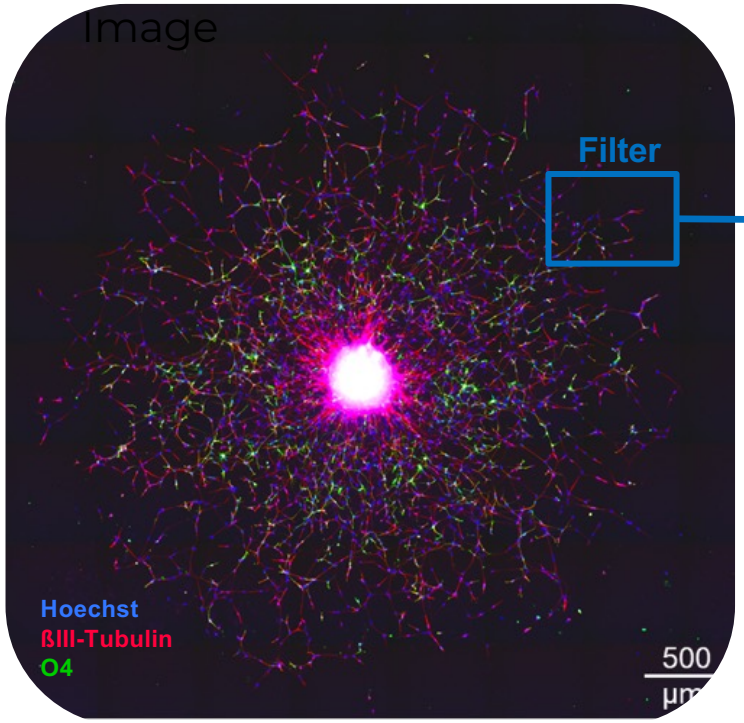
h-human; r-rat; NPC-neural progenitor cell; NCC-neural crest cell; RG-radial glia; Neu-neuron; Oligo-oligodendrocyte; ini-initiation; matur-maturation; MEA-microelectrode array

Crofton & Mundy 2021, Table 2.3

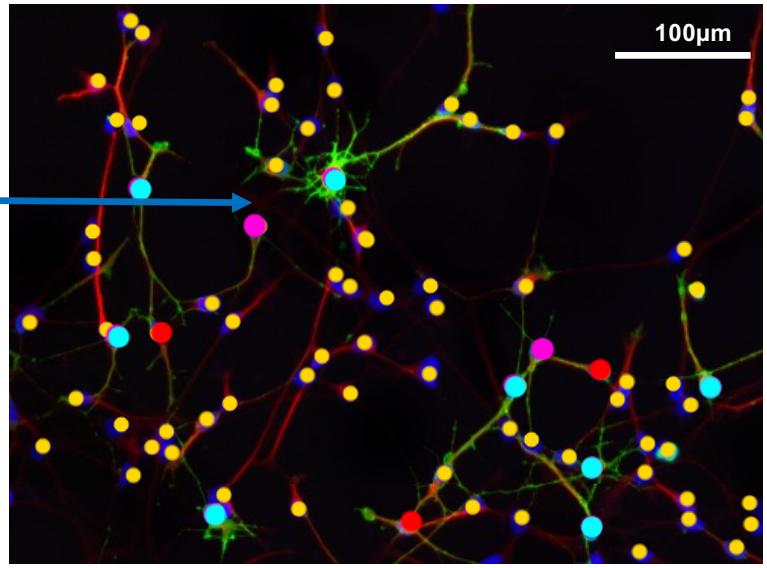

Hoechst
βIIITub
O4

Artificial Intelligence-based Cell Identification

Multichannel Neurosphere Image



AI learns from human ground truth



- Cellomics Nuclei
- Human annotations = Ground Truth

New run with different parameters

Comparing Results

- True Positives (noted by human + AI)
- False Positives (only noted by AI)
- False Negatives (only by human)
- True Negatives (not noted by either)

Förster et al. 2022

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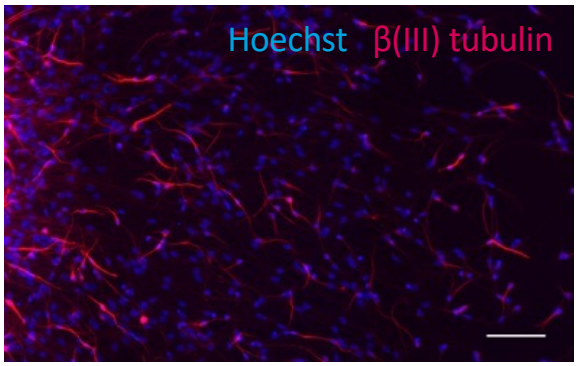
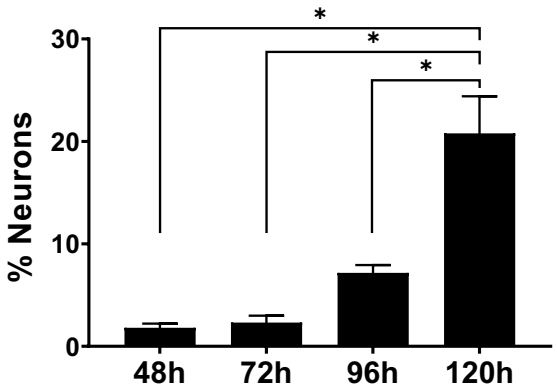
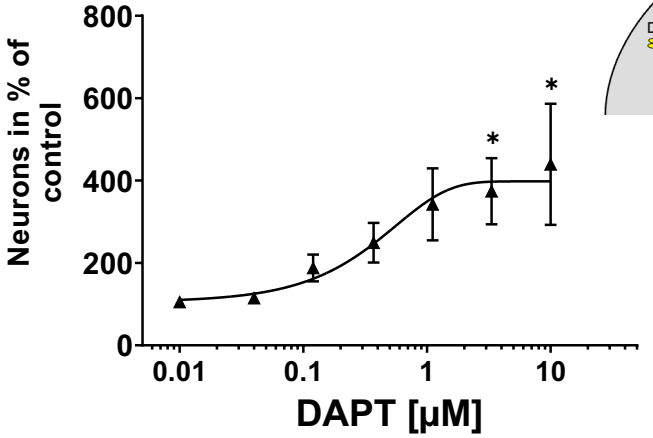
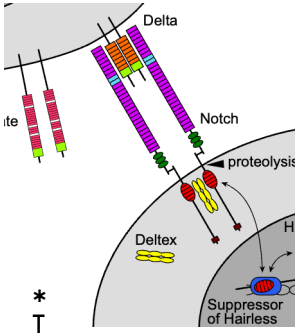
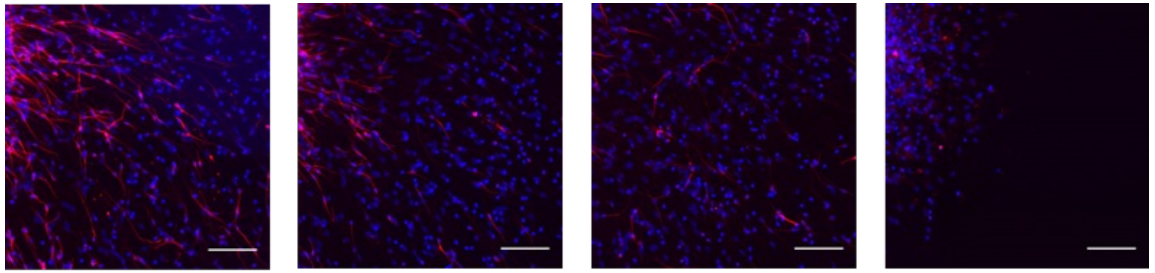
Wissenschaftliche Validierung – Neuronale Differenzierung

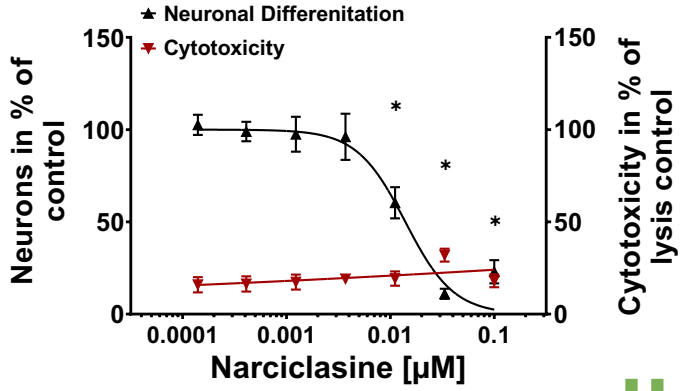






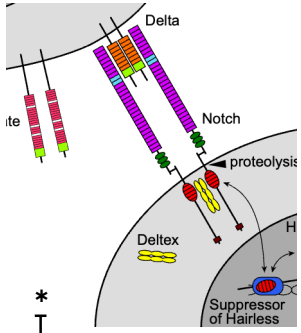






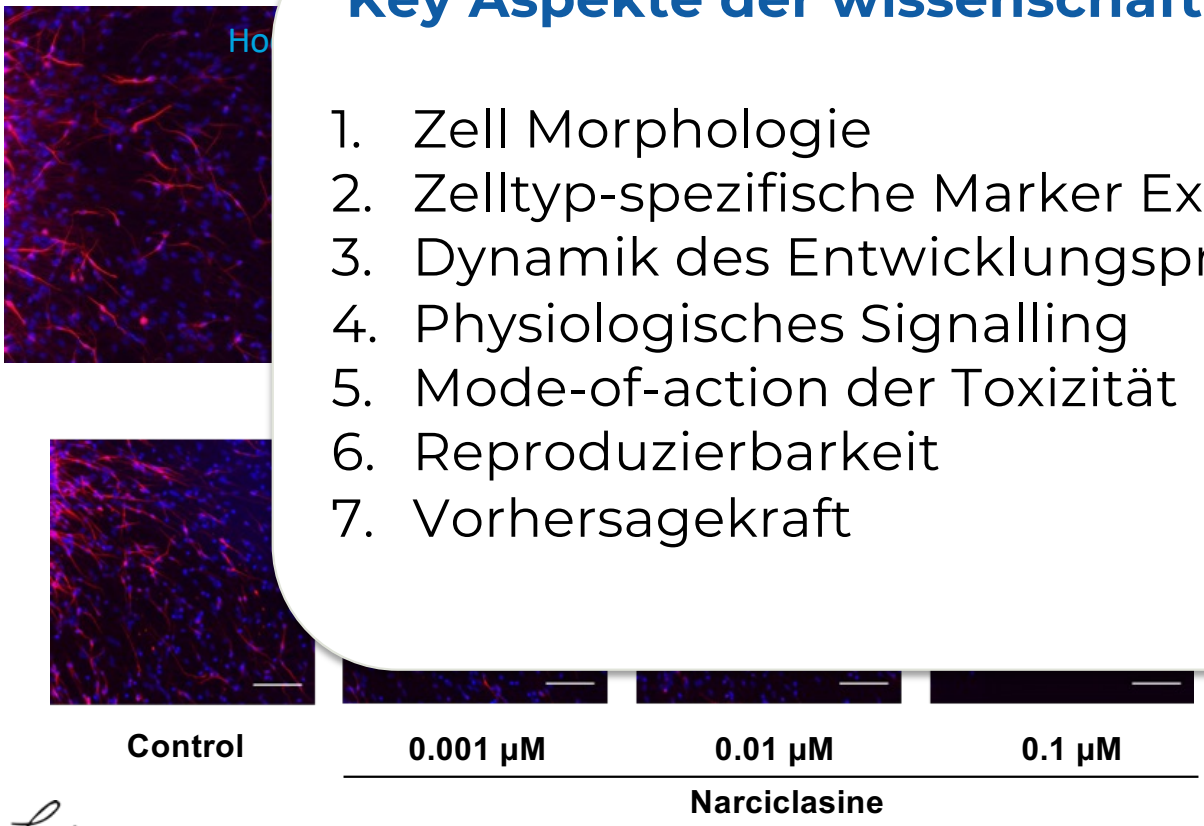
Koch et al. 2022

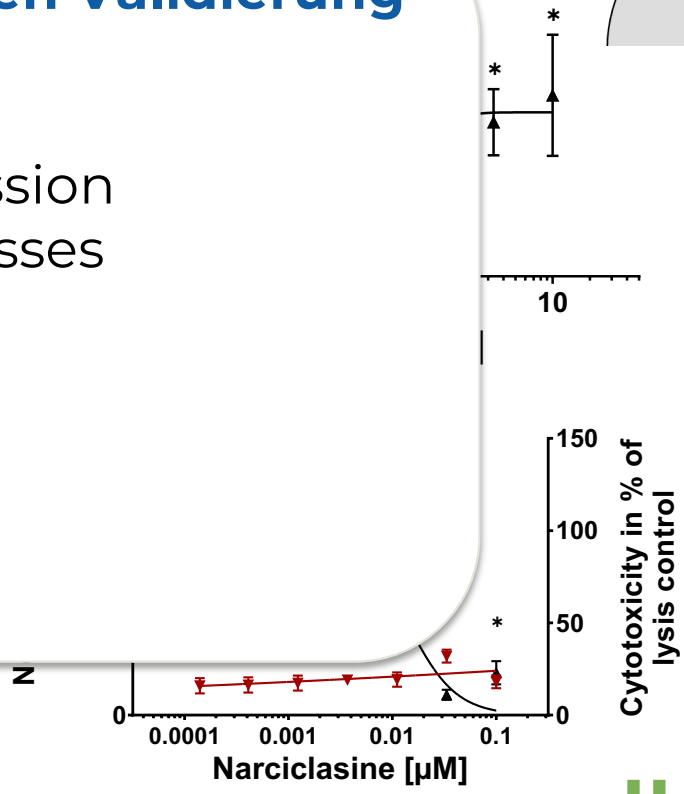
Wissenschaftliche Validierung – Neuronale Differenzierung



Key Aspekte der wissenschaftlichen Validierung

1. Zell Morphologie
2. Zelltyp-spezifische Marker Expression
3. Dynamik des Entwicklungsprozesses
4. Physiologisches Signalling
5. Mode-of-action der Toxizität
6. Reproduzierbarkeit
7. Vorhersagekraft





Koch et al. 2022

Datenevaluierung DNT EU-IVB & Klassifizierungs Modelle

Experimenteller Hintergrund

Vor-Prozessierung

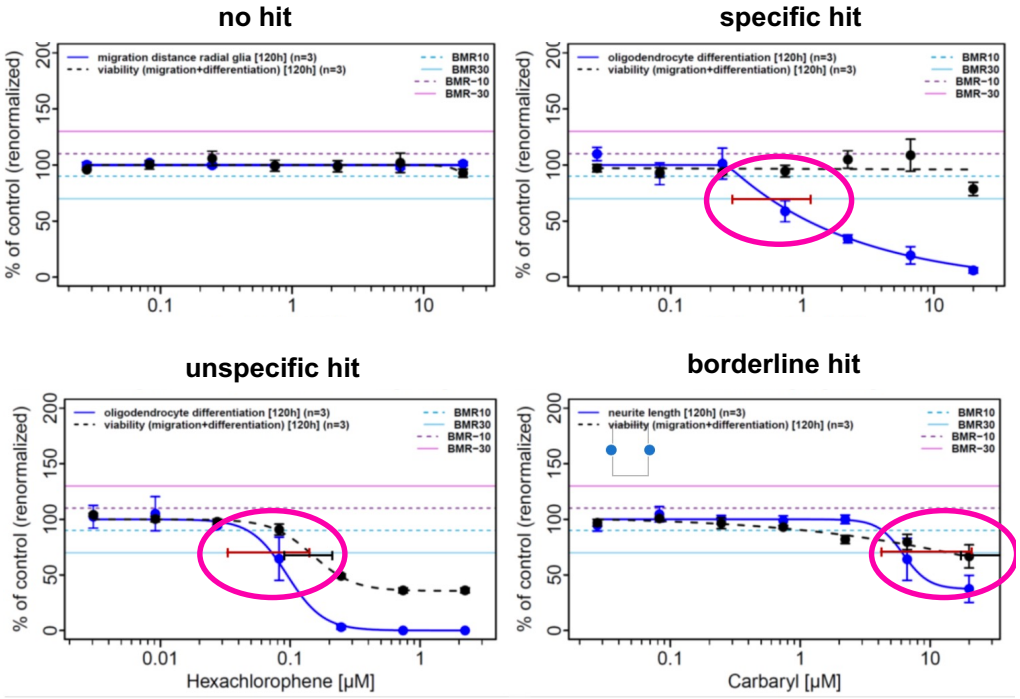
Re-Normalisierung

‘Best Fit’ Kurven Fitting

Daten Zusammenfassung - Median

BMC und CI Abschätzung – Confidence Bands

Klassifizierung



https://github.com/iuf-duesseldorf/fritsche-lab-**CRStats**

Keßel et al. BioRxiv: doi: https://doi.org/10.1101/2022.10.18.512648; Blum et al. 2022

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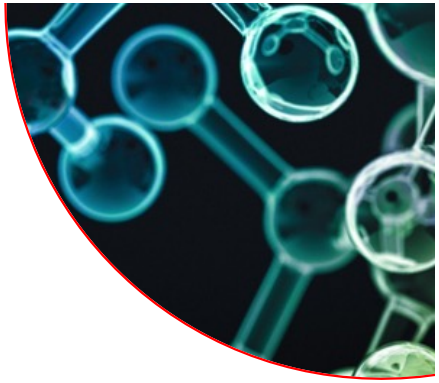
Prädiktive Kapazität – DNT EU-IVB



Positive controls	specific + brdl. + cytotox	specific + brdl.	specific
Cadmium chloride	TP	TP	TP
Chlorpyrifos	TP	TP	FN
Dexamethasone	TP	TP	TP
Hexachlorophene	TP	TP	TP
Lead (II) acetate trihydrate	TP	TP	TP
Manganese (II) chloride	TP	TP	TP
Methylmercury chloride	TP	TP	TP
PBDE 47	TP	TP	TP
PBDE 99	TP	TP	FN
(±) Ketamine hydrochloride	FN	FN	FN
5,5-Diphenylhydantoin	FN	FN	FN
Acrylamide	TP	TP	TP
all-trans-Retinoic acid	TP	TP	TP
Chlorpromazine hydrochloride	TP	TP	TP
Deltamethrin	TP	TP	TP
Domoic acid	FN	FN	FN
Haloperidol	TP	TP	TP
Maneb	TP	TP	FN
Methylazoxymethanol acetate	TP	TP	TP
Nicotine	FN	FN	FN
Paraquat dichloride hydrate	TP	TP	TP
PFOA	TP	FN	FN
PFOSK	TP	TP	TP
Sodium valproate	TP	TP	TP
Tebuconazole	TP	TP	TP
Tributyltin chloride	TP	TP	TP
Trichlorfon	TP	TP	TP
Triethyl-tin bromide	TP	TP	FN

		specific + brdl. + cytotox	specific + brdl.	specific
Negative controls	Acetaminophen	TN	TN	TN
	Amoxicillin	TN	TN	TN
	Aspirin	TN	TN	TN
	Buspirone	FP	TN	TN
	Chlorpheniramine maleate	TN	TN	TN
	D-Glucitol	TN	TN	TN
	Diethylene glycol	TN	TN	TN
	D-Mannitol	TN	TN	TN
	Doxylamine succinate	TN	TN	TN
	Famotidine	TN	TN	TN
	Ibuprofen	TN	TN	TN
	Metformin	TN	TN	TN
	Metoprolol	TN	TN	TN
	Penicillin	TN	TN	TN
	Saccharin	TN	TN	TN
	Sodium benzoate	TN	TN	TN
	Warfarin	TN	TN	TN

Performance [%]	Sensitivity	86	82	68
	Specificity	94	100	100
	Accuracy	89	89	80
	Balanced accuracy	90	91	84
	PPV	96	100	100
	F1 score	91	91	84
	MCC	78	80	67

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Blum et al. Chemosphere 2022

IVB Vorhersagekraft in Abhängigkeit von Biostatistik

Experimenteller Hintergrund

Vor-Prozessierung

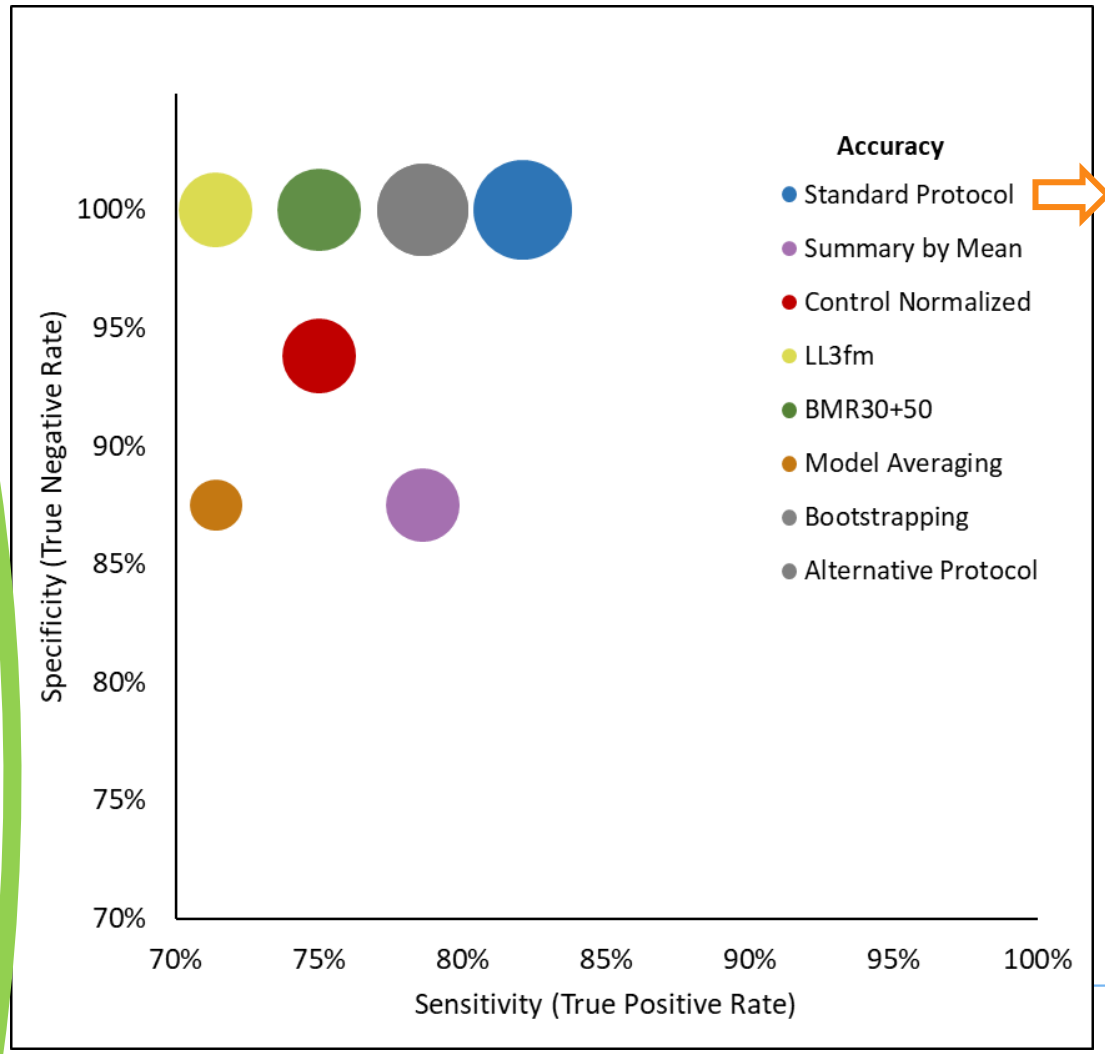
Re-Normalisierung

'Best Fit' Kurven Fitting

Daten Zusammenfassung - Median

BMC und CI Abschätzung – Confidence Bands

Klassifizierung



- Plattenreplikate zusammengefasst durch den Median
- Re-Normalisierung nach Kontroll-Normalisierung
- Best-Fit-Ansatz (Akaike Information Criterion) aus 6 Fitting-Modellen
- BMC und CI-Schätzung durch inverse Regression
- BMR10, 30 und 25 (je nach Endpunkt)

Keßel et al. BioRxiv
doi: https://doi.org/10.1101/2022.10.18.512648

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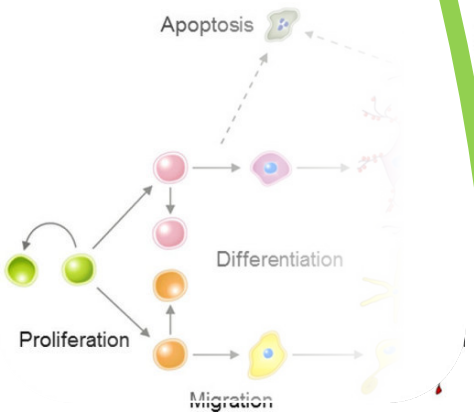
Vorläufiges OECD Guidance Document



EXTERNAL SCIENTIFIC REPORT

APPROVED: 18 October 2021

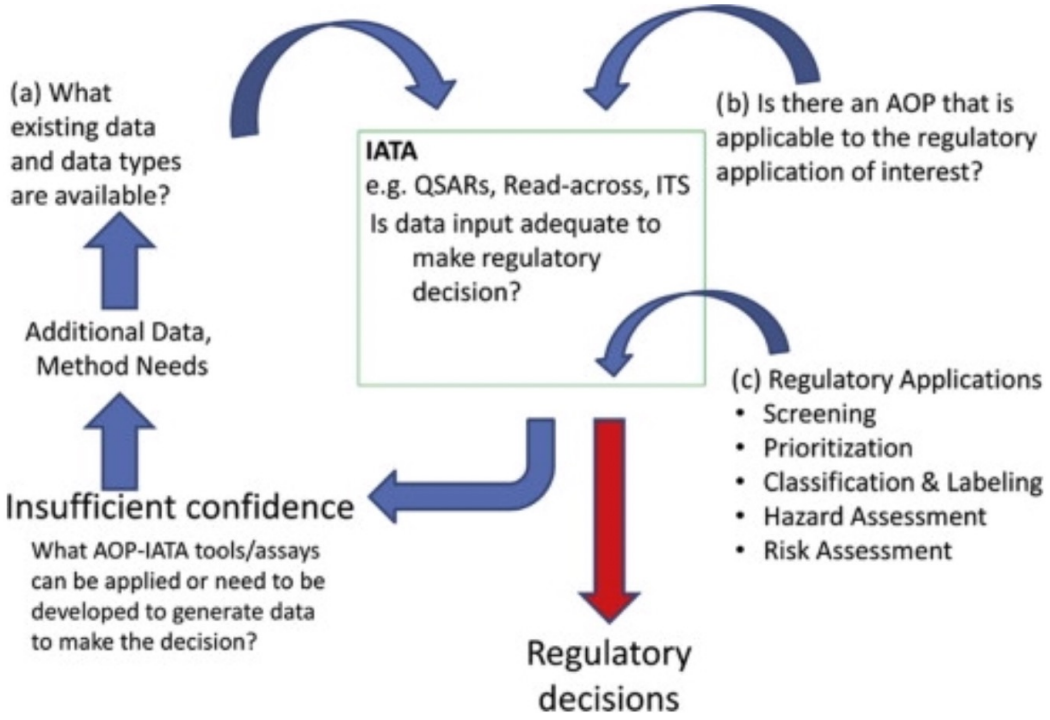
doi:10.2903/sp.efsa.2021.EN-6924

2023

External Scien… …nterpretation of Data from the Develop… …y In Vitro Testing Assays for Use in Int… …for Testing and As…

Kevin M Crofton[1] and W… …dy[2],

Die DNT IVB im AOP-informierten IATA Kontext



Tollefsen et al. Reg Toxicol Pharmacol 2014

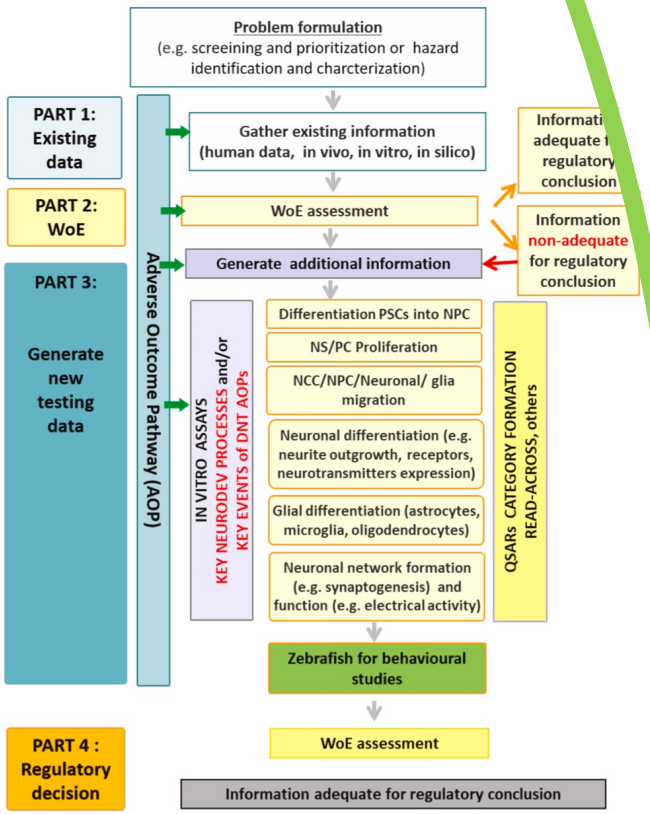
EXTERNAL SCIENTIFIC REPORT

APPROVED: 18 October 2021
doi:10.2903/sp.efsa.2021.EN-6924

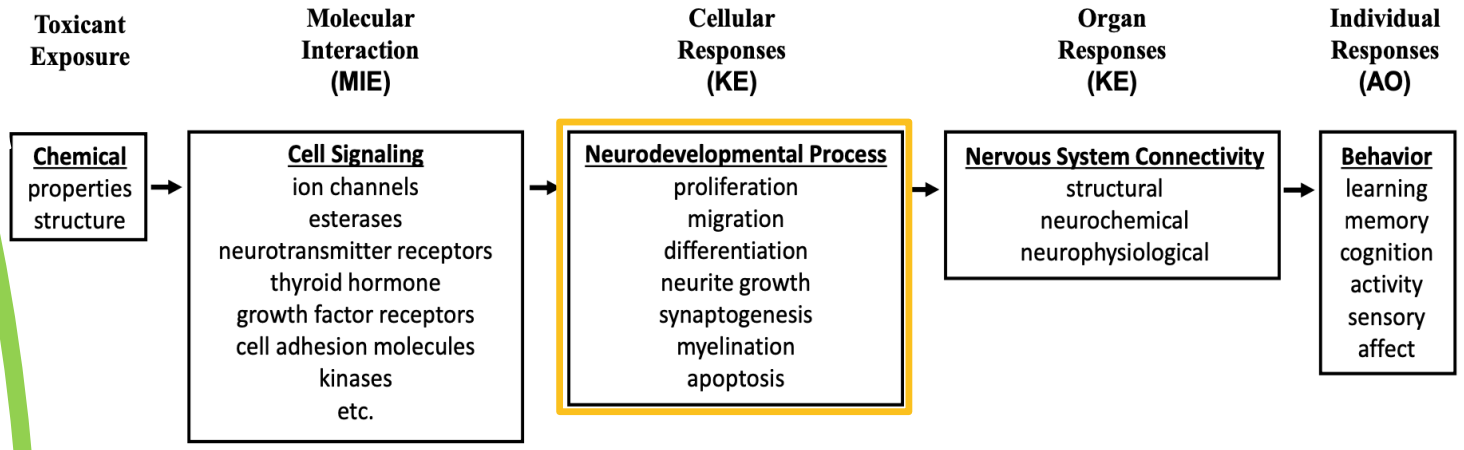
External Scientific Report on the Interpreta from the Developmental Neurotoxicity In V Assays for Use in Integrated Approaches for Assessment

Kevin M Crofton[1] and William R. Mundy[2],

Die DNT IVB im AOP-informierten IATA Kontext



Sachana et al. Reproduct Toxicol 2021



Unsicherheiten bei der Nutzung von AOPs für DNT:

- Zahl der DNT AOPs ist sehr gering (Sachana et al. Reproduct Toxicol 2021)
- Assays messen KE und nicht MIEs -> Limitierung für in silico
- Annahme, dass ein in vitro gestörtes KE auch das Potential hat, diesen in vivo zu beeinträchtigen

Nutzung der Evidenz aus Ergebnissen der DNT IVB

Evidenz aus der DNT IVB sollte von mehreren Faktoren geleitet werden, darunter:

1. die Konsistenz der innerhalb der Batterie selbst abgeleiteten in vitro Daten;
2. die biologische Plausibilität auf der Grundlage bestehender AOPs für schädliche neurologische Entwicklungsergebnisse und verfügbarer in vivo Daten;
3. die Einbeziehung verfügbarer IVIVE Expositionsmodelle
4. die Abwägung bekannter Unsicherheiten mit den regulatorischen Anforderungen.

Diese Faktoren sind alle in den IATA-Rahmen integriert.

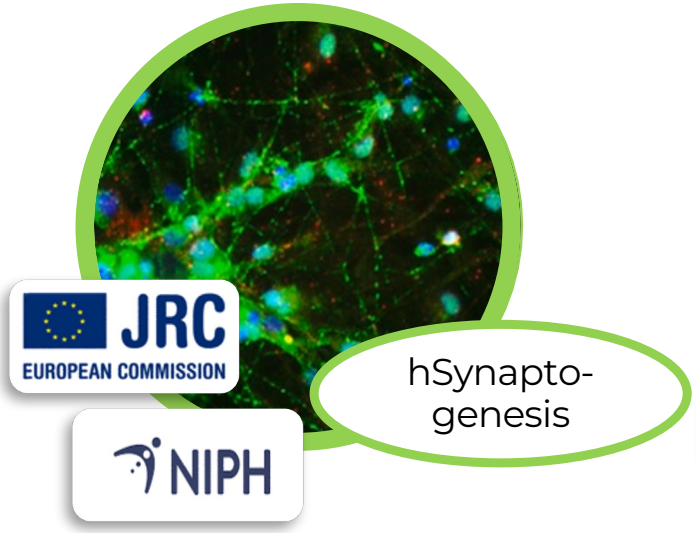
Unsicherheiten nicht spezifisch für die DNT IVB

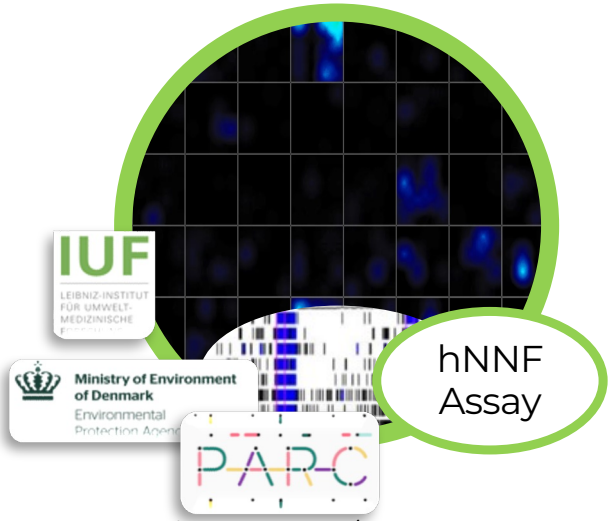
- Einhaltung der Leitlinien für die Berichterstattung über Testsysteme und -methoden, Datenanalysen und Transparenz (OECD GD211 -> ToxTemps (Krebs et al. 2019)).
- Unbekannte metabolische Kompetenz der DNT IVB Assays.
- Limitierungen in der Testung von Volatilen/Substanzen nicht löslich in DMSO.
- Limitierte Expositionsdauer.
- Potenzen basieren auf nominalen Mediumkonzentrationen.

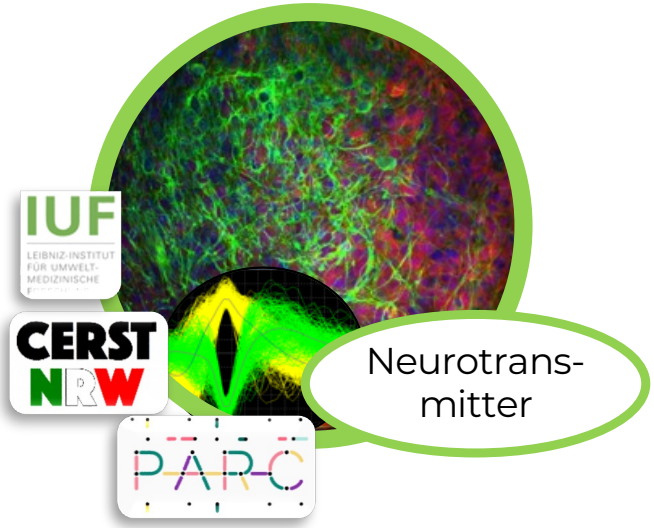
Unsicherheiten spezifisch für die DNT IVB

- Das Fehlen von Tests für einige zelluläre Prozesse und systemische Prozesse, von denen bekannt ist, dass sie für die normale neurologische Entwicklung entscheidend sind.
- Notwendigkeit der Entwicklung zusätzlicher AOPs, um die Kartierung der in der DNT IVB erfassten KEs zu verbessern.
- Eine relativ begrenzte Anzahl von getesteten Chemikalien im Vergleich zu den derzeit akzeptierten Batterien (z. B. ER-Aktivierung).
- Unsicherheit in Bezug auf die allgemeine Spezifität und Sensitivität der DNT IVB aufgrund begrenzter Tests von DNT-Referenzchemikalien und Vergleich der Ergebnisse mit einer kuratierten Datenbank für in vivo DNT-Studien.
- Ein Bedarf an einer konsensbasierten und regulatorisch gesteuerten, abgestuften Teststrategie, die in den IATAs verwendet werden sollte.

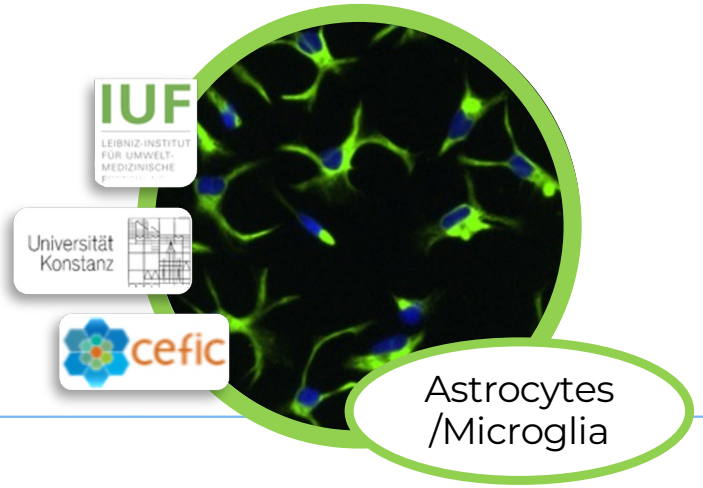
DNT IVB Lückenschließung

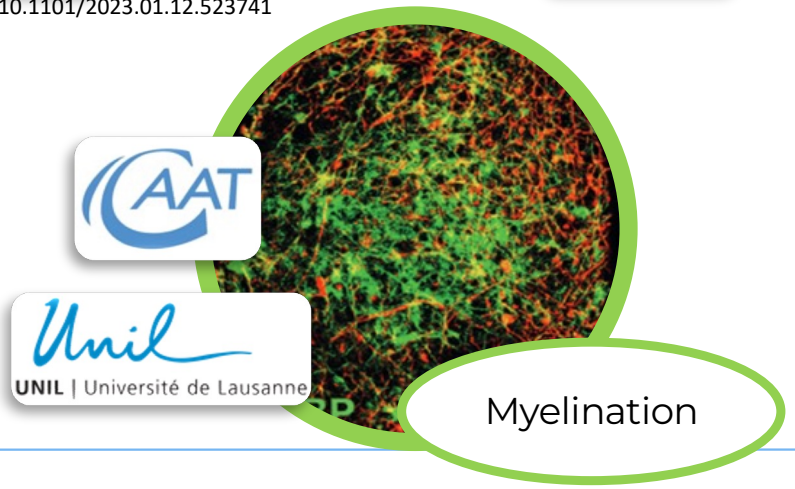




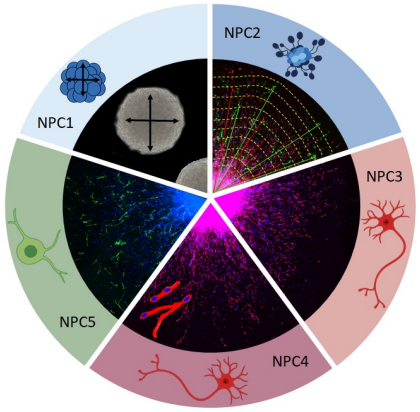


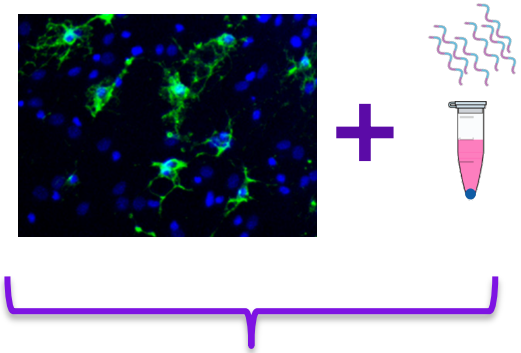
Bartmann et al. BioRXiv 10.1101/2023.01.12.523741

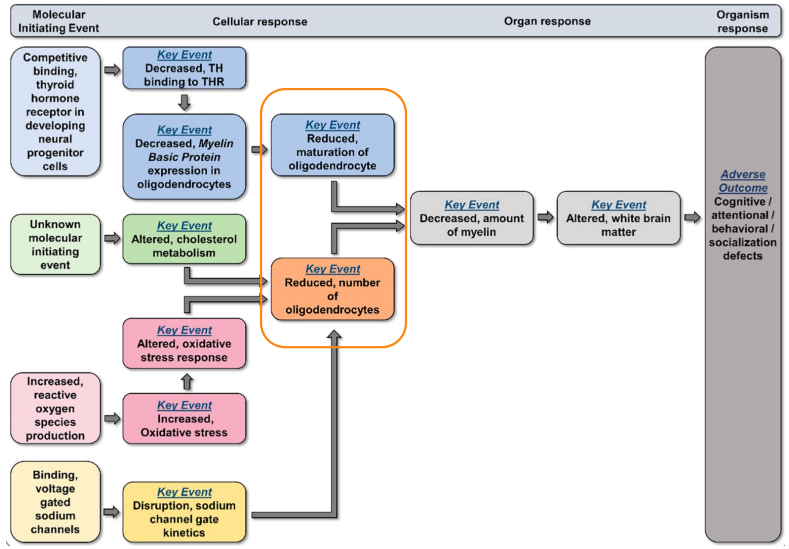




Phenomics und Transcrip-tomics für DNT-AOP Entwicklung

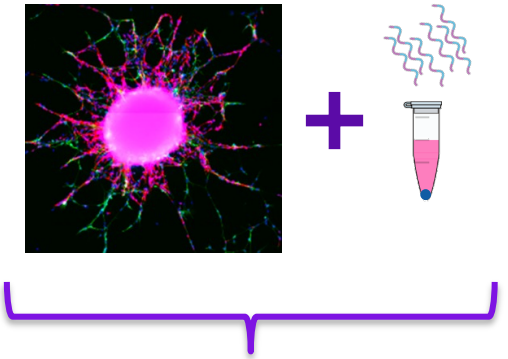


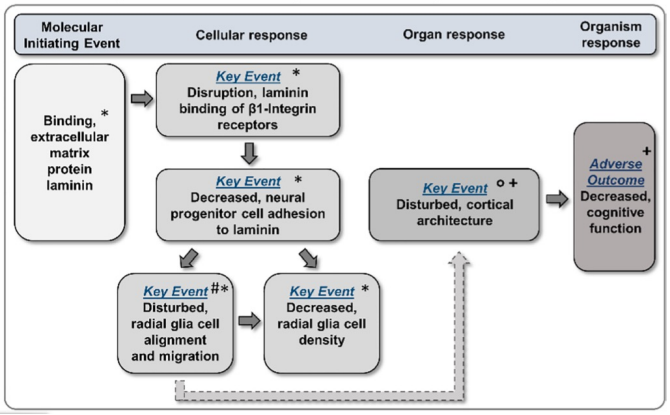




Klose et al., 2021, Cell. Biol. Toxicol.

Klose et al., 2021, ALTEX





Klose et al., 2022, Cell. Biol. Toxicol.

Barenys et al., 2016, Arch. Toxicol.

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Fallstudien für regulatorische Anwendungen der DNT IVB

Case Study 1
Hazard identification

efsa
European Food Safety Authority

Case Study 2
Screening and Prioritization

National Toxicology Program
U.S. Department of Health and Human Services

Endpoint (Test method; BMR)	Deltamethrin (µM)	Flufenacet (µM)
NCC migration (UKN2; BMC25)	18.4^{s}	>100
Radial glia migration (NPC2a, 120h; BMC10)	16.3^{us}	>20
Neurite length (NPC4; BMC30)	14.9^{us}	>20
Neurite area (NPC4; BMC30)	15.9^{us}	>20
Oligodendrocyte differentiation (NPC5; BMC30)	0.6^{s}	7.8^{us}
Neurite are (UKN5; BMC25)	112.8^{us}	>100
Rat neuronal network formation (rNNF; BMC50)	0.5^{s}	20
Human neuronal network formation (hNNF; BMC50)	4.1^{s}	>20

s = specific hit; us = unspecific hit

Masjosthusmann et al. EFSA supp publ 2020

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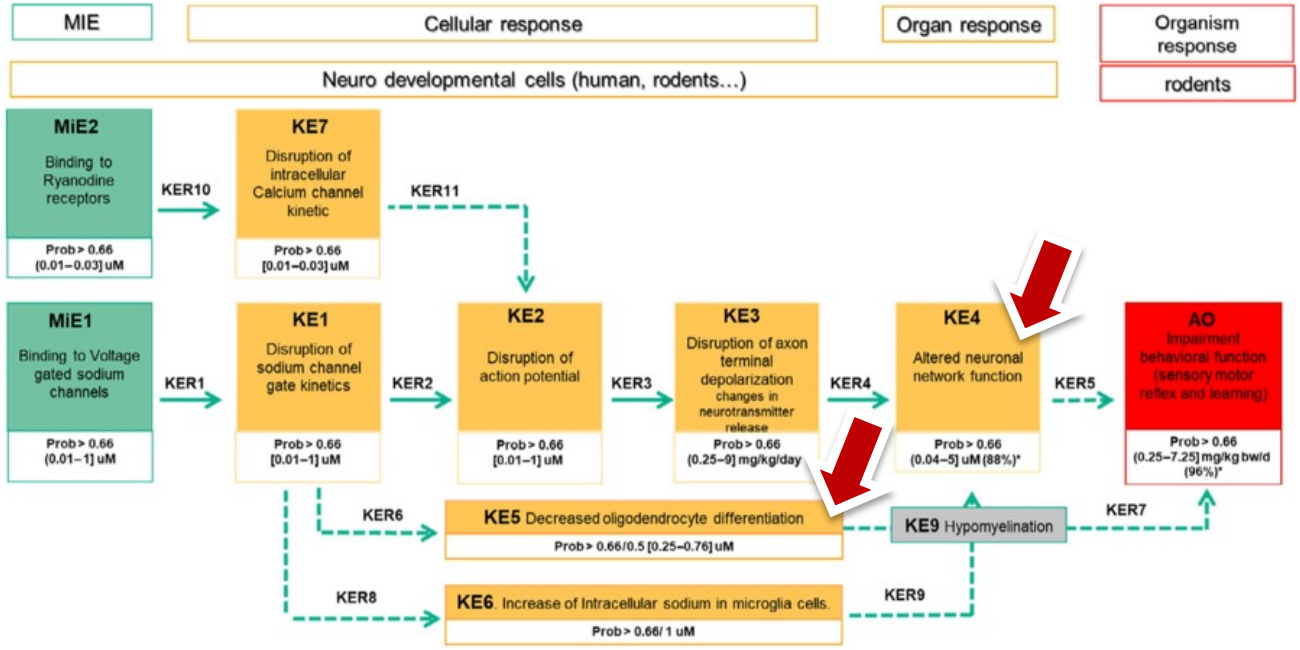

AOP-informed IATA

IATA – Integrated Approaches for Testing and Assessment

Hernandez et al. EFSA J 2021

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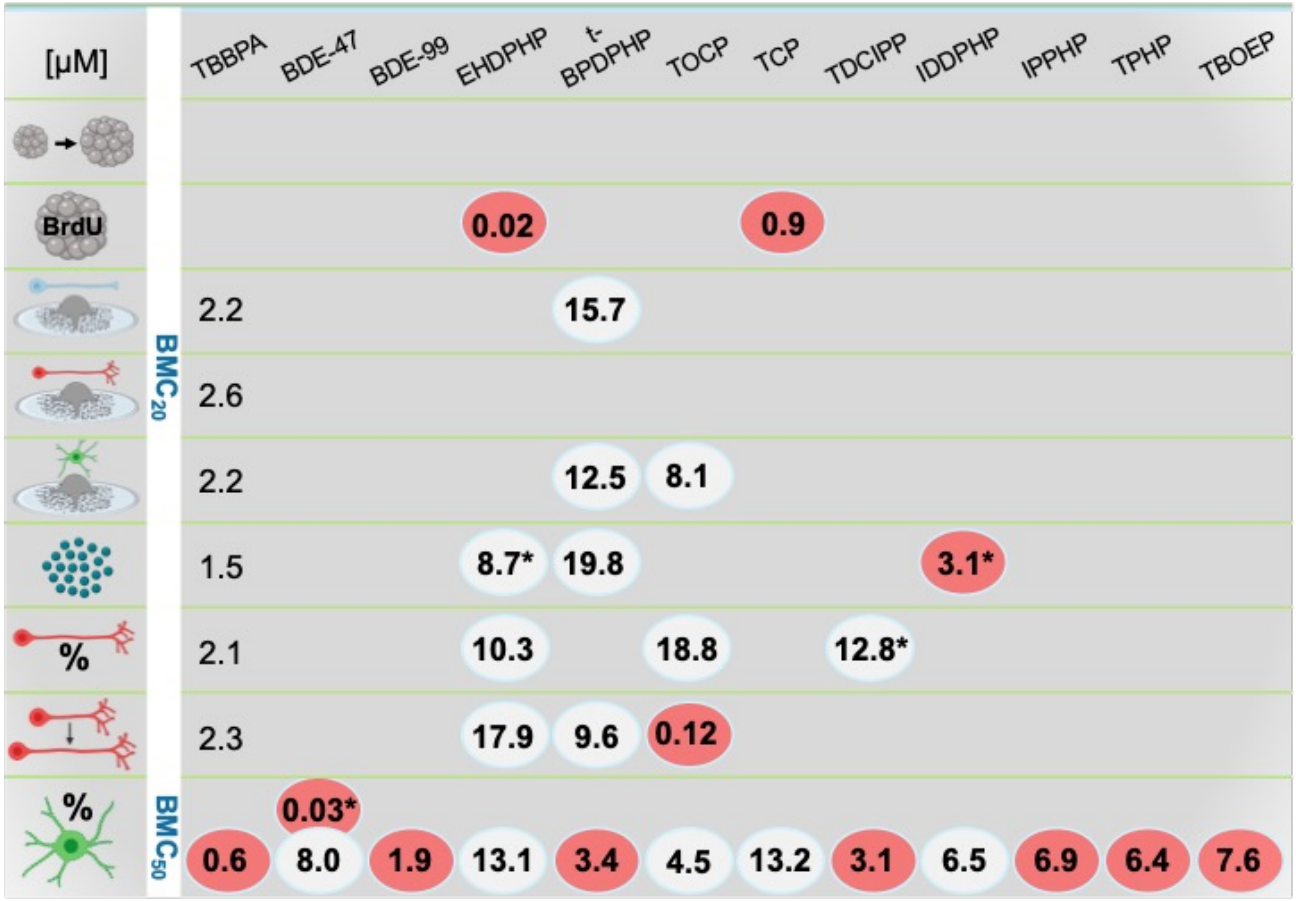

Klose et al. 2020; Hernandez et al. EFSA J 2021

Case Studies for regulatory Applications of the DNT IVB

Case Study 1
Hazard identification

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European Food Safety Authority

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National Toxicology Program
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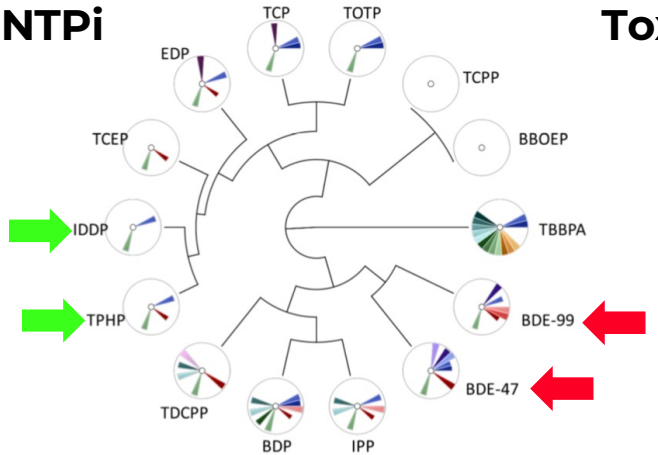
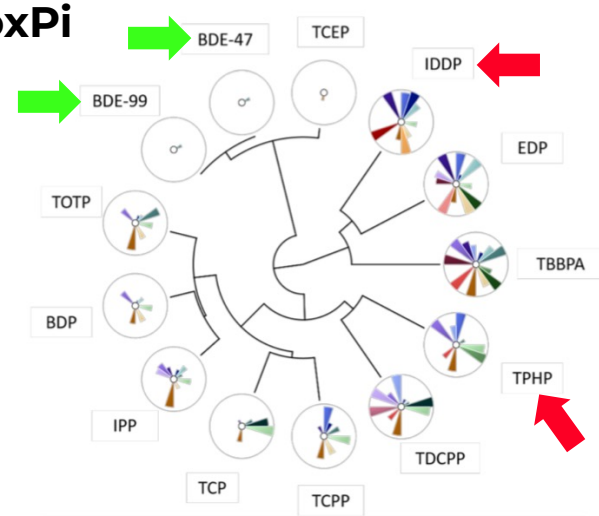
DNTPi



DNT endpoint	Weight	Metrics	Color	DNT endpoint	Weight	Metrics	Color
viability (UKN2)	1 (4,0%)	1		migration distance oligodendrocytes (NPC2c)	1 (4,0%)	1	
migration (UKN2)	1 (4,0%)	1		neuronal differentiation (NPC3)	1 (4,0%)	1	
viability (UKN4)	1 (4,0%)	1		neurite length (NPC4)	1 (4,0%)	1	
neurite area (UKN4)	1 (4,0%)	1		neurite area (NPC4)	1 (4,0%)	1	
viability (UKN5)	1 (4,0%)	1		oligodendrocyte differentiation (NPC5)	1 (4,0%)	1	
neurite area (UKN5)	1 (4,0%)	1		cell number (NPC2-5)	1 (4,0%)	1	
proliferation BrdU (NPC1a)	1 (4,0%)	1		cytotoxicity (72 NPC2-5)	1 (4,0%)	1	
proliferation area (NPC1b)	1 (4,0%)	1		cytotoxicity (120h; NPC2-5)	1 (4,0%)	1	
viability (NPC1)	1 (4,0%)	1		viability (120h; NPC2-5)	1 (4,0%)	1	
cytotoxicity (NPC1)	1 (4,0%)	1		network formation (NNF)	1 (4,0%)	1	
migration distance radial glia (NPC2a; 72h)	1 (4,0%)	1		viability (NNF)	1 (4,0%)	1	
migration distance radial glia (NPC2a; 120h)	1 (4,0%)	1		cytotoxicity (NNF)	1 (4,0%)	1	
migration distance neurons (NPC2b)	1 (4,0%)	1					

ToxPi



intended target family	Weight	Metrics	Color	intended target family	Weight	Metrics	Color
-	1 (5,0%)	2		ion channel	1 (5,0%)	1	
background measurement	1 (5,0%)	12		kinase	1 (5,0%)	1	
cell adhesion molecules	1 (5,0%)	7		malformation	1 (5,0%)	4	
cell cycle	1 (5,0%)	17		misc protein	1 (5,0%)	1	
cell morphology	1 (5,0%)	3		nuclear receptor	1 (5,0%)	29	
cyp	1 (5,0%)	5		phosphatase	1 (5,0%)	1	
cytokine	1 (5,0%)	20		protease	1 (5,0%)	7	
mixed	1 (5,0%)	6		protease inhibitor	1 (5,0%)	1	
gpcr	1 (5,0%)	4		steroid hormone	1 (5,0%)	6	
growth factor	1 (5,0%)	2		transporter	1 (5,0%)	2	

Klose et al. 2020; Masjosthusmann et al. 2021

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Stakeholders analysis in the EU

- **A different uncertainty level can be tolerated depending on the Regulatory Problem Formulation.**

Problem formulation	Validation	Interlaboratory/reproducibility data	Regulatory change	Tiered approach	Laboratory capacity (GLP CROs)	Map better the uncertainties	Exposure assessment GD
Screening/Prioritization/ tailoring future studies/read across grouping/WoE	NAV accepted: Scientific Validation (readiness criteria) enough, for the current DNT-IVB (17 test)	YES. Good to have but NAMs are and can already being used for this purpose.	NO	NO	NO	NO	NO
Hazard identification and characterization as part of the data requirements		YES	YES[1]	YES. It has to be design for each EU legislation	2 CROs needed	In vivo/in vitro correlation data OECD IVB GD for method description and interpretation IATA case studies for HIC	QIVIVE Reverse dosimetry

[1] The group recommends an harmonized approach among different regulations in EU when reviewing the DR.

NAM validation: https://doi.org/10.1016/j.yrtph.2020.104592

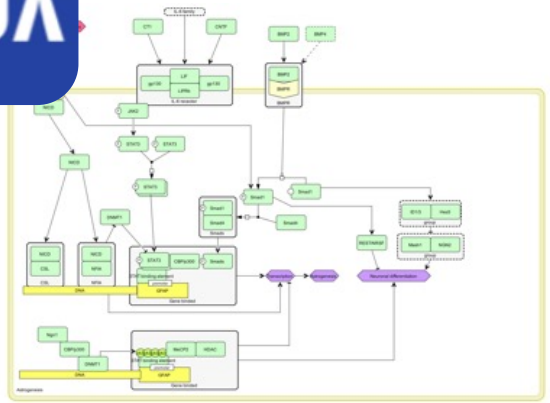
with courtesy of Andrea Terron, EFSA

DNT IVB in derzeitigen internationalen Projekten

ASPIS

ONTOX

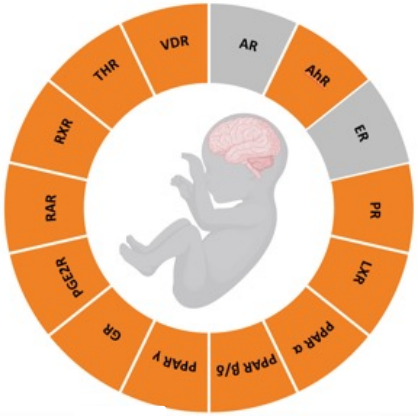
RISK HUNT3R



US-NTP

PARC

ENDpoiNTs



DNTOX

- Founded in 2022
- Investors‘ round closed
- Operational in 01/2023
- GLP accreditation strived for in 2023

Methoden Verfügbarkeit

DNT

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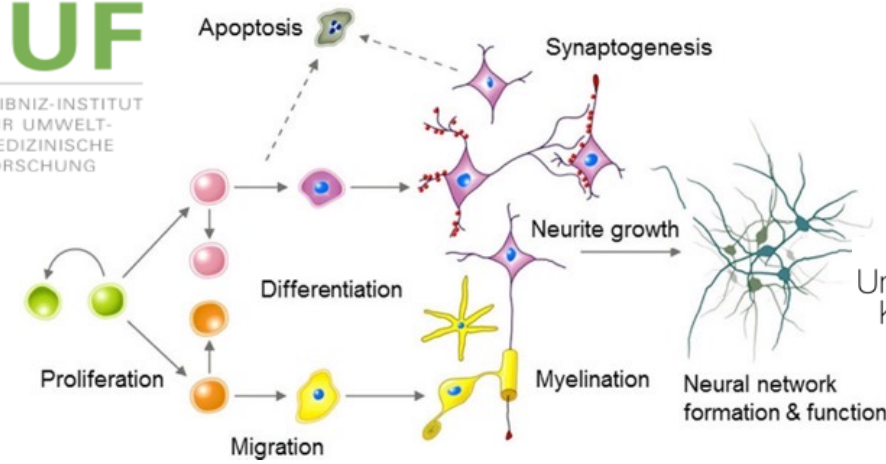
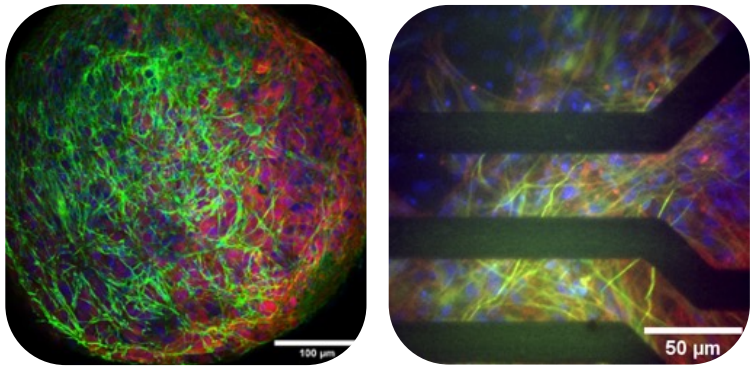


Universität Konstanz

ANT



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Dr. Magda Sachana (OECD)

DNTOX

efsa European Food Safety Authority

United States Environmental Protection Agency

National Toxicology Program
U.S. Department of Health and Human Services

cefic

LRI The Long-range Research initiative

CERST NRW

DFG

Bundesministerium für Bildung und Forschung

Ministry of Environment of Denmark
Environmental Protection Agency

Leibniz

Leibniz Association

ONTOX

ENDpoiNTs

PARC

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