PREMIER

PRIORITISATION AND RISK EVALUATION OF MEDICINES IN THE ENVIRONMENT

PRIORITISATION AND RISK EVALUATION OF MEDICINES IN THE ENVIRONMENT

Tools to assess the environmental impact of pharmaceuticals in Europe

Instrumenten voor milieurisicobeoordeling van medicijnen in Europa

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 875508.
The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

PREMIER KENGETALLEN

Looptijd: 01/09/2020 tot 30/08/2026
Jaren: 6 (2020-26)

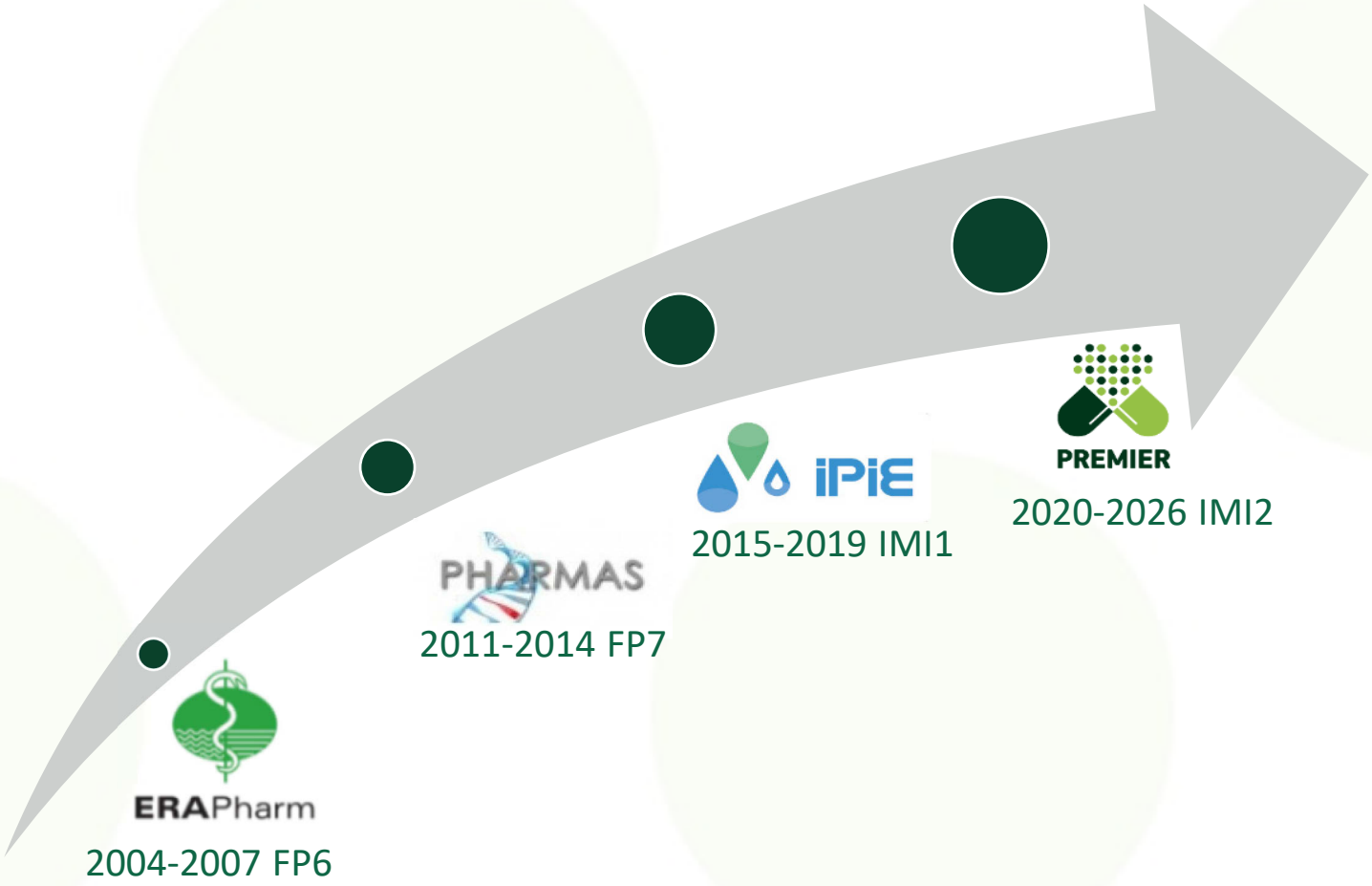
EFPIA bedrijven: 10
Academisch & MKB's: 15

Totaal Budget: € 9 Miljoen
IMI bijdrage: € 4,5 Miljoen (in cash)
EFPIA bijdrage : € 4,5 Miljoen (in kind)

Projectcoordinator:
Ad Ragas
Radboud Universiteit Nijmegen

Projectleider:
Stewart Owen
AstraZeneca AB

Historie van onderzoek naar medicijnresten



De uitdaging van PREMIER

De huidige strategie voor milieurisicobeoordeling van medicijnen is lastig te implementeren voor medicijnen die al voor 2006 op de markt waren, omdat:

Tijdrovend

Kostbaar

Dierenleed (dierproeven)

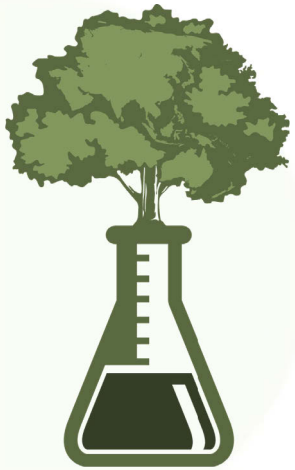
Gestuurd obv marktautorisatie (toelating)

Geef focus op medicijnen die de grootste problemen veroorzaken

Vereist een geidentificeerde eigenaar die de tests uitvoert en betaalt

VISIE

Bijdragen aan een duurzame toekomst door de milieurisico's van medicijnen pro-actief te beheersen



MISSIE

Doelstellingen:

1. **Instrumenten** voor milieurisicobeoordeling van medicijn(rest)en ontwikkelen
2. De haalbaarheid van **groene medicijnen** onderzoeken
3. Instrumenten voor **prioritering** van milieurisico's van medicijnen
4. Het genereren van milieurelevante gegevens van **25 medicijnen**

5. Toegankelijke **database** met milieurelevante egienschappen van geneesmiddelen.
6. Een **informatie- en beoordelingssysteem** van milieurisico's van humaan medicijngebruik
7. Handleidingen voor eindgebruikers

UITDAGINGEN

Maximalisatie van dataintegriteit

Voorkomen van duplicatie

Optimaal databeheer en het voorkomen foutieve risico-interpretaties

DEELNEMERS – CONSORTIUM

Onderzoeksinstellingen

Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

Fraunhofer ITEM

eawag aquatic research

LEUPHANA UNIVERSITÄT LÜNEBURG

Radboud University

IN DEI NOMINE FELICITER

UNIVERSITY of York

GÖTEBORGS UNIVERSITET

UNIVERSITY OF HELSINKI

UNIVERSITY OF EXETER

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

Regulerende instanties

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

MKB

teamit RESEARCH

eco logic

E·C·T Oekotoxikologie GmbH

Farmaceutische Industrie

Lilly

Roche

BAYER

Bristol Myers Squibb

MSD

AstraZeneca

SANOFI

NOVARTIS

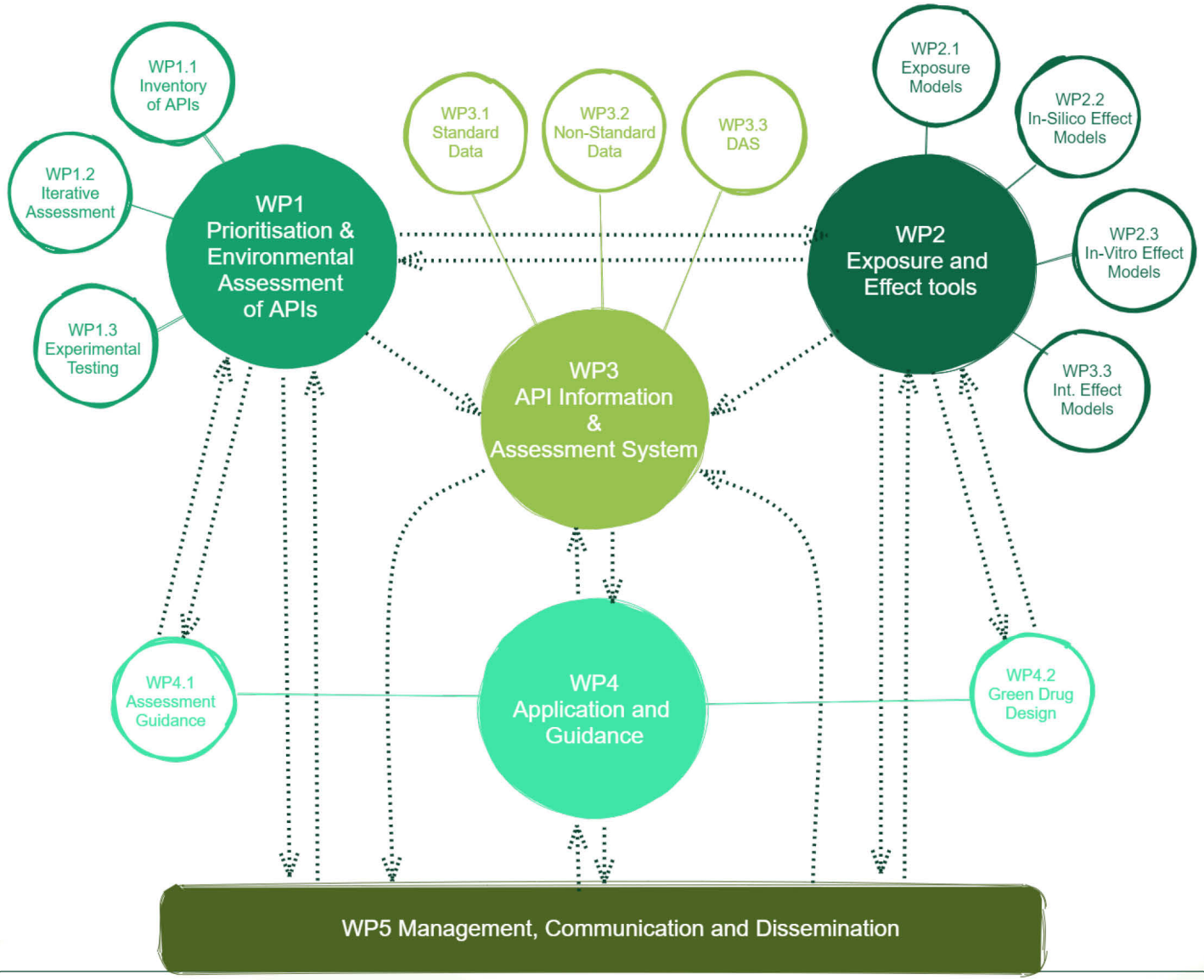
gsk

SERVIER

imi innovative medicines initiative

efpia

STRUCTUUR


WP1.1 Inventory of APIs
WP1.2 Iterative Assessment
WP1.3 Experimental Testing
WP1 Prioritisation & Environmental Assessment of APIs
WP3.1 Standard Data
WP3.2 Non-Standard Data
WP3.3 DAS
WP2.1 Exposure Models
WP2.2 In-Silico Effect Models
WP2.3 In-Vitro Effect Models
WP3.3 Int. Effect Models
WP2 Exposure and Effect tools
WP3 API Information & Assessment System
WP4.1 Assessment Guidance
WP4 Application and Guidance
WP4.2 Green Drug Design
WP5 Management, Communication and Dissemination

WP LEIDERS

WP1	WP2	WP3	WP4	WP5
Prioritisation & Environmental Assessment of APIs	Exposure and Effects Tools	API Information & Assessment System	Guidance & Application	Management, Communication and Dissemination

Ad Ragas (Radboud)

Andreas Haener (Roche)

Alistair Boxall (York)

Stewart Owen (AZ)

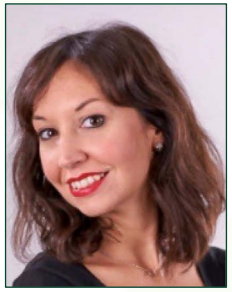
Adam Nellis (Simomics)

Reinhard Laenge (Bayer)

Caroline Moermond (RIVM)

Jutta Hellstern (Novartis)

Susanna Bicknell (Radboud)



Maica Llavero (TEAM-IT)

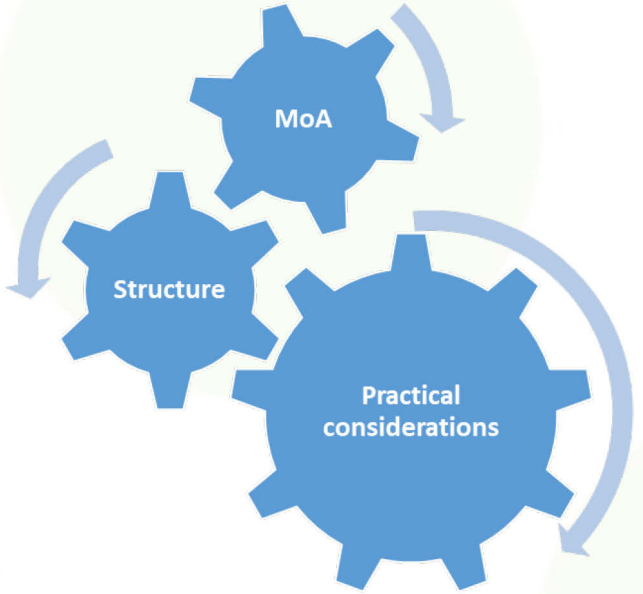
PRIORITERING EN SELECTIE VAN STOFFEN

Art 57 Database

	UGOT_Name	UGOT_CAS	UGOTID	ART57_Naam	ART57_CAS	ART57_SMILES
2	L-alpha-Glycerophosphorylethanolamin	33049-08-0	UGOT1106	(R)-Alpha-Glycerophosphorylethanolamine	33049-08-0	C(COP(=O)(O)OCC(C
3	1,4-Benzoquinone	106-51-4	UGOT1107	1,4-Benzoquinone	106-51-4*	C1=CC(=O)C=CC1=O
4	Iobenguane (131I)	77679-27-7	UGOT1108	131i-Meta-Iodobenzyl-Guanidine Sulfate	-	-
5	Methacetin methoxy-C-13	72156-70-8	UGOT1109	13c-Methacetin	72156-70-8	CC(=O)NC1=CC=C(C=
6	2-(2-Aminoethoxy)ethanol	929-06-6	UGOT1110	2-(2-Aminoethoxy)ethanol	929-06-6	C(COCCO)N
7	2,2,3,3-Tetrahydroxy-2,3-dihydronaphth	100343-43-9	UGOT1111	2,2,3,3-Tetrahydroxynaphthalene-1,4-Dione	100343-43-9	C1=CC=C2C(=C1)C(=
8	2,3-Dimercapto-1-propanesulfonic acid	74-61-3	UGOT1112	2,3-Dimercapto-1-propanesulfonic acid	74-61-3	C(C(CS(=O)(=O)O)S)S
9	Dichlorobenzyl alcohol	1777-82-8	UGOT1113	2,4 Dichlorobenzyl Alcohol	1777-82-8	C1=CC(=C(C=C1Cl)Cl
10	2-mercaptobenzothiazole	149-30-4	UGOT1114	2-mercaptobenzothiazole	149-30-4	C1=CC=C2C(=C1)NC(
11	2-Naphthol	135-19-3	UGOT1115	2-naphthol	135-19-3*	C1=CC=C2C=C(C=CC
12	Isopropyl alcohol	67-63-0	UGOT1116	2-propanol	67-63-0*	CC(C)O
13	Butedronic acid	51395-42-7	UGOT1117	3,3-Diphosphono-1,2-Propanedicarboxylic Acid	51395-42-7	C(C(C(P(=O)(O)O)P(=
14	3-Aminophenol	591-27-5	UGOT1118	3-Aminophenol	591-27-5	C1=CC(=CC(=C1)O)N
15	4-(Isopropylamino)diphenylamine	101-72-4	UGOT1119	4-(Isopropylamino)diphenylamine	101-72-4	CC(C)NC1=CC=C(C=C
16	4-Dimethylaminophenol hydrochloride	5882-48-4	UGOT1120	4-Dimethylaminophenol-Hydrochloride	5882-48-4	CN(C)C1=CC=C(C=C1
17	Aminolevulinic acid	106-60-5	UGOT1121	5-Aminolevulinic Acid	106-60-5	C(CC(=O)O)C(=O)CN
18	5-Ethyl-1-aza-3,7-dioxabicyclo[3.3.0]oct	7747-35-5	UGOT1122	7-Ethylbicyclooxazolidine	7747-35-5	CCC12COCN1COC2
19	Abacavir	136470-78-5	UGOT1123	Abacavir	136470-78-5*	C1CC1NC2=C3C(=NC
20	Abemaciclib	1231929-97-7	UGOT1124	Abemaciclib	1231929-97-7	CCN1CCN(CC1)CC2=
21	Acamprosate	77337-76-9	UGOT1125	Acamprosate	77337-76-9	CC(=O)NCCCS(=O)(=
22	Acarbose	56180-94-0	UGOT1126	Acarbose	56180-94-0	CC1C(C(C(C(O1)OC2

Prioritization Pipeline

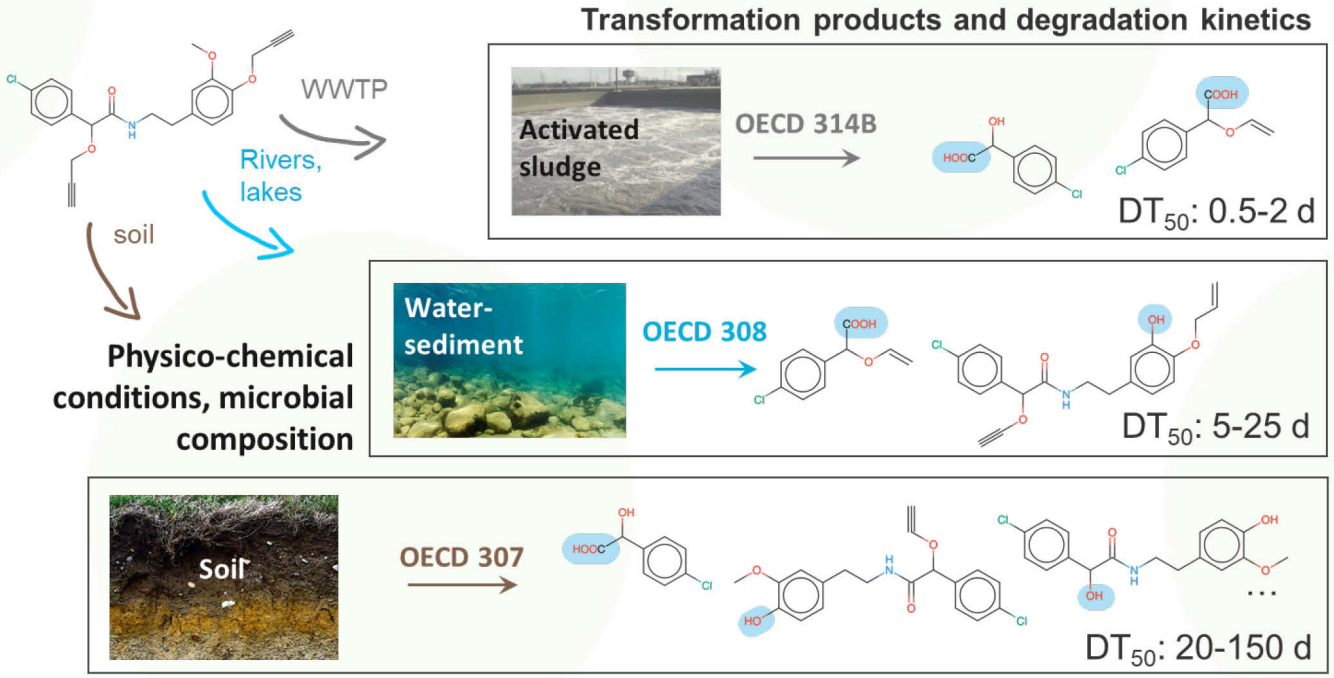
823 APIs without ecotox data



Candidates for Testing

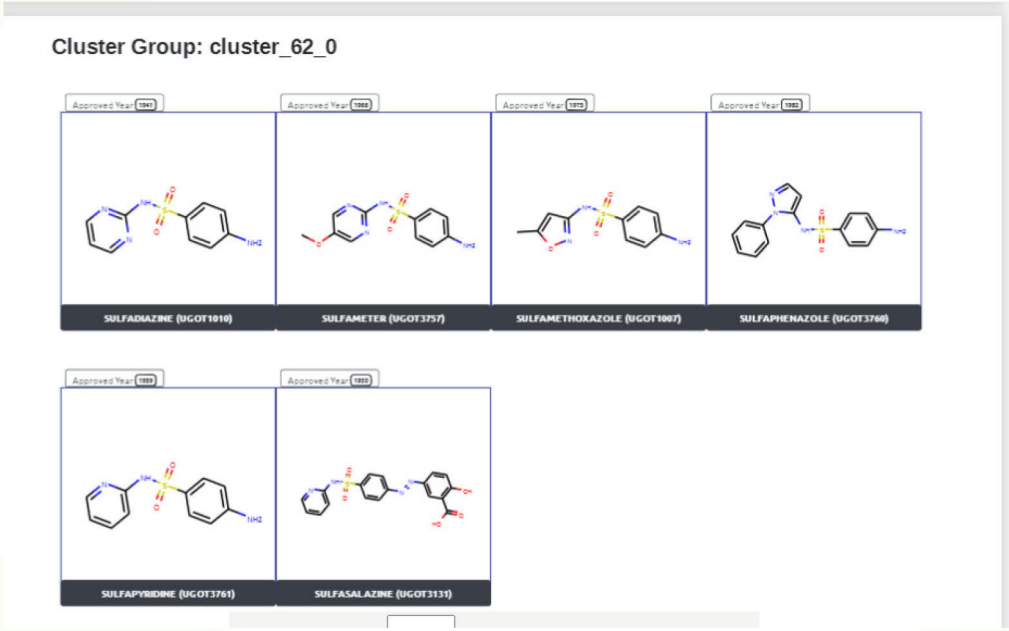
- **Muscle relaxants**
- **Prostaglandin analogues**
- **Antipsychotic drugs**
- **Antithrombotic agents**
- **Cough suppressants**

STRUCTUURWERKINGSRELATIES

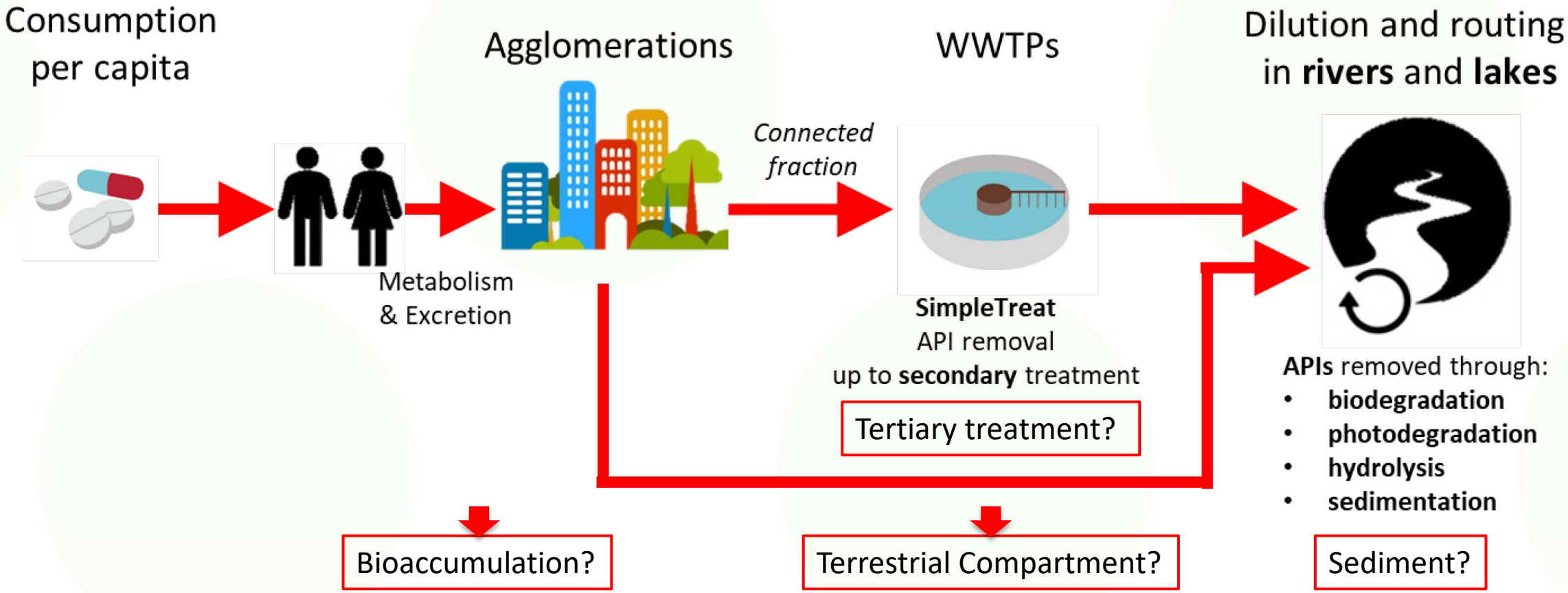


Biodegradation Modelling

Clustering APIs

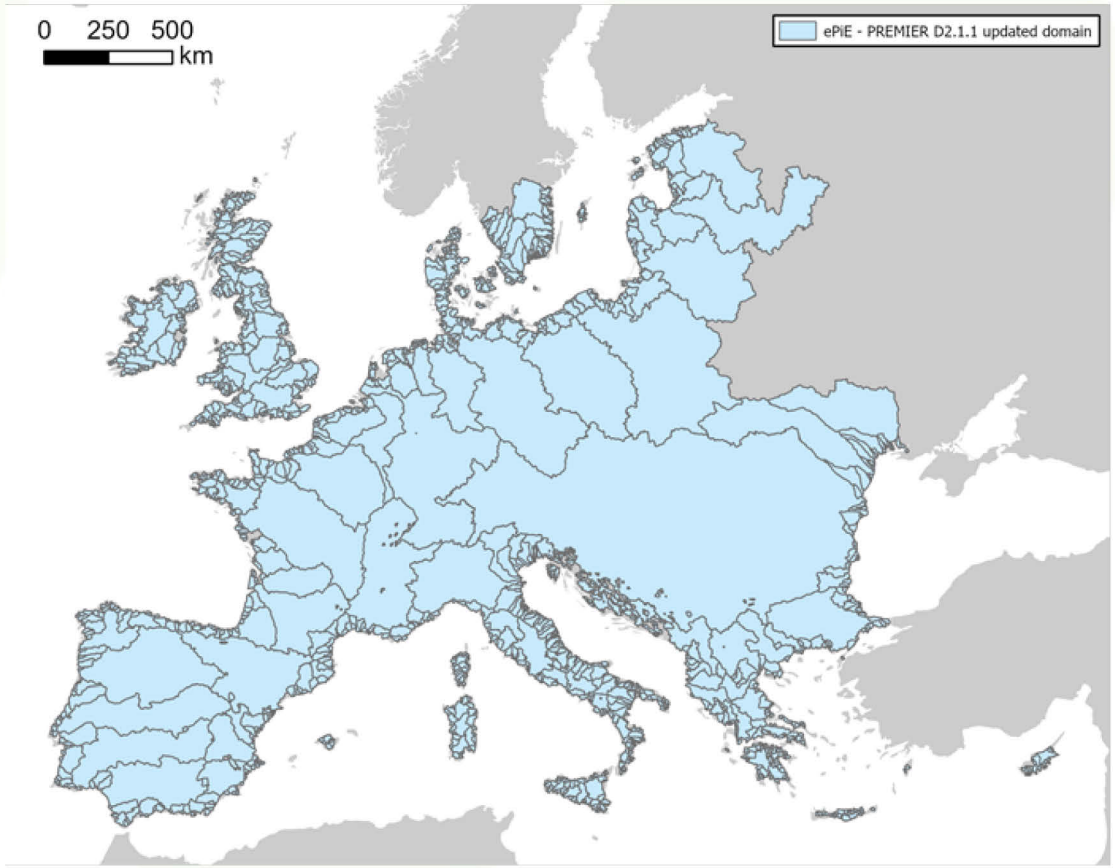


BLOOTSTELLINGSCONCENTRATIES: ePiE

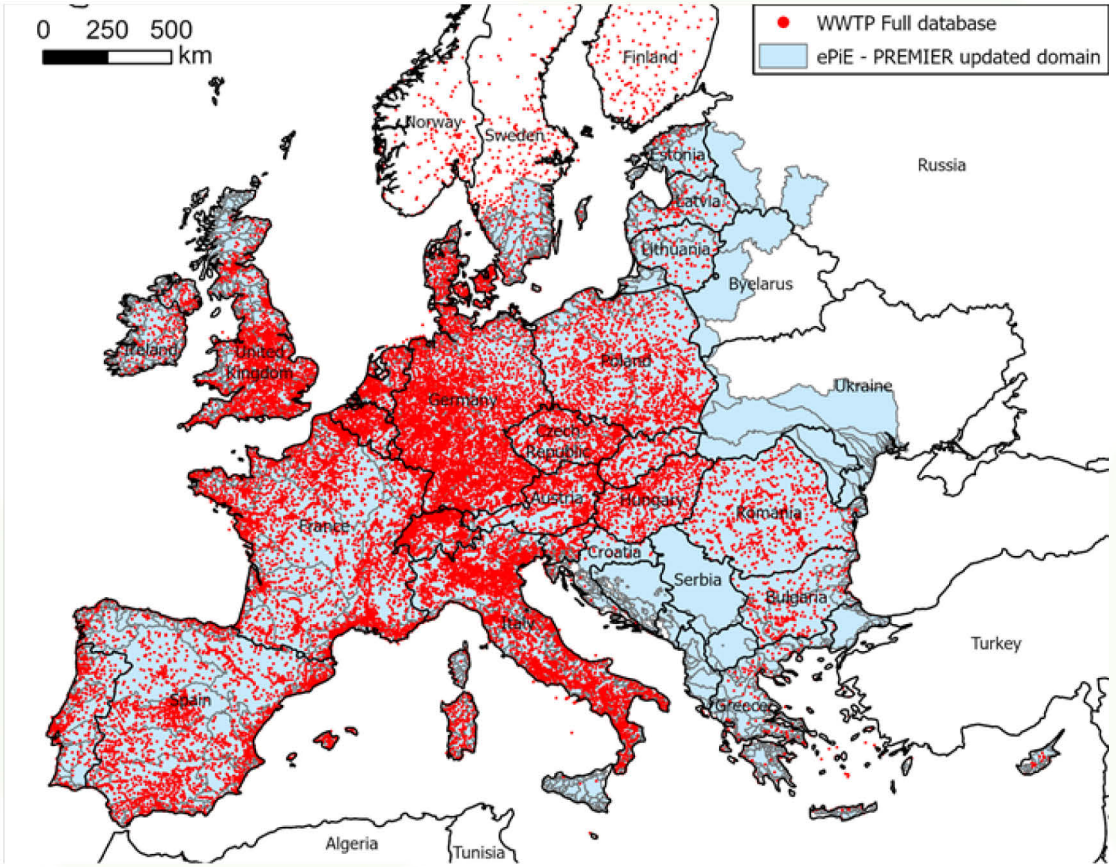


Ruimtelijk expliciet model

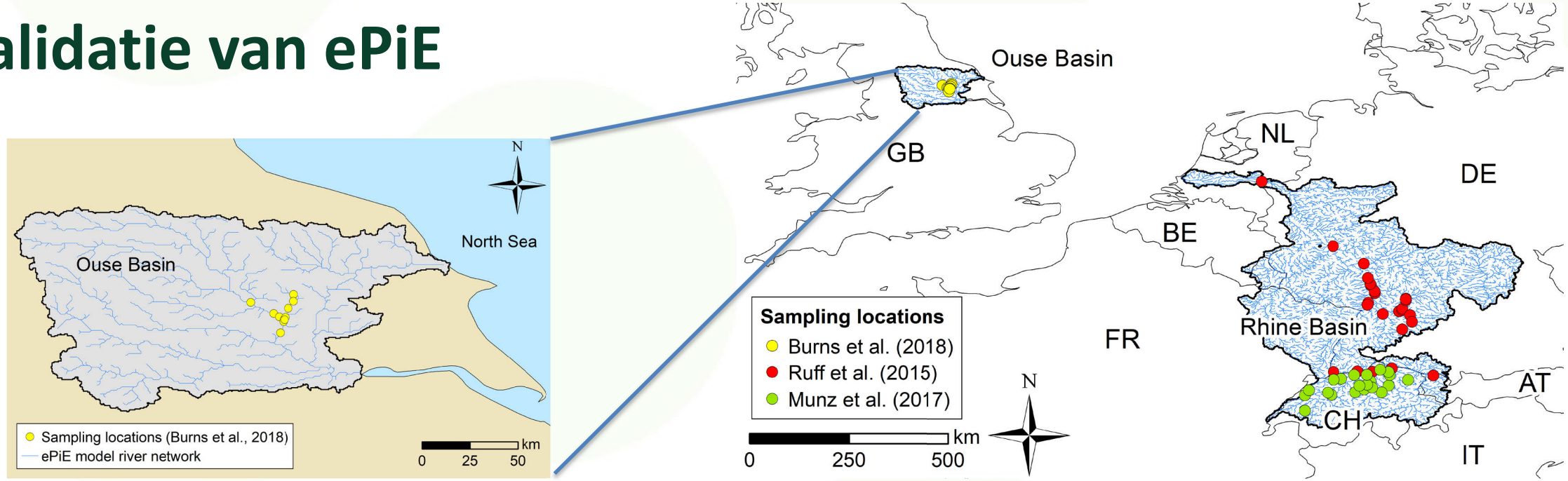
1474 river basins (>100 km^2)

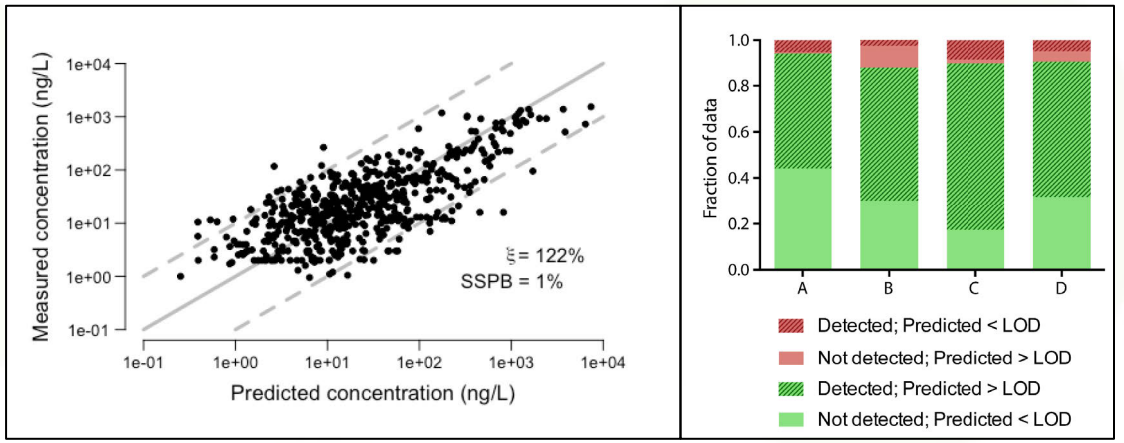


26,582 WWTPs



Validatie van ePiE





EFFECTSTUDIES

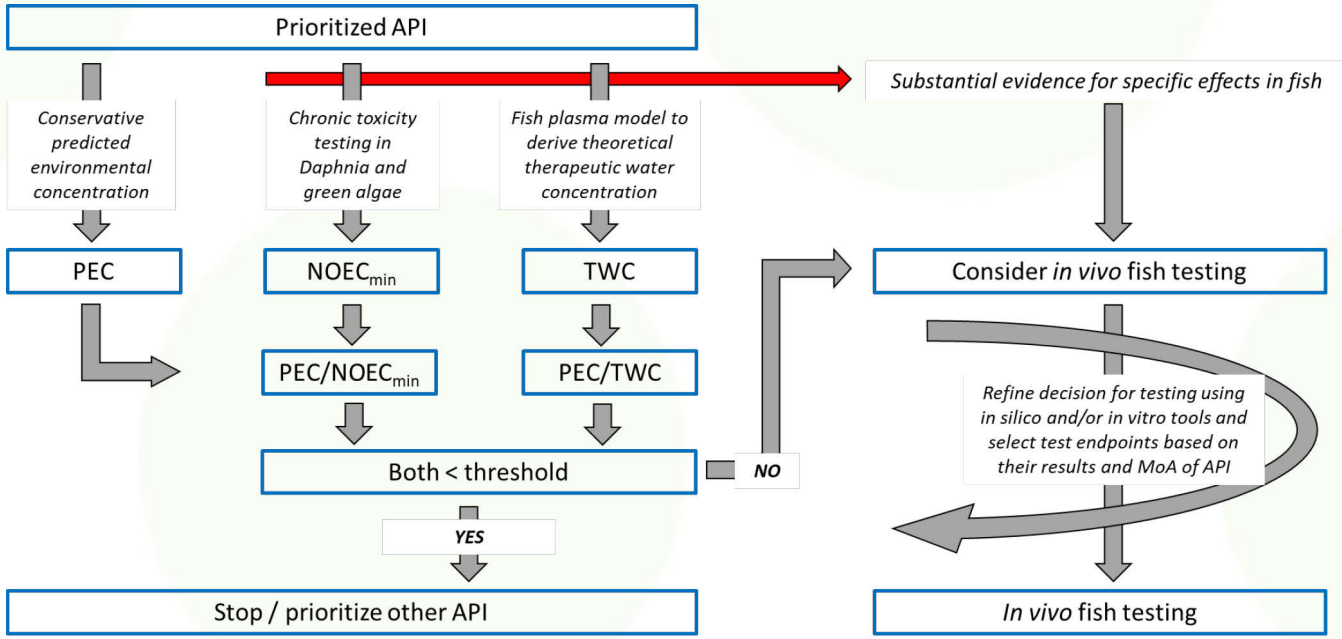
Opinion Paper (in preparation):

Minimising experimental testing on fish for legacy pharmaceuticals

Anja Coors, Ross Brown, Sam Maynard, Stewart Owen, Alison Perkins, Charles R. Tyler

(*Fish team working across PREMIER WPs 1 & 2*)

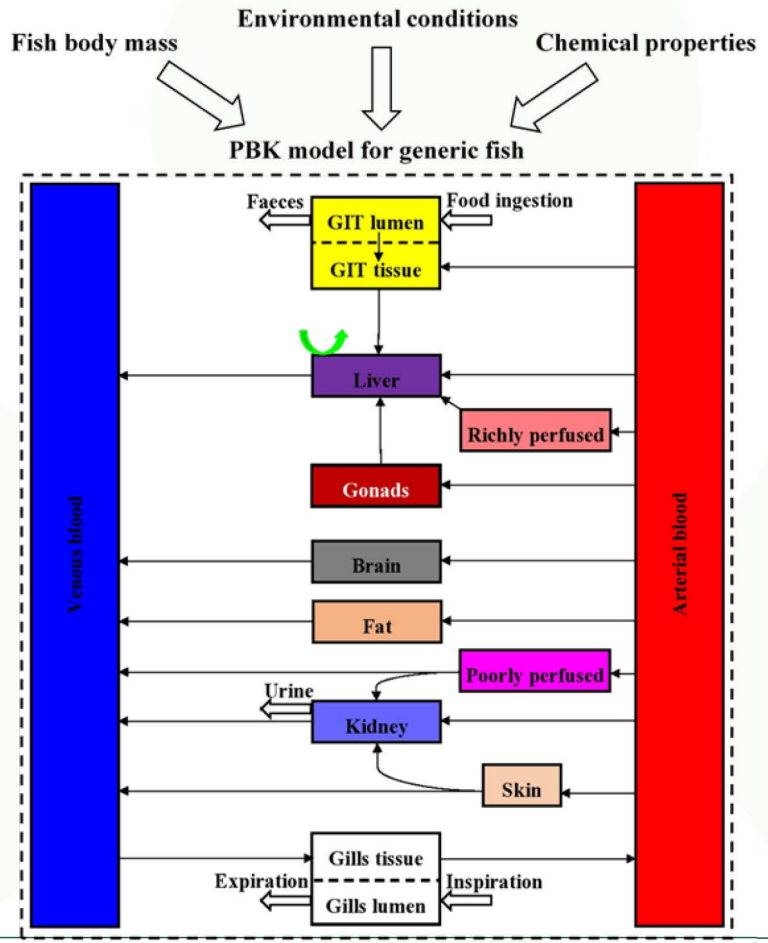
- Objective: Ensure that *in vivo* testing with fish is avoided as much as possible
- Developed & verified using EPAR data (Gunnarsson *et al.* 2019)
- To be applied in WP1 to (potential) case study APIs, but also to reach out beyond just PREMIER
- Decision tree developed using a risk-based approach and available knowledge on specific effects in fish
- Planned submission to GA in October and to IEAM in November (2021)



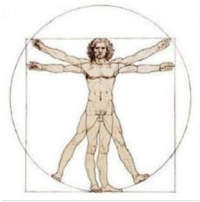
EFFECTSTUDIES

TOXICOKINETIEK

In vitro vis assays:
- Absorptie
- Metabolisme

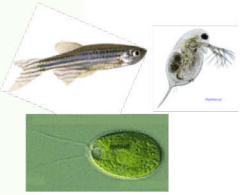


TOXICODYNAMIEK

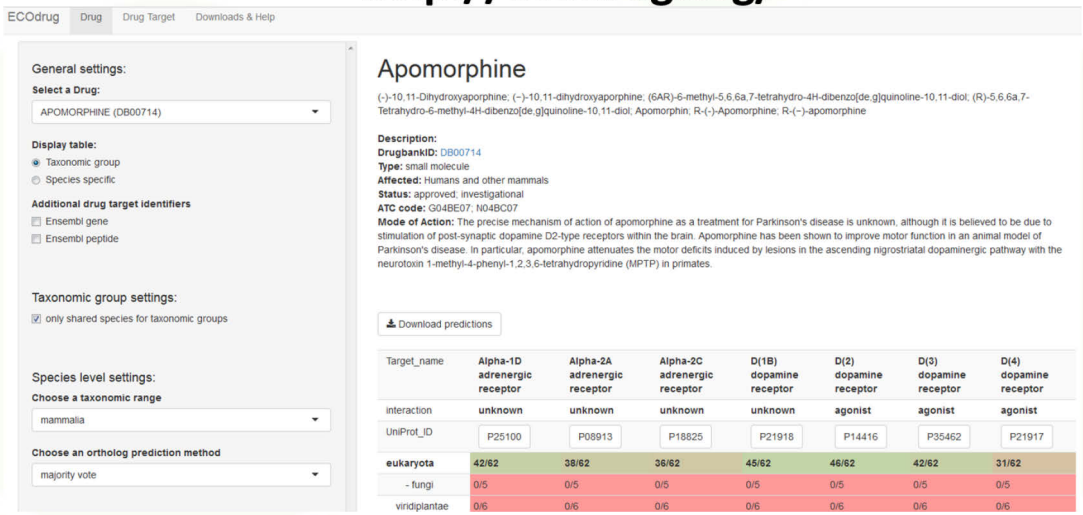


Are pharmacological effects conserved?

Prediction of orthologs of drug targets is a first step to answer this question

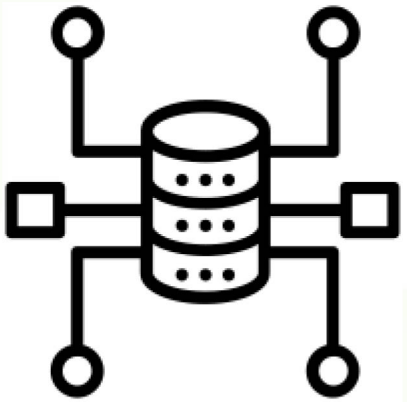


http://ecodrug.org/



DATABASE

Database Structure



Importing data from iPiE

iPiE-SYS

The SALTS issue

Data Quality

Score	
R1	Reliable without restrictions: All critical reliability criteri contain flaws that affect the reliability of the study.
R2	Reliable with restrictions: The study is generally well des
R3	Not reliable: Not all critical reliability criteria for this stu
R4	Not assignable: Information needed to make an assessme details and that are only listed in abstracts or secondary assessment of reliability for one or more vital paramet

[a]Adapted from Klimisch et al. [3].

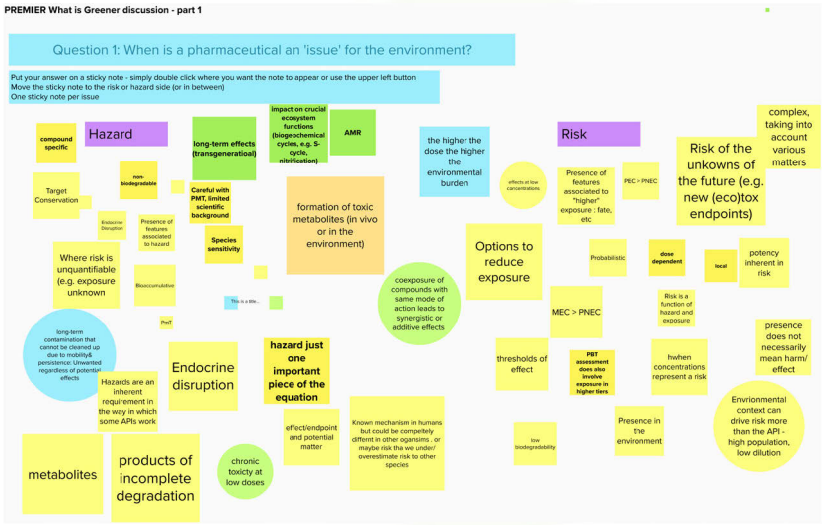
Data Extraction Sheets

	AQ	AR	AS	AT	AU	AV
1	**Environment table:**					
2	**Environment Type**	**Parameter**	**Value Text**	**Value Lower**	**Value Upper**	**Value Unit**
3	Culture media	Temperature				C
4	Culture media	pH				NA
5	Culture media	Salinity				
6	Culture media	Hardness				
7	Culture media	Enter name & concentration of ion			for each buffer/ion)	
8	Culture media	Ionic strength				M
9	Culture media	Total Organic Carbon (TOC)				
10	Culture media	Dissolved Organic Carbon (DOC)				
11	Culture media	Microbial biomass				cell number
12	Culture media	Oxygen content				

Value Range/Text
Value for the environmental parameter where this is text (eg room temperature). For exact number values and ranges please use the columns named "value

TOEPASSING & ONDERSTEUNING

Workshop on What are greener APIs?



Stakeholder Survey

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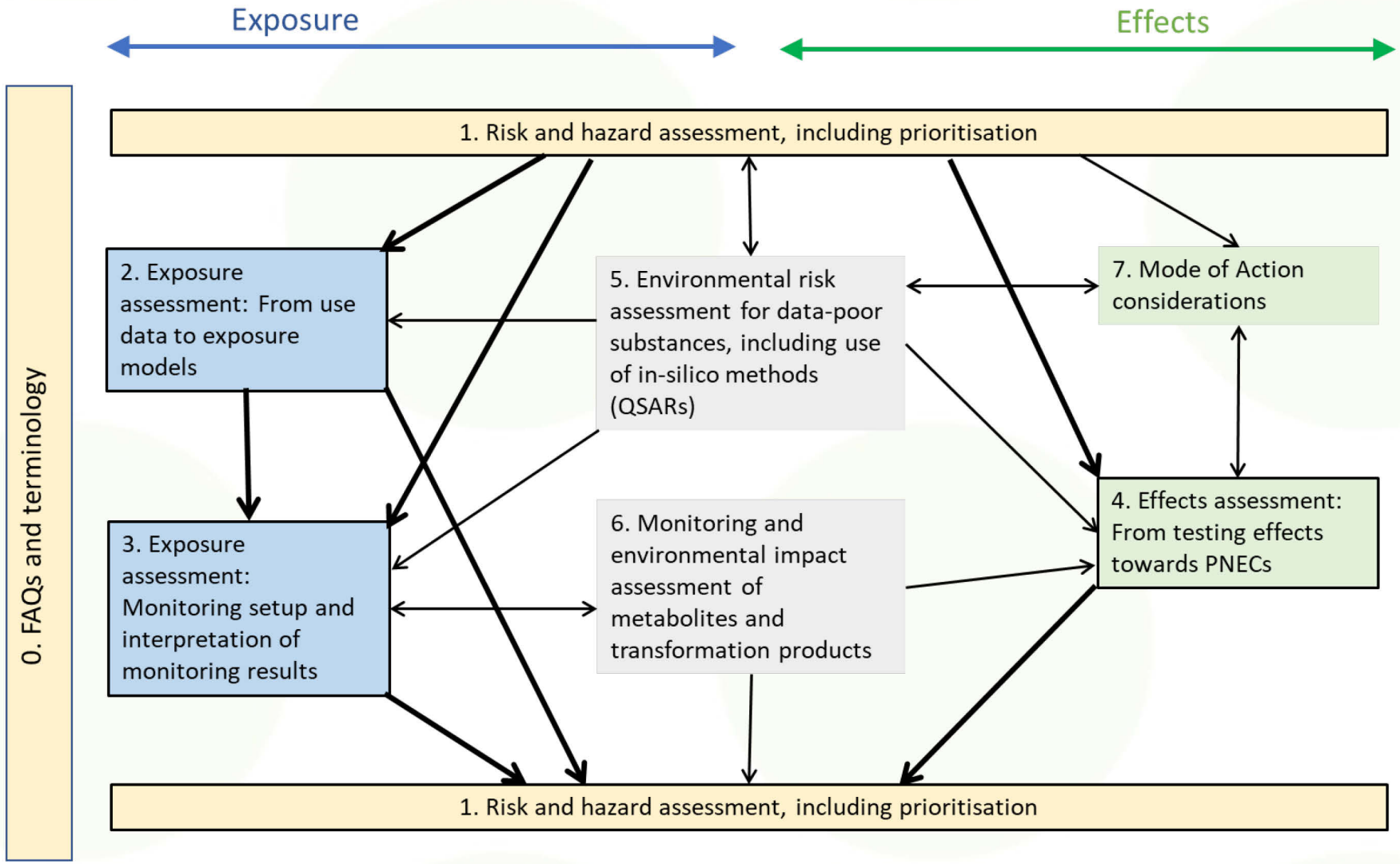
View this email in your browser

What are the needs of stakeholders regarding the environmental risk assessment of pharmaceuticals? Participate in our Survey!

The survey is now online until the 19 July!!

Interviews on Designing Green APIs

PRAKTISCHE HANDLEIDINGEN



DANK VOOR UW AANDACHT!