Hvad gør vi når der ikke er grænseværdier i drikkevand?

Risikoscreenings-værktøj udviklet i VUDP PharmaRisk projekt

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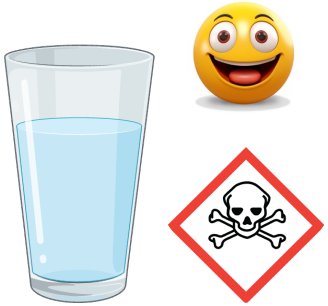
Kvantitativ Non-Target Kemisk Analyse (qNTA) → Sundhedsrisiko-screening

Højtopløsningsmassespektrometri (HRMS)

~1%



Sundhedsrisiko-screening

GUIDANCE

ECHA EUROPEAN CHEMICALS AGENCY efsa JOURNAL

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Guidance document on the impact of water treatment processes on residues of active substances or their metabolites in water abstracted for the production of drinking water

European Chemicals Agency (ECHA) and European Food Safety Authority (EFSA), Roberta Hofman-Caris, Milou Dingemans, Astrid Reus, Sanah Majid Shaikh, Julian Muñoz Sierra, Ursula Karges, Tim aus der Beek, Eugénia Nogueiro, Christopher Lythgo, Juan Manuel Parra Morte, Maria Bastaki, Rositsa Serafimova, Anja Friel, Daniele Court Marques, Andreas Uphoff, Lucie Bielska, Claudio Putzu, Laura Ruggeri and Paschalina Papadaki

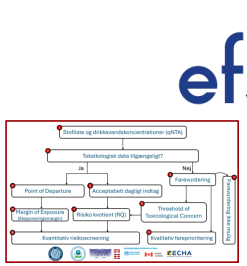
Abstract

This guidance document provides a tiered framework for risk assessors and facilitates risk managers in making decisions concerning the approval of active substances (AS) that are chemicals in plant protection products (PPPs) and biocidal products, and authorisation of the products. Based on the approaches presented in this document, a conclusion can be drawn on the impact of water treatment processes on residues of the AS or its metabolites in surface water and/or groundwater abstracted for the production of drinking water, i.e. the formation of transformation products (TPs). This guidance enables the identification of actual public health concerns from exposure to harmful compounds generated during the processing of water for the production of drinking water, and it focuses on water treatment methods commonly used in the European Union (EU). The tiered framework determines whether residues from PPP use or residues from biocidal product use can be present in water at water abstraction locations. Approaches, including experimental methods, are described that can be used to assess whether harmful TPs may form during water treatment and, if so, how to assess the impact of exposure to these water treatment TPs (tTPs) and other residues including environmental TPs (eTPs) on human and domesticated animal health through the consumption of TPs via drinking water. The types of studies or information that would be required are described while avoiding vertebrate testing as much as possible. The framework integrates the use of weight-of-evidence and, when possible alternative (new approach) methods to avoid as far as possible the need for additional testing.

Keywords: transformation products, genotoxicity, disinfection, risk assessment, plant protection products, biocidal products, groundwater

*"Denne vejledning gør det muligt at **identificere faktiske folkesundhedsbekymringer** som følge af **eksponering for skadelige forbindelser**, der genereres under … produktion af **drikkevand**…"*

Vandværk 1	Vandværk 3	Vandværk 10	Vandværk 12	Vandværk 14	Vandværk 17
6.31	0.00	1487	30.36	0.00	69.34
1.41	0.33	202	3.39	0.00	2.78
1.08	11.8	0.00	0.00	0.00	0.00
0.59	2.24	0.00	2.34	10.5	0.52
0.11	0.09	0.00	0.05	0.00	0.15
0.09	0.16	0.26	0.00	0.00	0.48
0.31	0.76	0.00	0.00	0.08	0.10
0.04	0.66	0.00	0.02	0.00	0.00
0.60	0.04	0.00	0.00	0.00	0.00



efsa EUROPEAN FOOD SAFETY AUTHORITY

VUDP FORENINGEN

InSa-Drikkevand

DTU

EFSA Guidance document

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GUIDANCE
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Guidance document on the impact of water treatment processes on residues of active substances or their metabolites in water abstracted for the production of drinking water

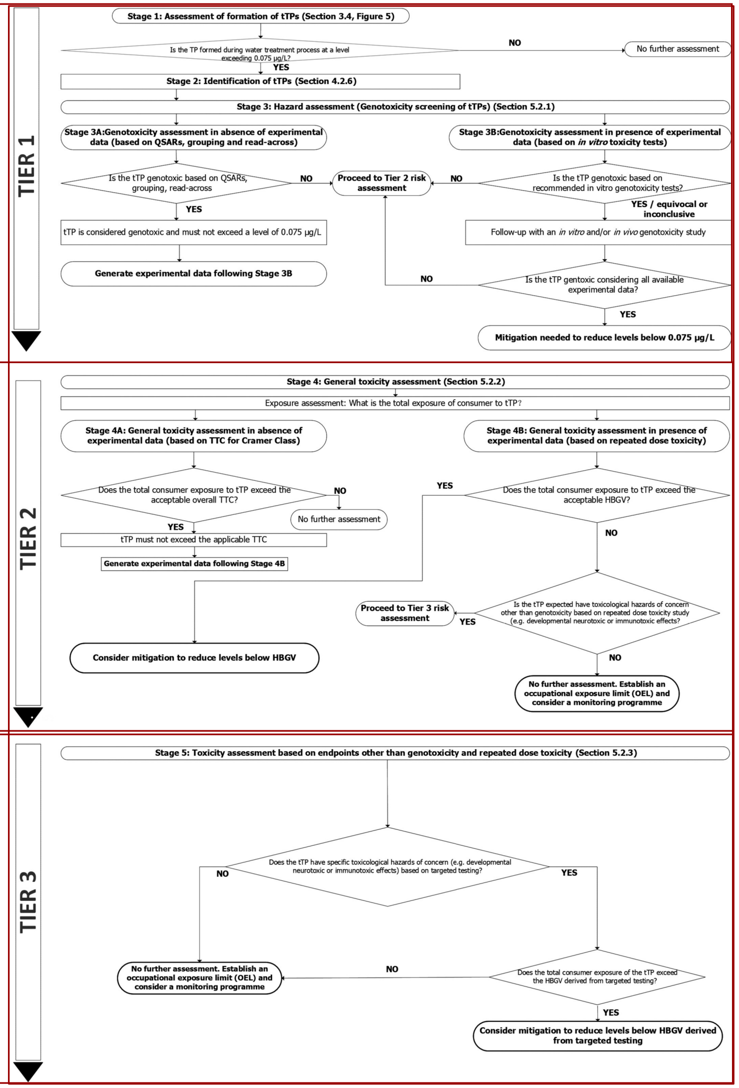
Genotoxicity screening

General toxicity assessment

In absence of experimental toxicological data -> Threshold of Toxicological Concern (TTC)

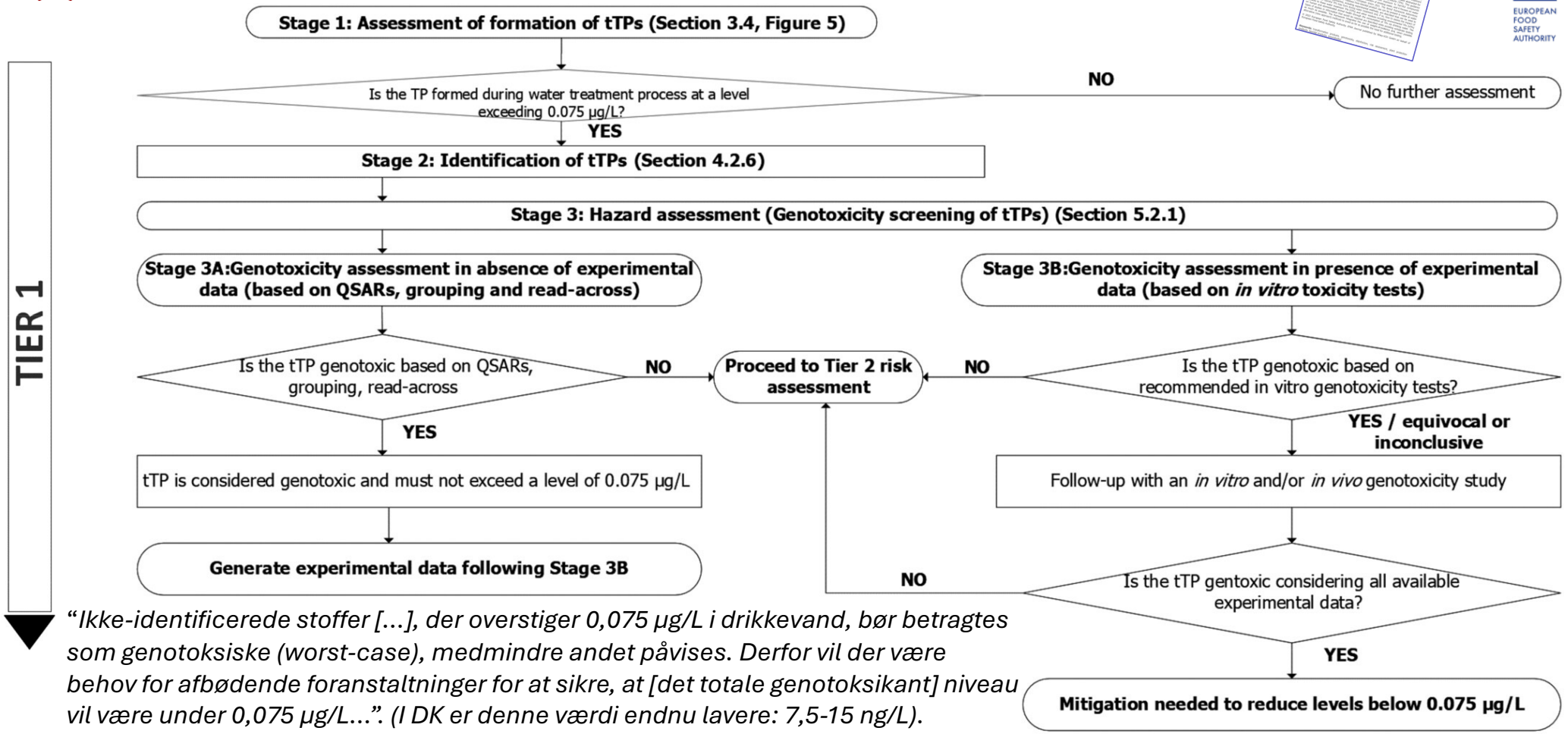
Refine risk assessment

Toxicity assessment based on other endpoints (e.g. developmental neurotoxicity, immunotoxic and reproductive effects). In vitro -> in vivo -> not 3R! / $$$!



TIER 1
Stage 1: Assessment of formation of tTPs (Section 3.4, Figure 5)
Is the TP formed during water treatment process at a level exceeding 0.075 µg/L?
NO
No further assessment
YES
Stage 2: Identification of tTPs (Section 4.2.6)
Stage 3: Hazard assessment (Genotoxicity screening of tTPs) (Section 5.2.1)
Stage 3A: Genotoxicity assessment in absence of experimental data (based on QSARs, grouping and read-across)
Stage 3B: Genotoxicity assessment in presence of experimental data (based on in vitro toxicity tests)
Is the tTP genotoxic based on QSARs, grouping, read-across
NO
Proceed to Tier 2 risk assessment
NO
Is the tTP genotoxic based on recommended in vitro genotoxicity tests?
YES
YES / equivocal or inconclusive
tTP is considered genotoxic and must not exceed a level of 0.075 µg/L
Follow-up with an in vitro and/or in vivo genotoxicity study
Generate experimental data following Stage 3B
NO
Is the tTP gentoxic considering all available experimental data?
YES
Mitigation needed to reduce levels below 0.075 µg/L
TIER 2
Stage 4: General toxicity assessment (Section 5.2.2)
Exposure assessment: What is the total exposure of consumer to tTP?
Stage 4A: General toxicity assessment in absence of experimental data (based on TTC for Cramer Class)
Stage 4B: General toxicity assessment in presence of experimental data (based on repeated dose toxicity)
Does the total consumer exposure to tTP exceed the acceptable overall TTC?
NO
No further assessment
YES
Does the total consumer exposure to tTP exceed the acceptable HBGV?
YES
tTP must not exceed the applicable TTC
Generate experimental data following Stage 4B
NO
Proceed to Tier 3 risk assessment
YES
Is the tTP expected have toxicological hazards of concern other than genotoxicity based on repeated dose toxicity study (e.g. developmental neurotoxic or immunotoxic effects?
Consider mitigation to reduce levels below HBGV
NO
No further assessment. Establish an occupational exposure limit (OEL) and consider a monitoring programme
TIER 3
Stage 5: Toxicity assessment based on endpoints other than genotoxicity and repeated dose toxicity (Section 5.2.3)
Does the tTP have specific toxicological hazards of concern (e.g. developmental neurotoxic or immunotoxic effects) based on targeted testing?
NO
YES
No further assessment. Establish an occupational exposure limit (OEL) and consider a monitoring programme
NO
Does the total consumer exposure of the tTP exceed the HBGV derived from targeted testing?
YES
Consider mitigation to reduce levels below HBGV derived from targeted testing

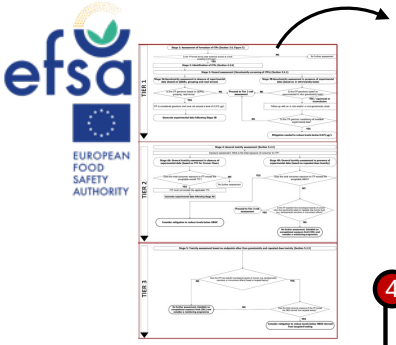
Tier 1: Genotoxicity screening



"Ikke-identificerede stoffer [...], der overstiger 0,075 µg/L i drikkevand, bør betragtes som genotoksiske (worst-case), medmindre andet påvises. Derfor vil der være behov for afbødende foranstaltninger for at sikre, at [det totale genotoksikant] niveau vil være under 0,075 µg/L...". (I DK er denne værdi endnu lavere: 7,5-15 ng/L).

Risk Screening Workflow

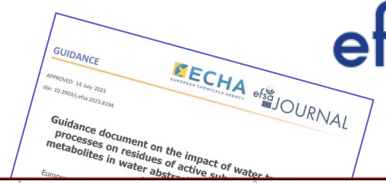
PharmaRisk



1. Stofliste og drikkevandskoncentrationer (qNTA)
2. Toksikologisk data tilgængeligt?
   - Ja
   - Nej
3. Farevurdering
4. Point of Departure
5. Acceptabelt dagligt indtag
6. Margin of Exposure (Eksponeringsmargin)
7. Risiko kvotient (RQ)
8. Threshold of Toxicological Concern
9. Kvantitativ risikoscreening
10. Kvalitativ fareprioritering
11. Farevurdering ikke mulig

InSa-Drikkevand

Risk Quotient (RQ) and Margin of Exposure (MoE)



Typical for pesticides and pharmaceuticals

$$RQ_{substance} = \frac{C_{substance}}{DWEL_{substance}}$$

1-20% af stofeksponering fra drikkevand acceptabel.

$$Drinking\ Water\ Equivalent\ Level\ (DWEL)\ \left(\frac{ng}{L}\right) = \frac{\mathbf{0.2}\times\boldsymbol{ADI}\times BW}{DWI}$$

ADI, acceptable daily intake (mg/kg/day); BW, body weight (kg) ; DWI, drinking water intake (L/day)

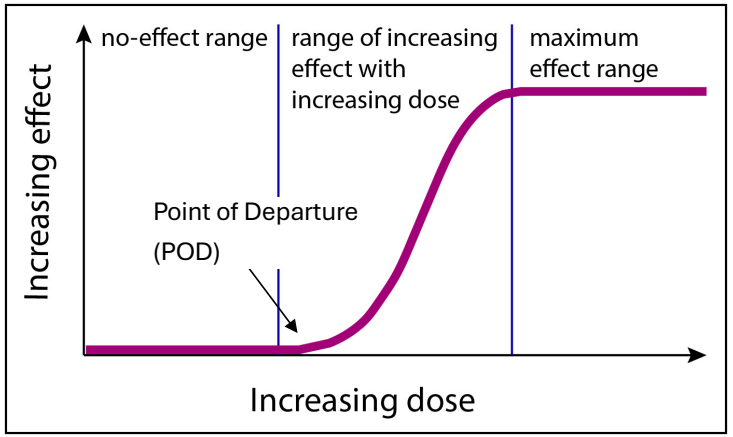
Age Groups	Body weight (kg)	DWI (L/day)
0-6 months	5.75	0.19
6-12 months	8.8	1
1-3 yrs	11.9	1.3
3-10 yrs	23.1	1.6
10-14yrs	43.4	2
14-18 yrs	61.3	2.25
Adults(>18 years)	70	2.25

Other substances with toxicological data "Eksponeringsmargin"

$$Margin\ of\ Exposure\ (MoE) = \mathbf{0.2}\,\frac{POD}{ADD}$$

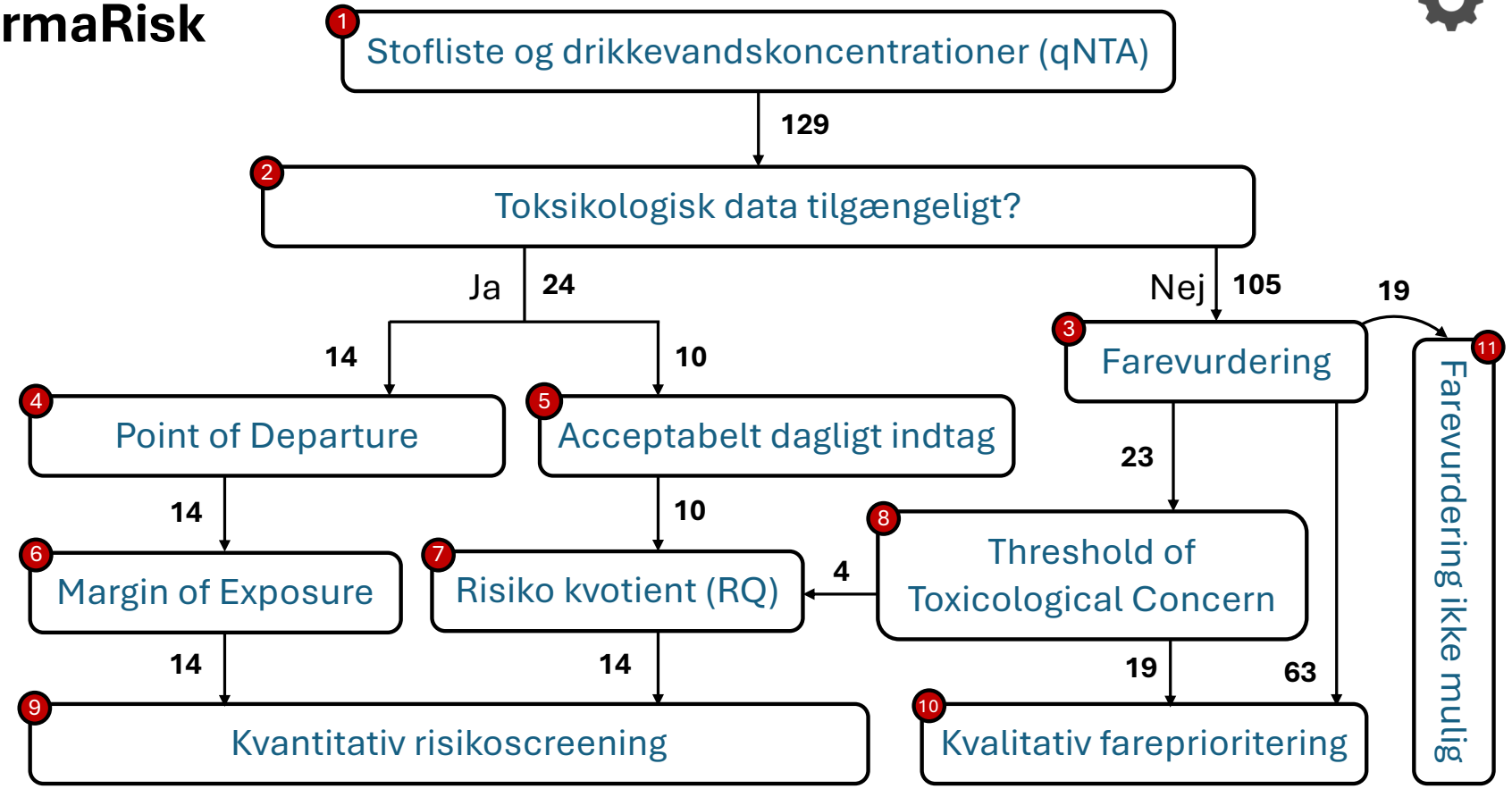
$$Average\ daily\ dose\ (ADD) = \frac{C_{substance}\times DWI}{BW}$$

Hvis MoE > 100 betragtes generelt som værende uden stor sundhedsmæssig bekymring.



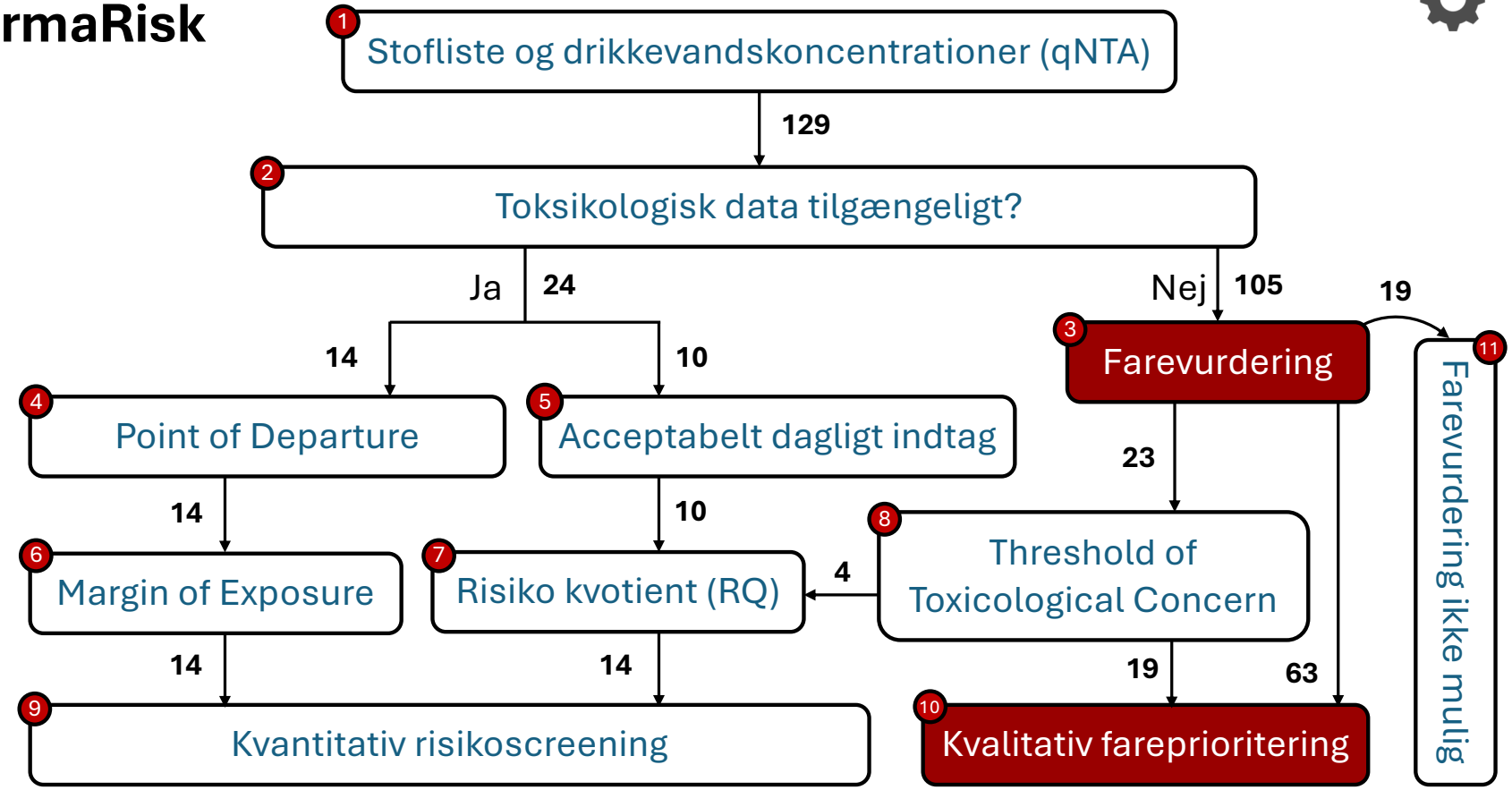
Risk Screening Workflow

PharmaRisk



Risk Screening Workflow

PharmaRisk



PharmaRisk – Fareprioritering

VH - Very High	H - High	M - Medium	L - Low	I - Inconclusive	No Data	Authoritat	Screening	*QSAR Model*

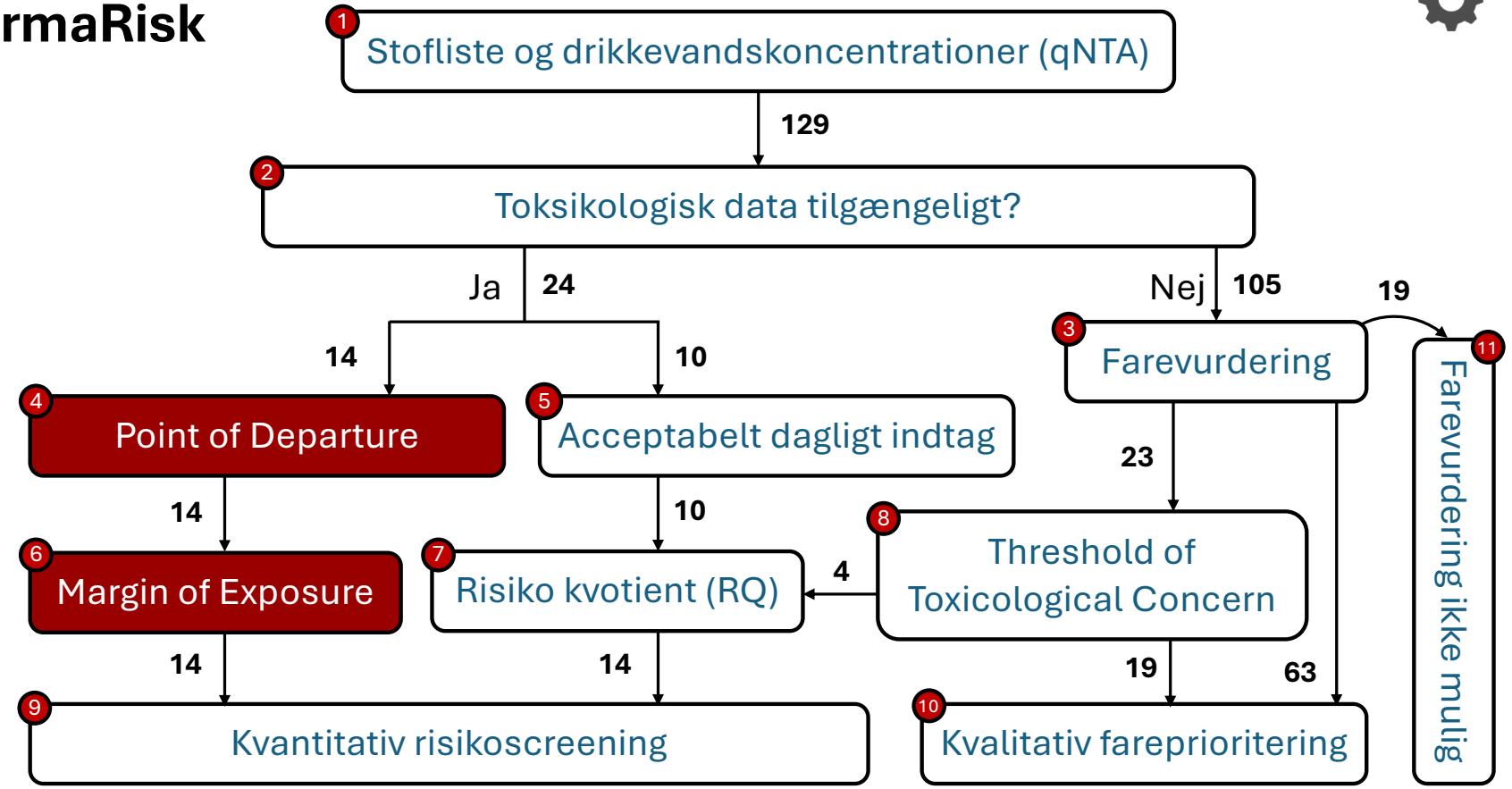
Human Health Effects

Acute Mammalian Toxicity | Neurotoxicity | Systemic Toxicity

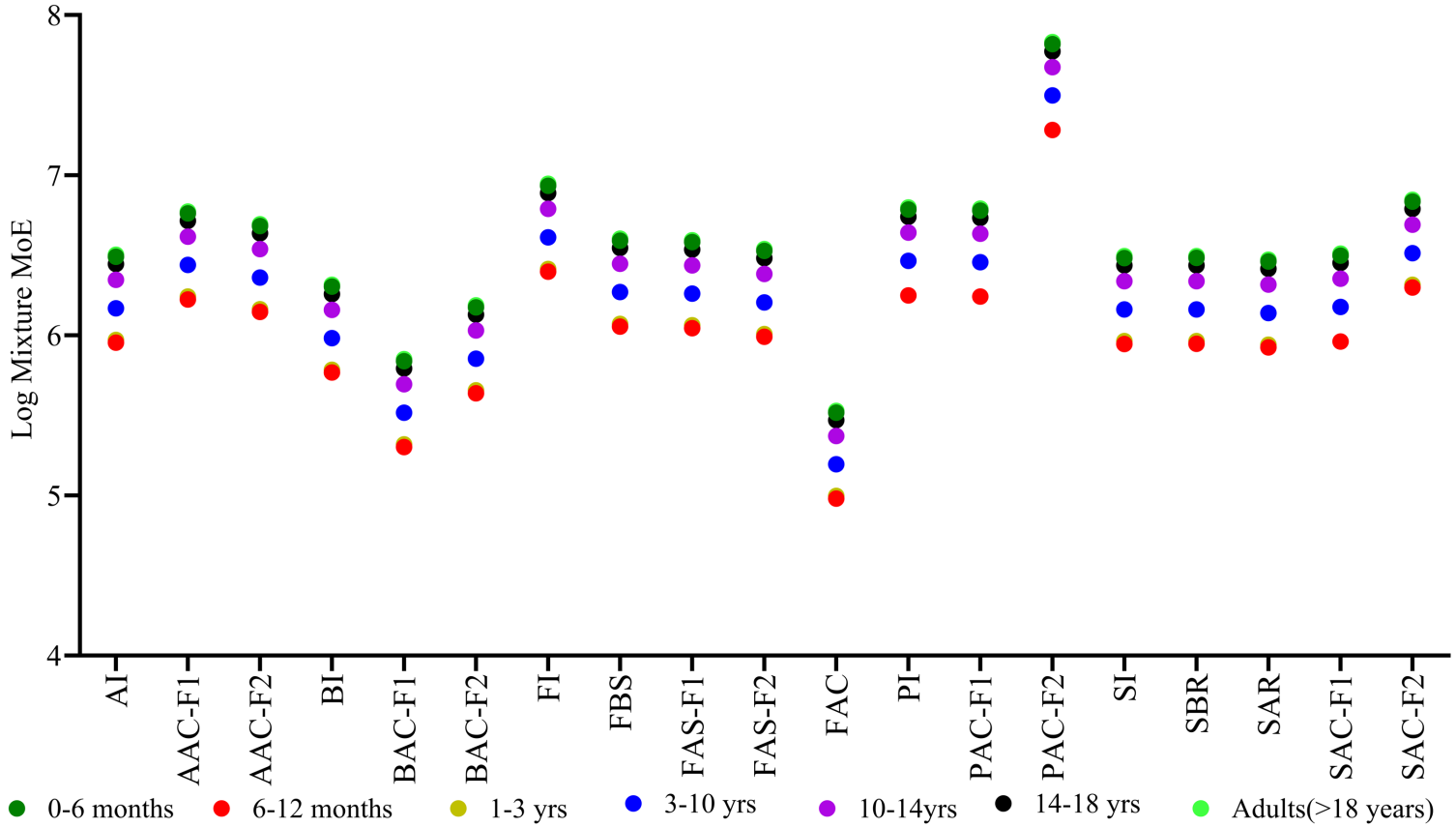
Compound name	SMILES	CAS	Oral	Inhalation	Dermal	Carcinogenicity	Genotoxicity Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Repeat Exposure	Single Exposure	Repeat Exposure	Single Exposure	Skin Sensitization	Skin Irritation	Eye Irritation	**Combined Hazard Score**
1-Hydroxyibuprofen	CC(C)C(C1=CC	53949-53-4	*M*				*I*	*H*		*H*								2.67
Ritalinic acid	C1=CC=C(C=C	19395-41-6	*M*				*I*	*H*		*H*								2.67
4-Hydroxyamphetamine	CC(CC1=CC=C	103-86-6	*H*				*L*	*H*		*H*						*H*		2.60
Naproxen	CC(C1=CC2=C	22204-53-1	H				L	*H*		H								2.50
Tramadol N-oxide	C[N+](C)(CC1C	147441-56-3	*M*				*I*			*H*								2.50
Nifedipine	CC1=C(C(C2=C	21829-25-4	H						M	**H**			M		M			2.40
1-(4-Chlorobenzhydryl)pipera	C1=CC=C(C=C	303-26-4	*H*				*L*	*H*		*L*					*H*	*H*		2.33
Tilidine	CCOC(=O)C1(C	51931-66-9	*H*				*L*			*H*								2.33
3,4-Methylenedioxypyrovalero	CCCC(C(=O)C1	687603-66-3	*M*				*L*	*H*		*H*								2.25
Atropine	CN1C2CCC1C(	51-55-8	M				*L*	*H*		H								2.25
Carboxyibuprofen	CC(CC1=CC=C	15935-54-3	*M*				*L*	*H*		*H*								2.25
Desmethylketoprofen methyl	COC(=O)CC1=C	24021-44-1	*M*				*L*	*H*		*H*								2.25
Hydrocortisone	CC12CCC(=O)C	50-23-7	*M*				*L*	H		*H*								2.25
N-Desmethylvenlafaxine	CNCC(C1=CC=	149289-30-5	*M*				*L*	*H*		*H*								2.25
N,N-Didesmethylvenlafaxine	COC1=CC=C(C	93413-77-5	*M*				*L*	*H*		*H*								2.25
O-Desmethylnaproxen	CC(C1=CC2=C	52079-10-4	*M*				*L*	*H*		*H*								2.25
Tapentadol	CCC(C(C)CN(C	175591-23-8	*M*				*L*	*H*		*H*								2.25
Venlafaxine	CN(C)CC(C1=C	93413-69-5	*M*				*L*	*H*		*H*								2.25
Norfentanyl	CCC(=O)N(C1=	1609-66-1	*H*				*L*	*L*		*H*						*H*		2.20
Dropropizine	C1=CC=C(C=C	17692-31-8	M				*L*	*H*		*L*					*H*	*H*		2.17
Methylprednisolone	CC1CC2C3CC(	83-43-2	L				*L*	H	M	*H*			H					2.17
Piracetam	C1CC(=O)N(C1	7491-74-9	M				*L*	*L*		*H*					*H*	*H*		2.17
1-(3-Chlorophenyl)piperazine	C1=CC(=CC(=C	6640-24-0	H				*L*	*L*		*L*					*H*	*H*		2.00
O-Desarylranolazine	CC1=CC=CC(=	172430-46-5	*H*				*L*	*H*		*L*								2.00
3-Hydroxycotinine	CN1C(CC(C1=C	34834-67-8	*M*				L			*H*								2.00
3-Hydroxydesloratadine	C1CC2=CC(=C	119410-08-1	*I*				*L*			*H*								2.00

Risk Screening Workflow

PharmaRisk

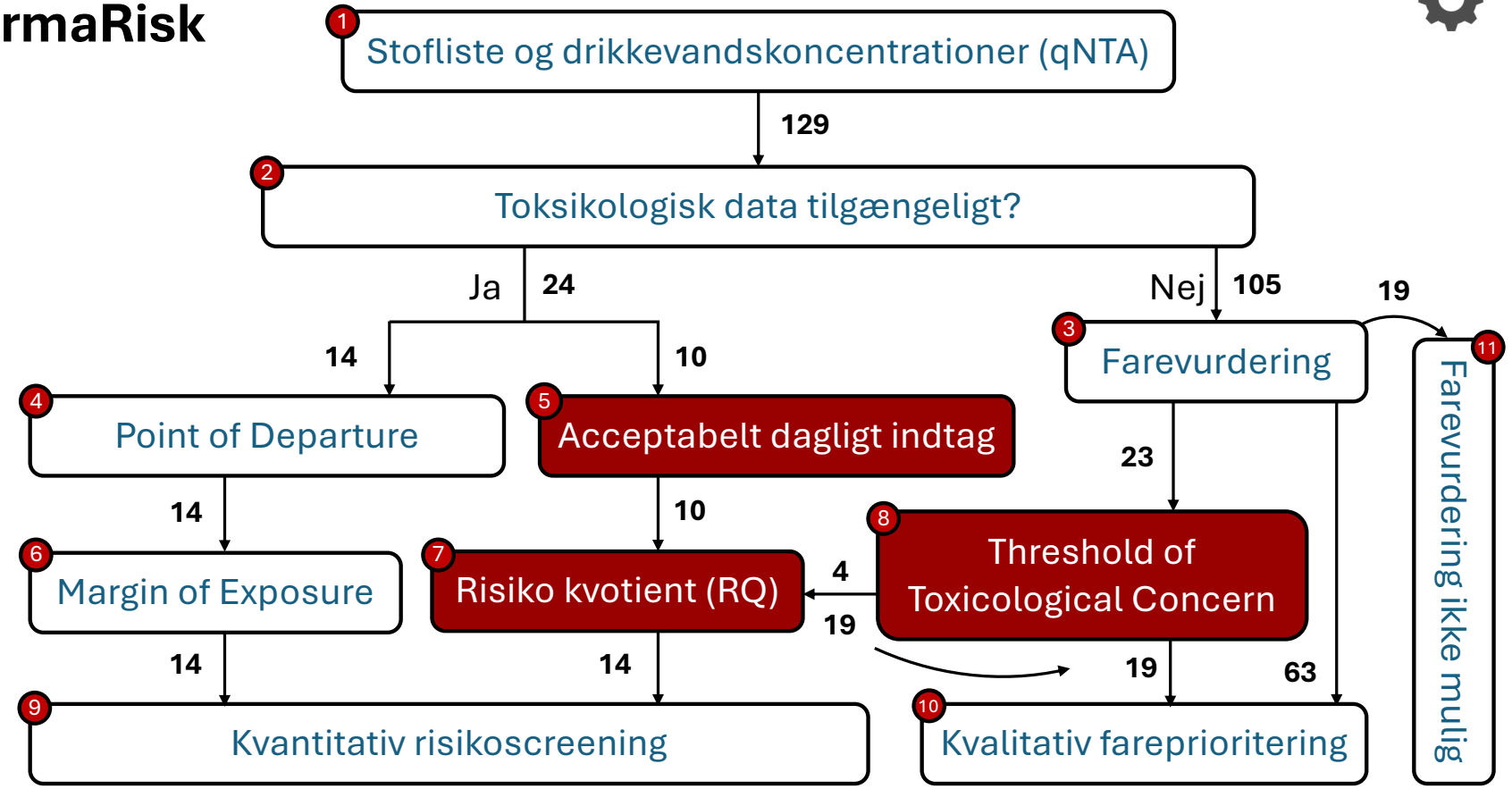


PharmaRisk – Eksponeringsmargin (MoE) for 14 stoffer



Risk Screening Workflow

PharmaRisk



Threshold of Toxicological Concern (TTC) – pragmatic screening tool for substances without toxicological data

Classification	TTC value in µg/person per day	TTC value in µg/kg bw per day[(a)]
Potential DNA-reactive mutagens and/or carcinogens	0.15	0.0025
Organophosphates and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1,800	30

Table 1: Structural classes for chemicals proposed in the Cramer scheme (Cramer et al., 1978)

Class I	Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity. This class would include normal constituents of the body (excluding hormones); simply-branched, acyclic aliphatic hydrocarbons; common carbohydrates; common terpenes; substances that are sulfonate or sulfamate salts, without any free primary amines
Class II	Substances which possess structures that are less innocuous than Class I substances, but do not contain structural features suggestive of toxicity like those substances in Class III. This class would include common components of food; substances containing no functional groups other than alcohol, aldehyde, side-chain ketone, acid, ester, or sodium, potassium or calcium sulfonate or sulfamate, or acyclic acetal or ketal and are either a monocycloalkanone or a bicyclic substance with or without a ring ketone
Class III	Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups. This class would include structures that contain elements other than carbon, hydrogen, oxygen, nitrogen or divalent sulfur; certain benzene derivatives; certain heterocyclic substances; aliphatic substances containing more than three types of functional groups

Ministry of Environment of Denmark
Environmental Protection Agency

*masse eksperiment

Ministry of Higher Education and Science Denmark

Marie Skłodowska-Curie Actions

DTU

Funded by the Horizon 2020 Framework Programme of the European Union

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Region Hovedstaden

REGION SJÆLLAND
– vi er til for dig

InSa-Drikkevand

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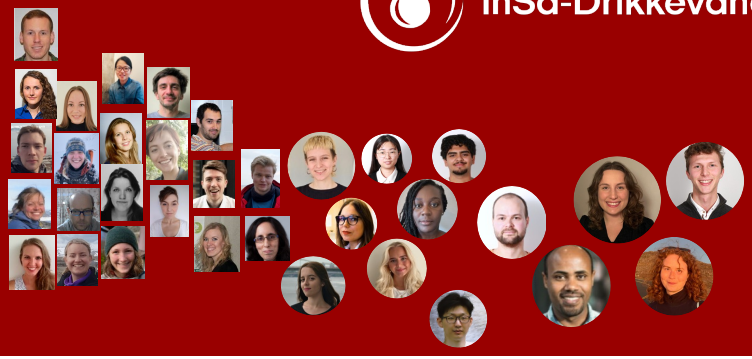

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