Environmental Risk Assessment

S. KAROLAK – M1 D2HP – 2024-2025

Some effects observed

Population decline due to sexual immaturation in 1980 Apopka lake, Florida
Florida Science, 1993

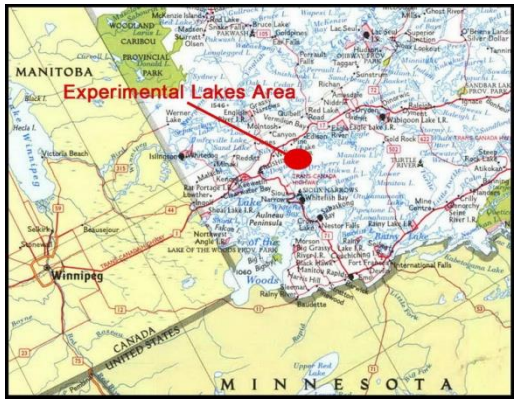
Diclofenac: 0,025 grammes/kg Mediterranean Sea
Scientific Council of the Lérins Islands 2020

Tramadol 1 µg/L in water for 42 days, impairs chub behavior with anxiolytic-like effects, less bold and less social individuals
Ecotoxicology and Environmental Safety, 2021

Renal failure, death due to Diclofenac in carcasses
Environmental Pollution, 2007

Diclofenac, 5µg / L, 28 days
Kidney damage
Bioaccumulation: kidney, liver, gills and muscle
Aquatic Toxicology, 2004

Clofibrate, 500 µg / L,
Growth retardation, malabsorption syndrome
Toxicology and Applied Pharmacology, 2008



58 small preserved lakes

FH

PD

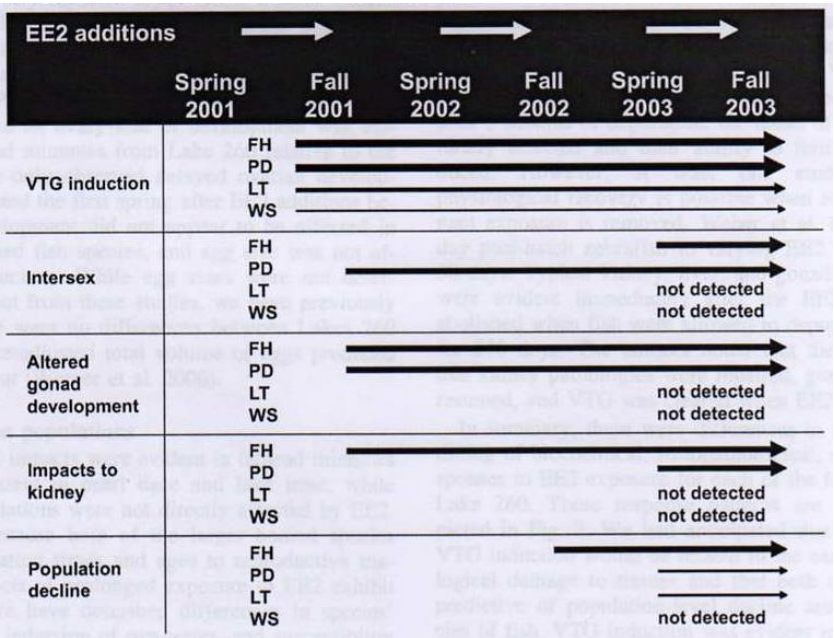
LT

WS

3 successive summers
Ethinylestradiol ≈ ng/L

Near extinction small fish
Reduction in the number of large fish

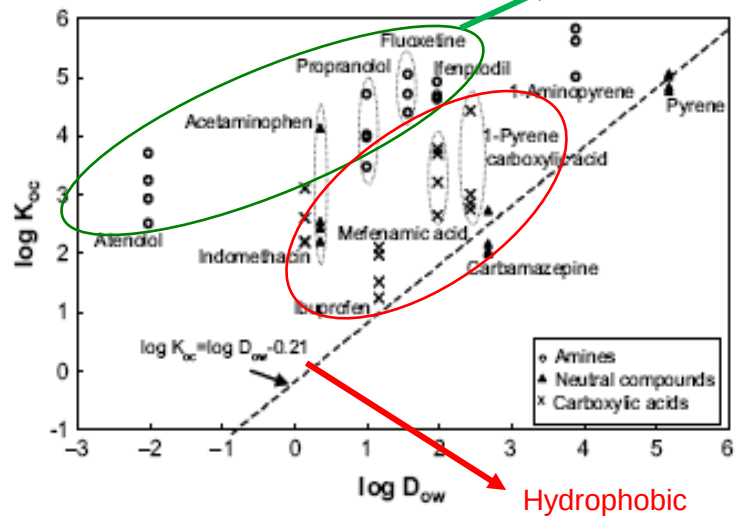
3 years later: normal return



Palace, V.P., R.E. Evans, K.G. Wautier, K.H. Mills, P.J. Blanchfield, B.J. Park, C.L. Baron, **K.A. Kidd**. 2009. Ethynylestradiol (EE2) added to a whole lake induced different biochemical, histopathological and population level responses in four species of wild fish. Can. J. Fish. Aquat. Sci. 66: 1920-1935.

Physicochemical parameters conditioning the fate of pharmaceuticals

+ others mechanisms



Hydrophobic interactions are the main mechanism of sorption

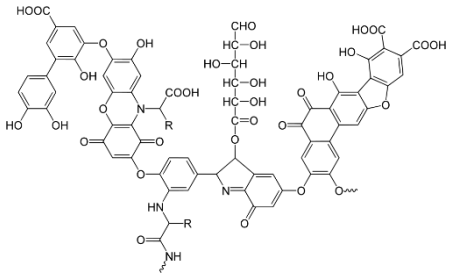
- **Mechanism for removal from water**
  - Sorption on soils and sediments
  - Bioaccumulation
  - Biodegradation
  - Photodegradation

- **Related to the molecule:**
  - pK_a
  - log K_d
  - log K_{oc} → Kd = K_{oc} x f_{oc} and K_{oc} = $C_{org.carbon}$ / C_{water}
  - Log $_{Kow}$

  Log K_{ow} > 5: sorbed to soils and sediments, remove from water
  Log K_{ow} < 2.5: poorly absorbed, mainly in water phase
  - K_H

- **Related to environment**
  - Temperature
  - Sun light: main abiotic elimination route

  New organic compounds : acridine carcinogenic and mutagenic photodegradation metabolite from CBZ
  $t_{1/2}$ cbz 2400-10 000 h ; $t_{1/2}$ ibu 19-230 h
  - Nature of the soil
  - Microorganism communities
  - Presence of divalent cations (Ca^{2+}, Mg^{2+}) → complexes with tetracyclines
  - Humic acids content → reversible association with cationic macrolides
  - Water salinity → adsorption to the sediment of estrone increases in see water



Risk assessment

- Assessment of contamination of water & drinking water resources

- Hazard assessment

Risk = exposure x hazard

First case:
Environmental risk assessment for a given location

Which molecules? what effects? on which species? Environmental risk? Health risk?

Prioritization

⇨ Inability to search for all pharmaceutical molecules

- Consumption → larger quantities consumed
- Toxicity → higher potential for toxicity
- Estimation of environmental concentrations
- Analytical capability → comparison MEC/PEC

Score of exposure

Score of hazard

Exposure score: Consumption data

Statistics from CNAM
Specific data: dispatchers, hospitals, region…

rank	Product	DCI	Therapeutic class	Number of boxes
1	**DOLIPRANE (17)**	PARACETAMOL	ANALGESIC	308,2 M
2	DAFALGAN	PARACETAMOL	ANALGESIC	71,6 M
3	LEVOTHYROX	LEVOTHYROXINE SODIQUE	DRUG FOR THYROIDE	31,6 M
4	KARDEGIC	ACIDE ACETYLSALICYLIQUE	ANTITHROMBOTIC	26,7 M
5	EFFERALGAN MED	PARACETAMOL	ANALGESIC	23,9 M
6	ZYMAD	COLECALCIFEROL	VITAMIN	23,2 M
7	SERESTA	OXAZEPAM	PSYCHOLEPTIC	18,4 M
8	MACROGOL	MACROGOL	LAXATIVE	17,8 M
9	**ELIQUIS (1)**	APIXABAN	ANTITHROMBOTIC	13,7 M
10	DAFALGAN CODEINE	PARACETAMOL + CODEINE	ANALGESIC	13,6 M
11	LAMALINE GELULE	PARACETAMOL + OPIACE + CAFEINE	ANALGESIC	13,4 M
12	VENTOLINE	SALBUTAMOL	PULMONARY OBSTRUCTION	12,8 M
13	METHADONE	METHADONE	CENTRAL NERVOUS SYSTEM DRUG	12,3 M
14	IZALGI	PARACETAMOL + OPIACE	ANALGESIC	12,1 M
15	AMOXICILLINE VIATRIS	AMOXICILLINE	ANTIBACTERIAL	11,5 M
16	PARACETAMOL BGA	PARACETAMOL	ANALGESIC	11,1 M
17	BISOPROLOL VIATRIS	BISOPROLOL	BETABLOCKER	10,7 M
18	ATORVASTATINE BGA	ATORVASTATINE	LIPID-MODIFYING AGENT	10,0 M
19	SPASFON CPR	PHLOROGLUCINOL	GASTROINTESTINAL DISORDER	9,7 M
20	BISOPROLOL REF	BISOPROLOL	BETABLOCKER	9,7 M

Data for year 2023

Assessment of quantity of paracetamol consumned during one year

rang	Product	DCI	Dose / number tablets per box	Number of boxes
1	DOLIPRANE	PARACETAMOL	500 mg / 16	308,2 M
2	DAFALGAN	PARACETAMOL	500 mg / 16	71,6 M
5	EFFERALGAN MED	PARACETAMOL	500 mg / 16	23,9 M
10	DAFALGAN CODEINE	PARACETAMOL + CODEINE	500 mg / 16	13,6 M
11	LAMALINE GELULE	PARACETAMOL + OPIACE + CAFEINE	300 mg / 16	13,4 M
14	IZALGI	PARACETAMOL + OPIACE	500 mg / 16	12,1 M
16	PARACETAMOL BGA	PARACETAMOL	500 mg / 16	11,1 M
			Total	453,9 M

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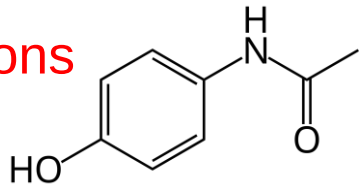
16	PARACETAMOL BGA	PARACETAMOL	500 mg / 16	11,1 M
			Total	453,9 M

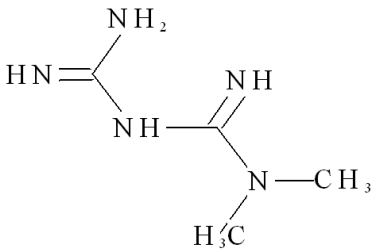
500 mg x 16 tablets x $453{,}9.10^6$ x 1/1000000000 = 3630 Tons

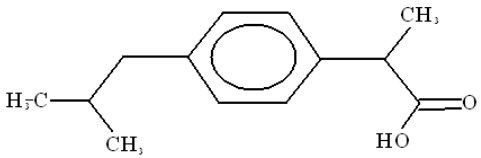


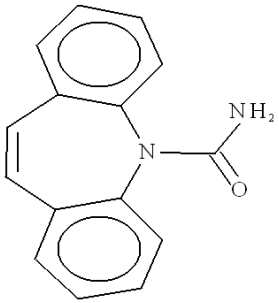
Exposure score: prediction of environmental levels

- Pharmacokinetic properties: fraction not metabolized? Metabolites?
- Percentage of removal in WWTPs

molecule	MM g/mol	logKow	Solubility mg/L	pKa	UMF (%)	WWTP removal
metformin	129,2	-2,64	1000000	12,4	100%	
ibuprofene	206,3	3,97	21	4,91	1-10%	99% (STE, 2009) 96% (WR 2009)
carbamazépine	236,3	2,45	17,7	13,9	1-2%	<0,1% (WR 2009)







MEC: Some data in the world

CBZ	country	concentration
WWTP influent	China	45
	Cyprus	460-4023
	Germany	1310
	India	22-900
	Portugal	50-673
WWTP effluent	China	34
	Cyprus	LOD-5520
	Germany	1542
	Greece	125
	India	22-840
	Japan	48-383
	Jordan	0.4-3.6
	Portugal	245-396
surface river	China	LOD-37.4
	Serbia	LOD-35.5
	Portugal	24.9-214
	Bangladesh	LOD-8.8
	Sweden	0.4-0.5
	USA	LOD-0.17
	Vietnam	LOD-0.53
underground water	Serbia	3.4
	Taiwan	0.4-37.9
	Italy	1.1
drinking water	China	0,5-38
	Serbie	LOD-8,7

10%

SMX	country	concentration
WWTP influent	Cyprus	178-350
	Germany	320.8
	India	55-2260
	Portugal	529-19118
WWTP effluent	Cyprus	LOD-290
	Germany	118.5
	Greece	80
	India	120-552
	Jordan	LOD-0.9
	Portugal	340-1679
surface river	Bangladesh	LOD-7.2
	China	0.4-115
	Portugal	43
	China	LOD-9
	Sweden	0.075-0.14
	USA	LOD-3.2
underground water	Taiwan	0.1-1820
drinking water	China	LOD-1,8
	USA	ND-0,39

50%

IBU	country	concentration
WWTP influent	Cyprus	1680-5315
	India	834-4460
	Portugal	LOD-4927
WWTP effluent	Cyprus	LOD-82
	India	145-2140
	Jordan	LOD-5.7
	Portugal	LOD-369
surface river	China	LOD-242
	Serbie	LOD-346
	Colombie	5-62
	Portugal	222-1317
	South Africa	524-17600
	Sweden	2.2
	USA	LOD-5
	Vietnam	0.1-0.6
underground water	Serbia	92
	Taiwan	7-837
drinking water	China	LOD-17
	USA	ND-1,2

95%

Measured concentrations (ng/L) review since 2013

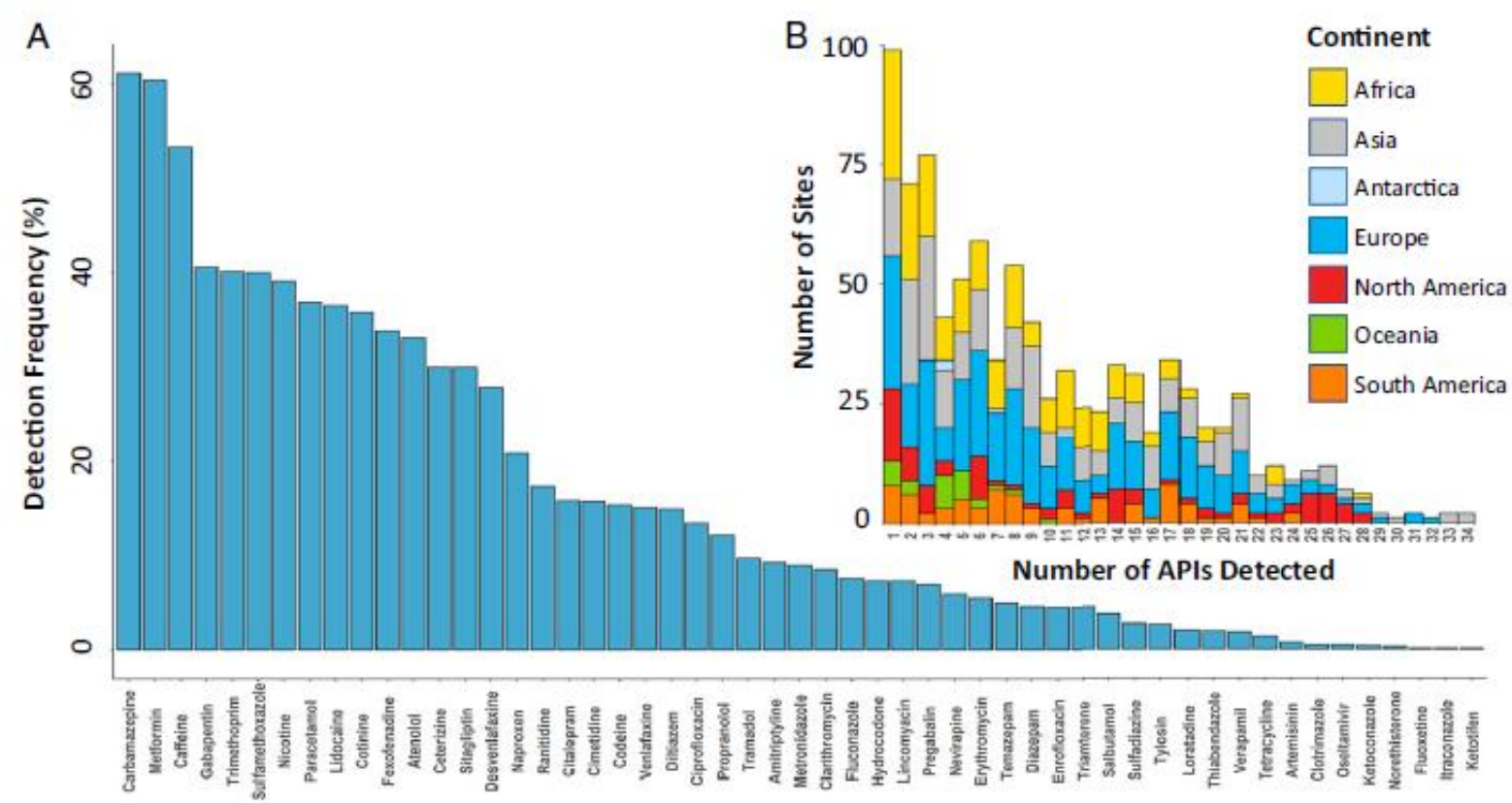
Percentage of removal in STP

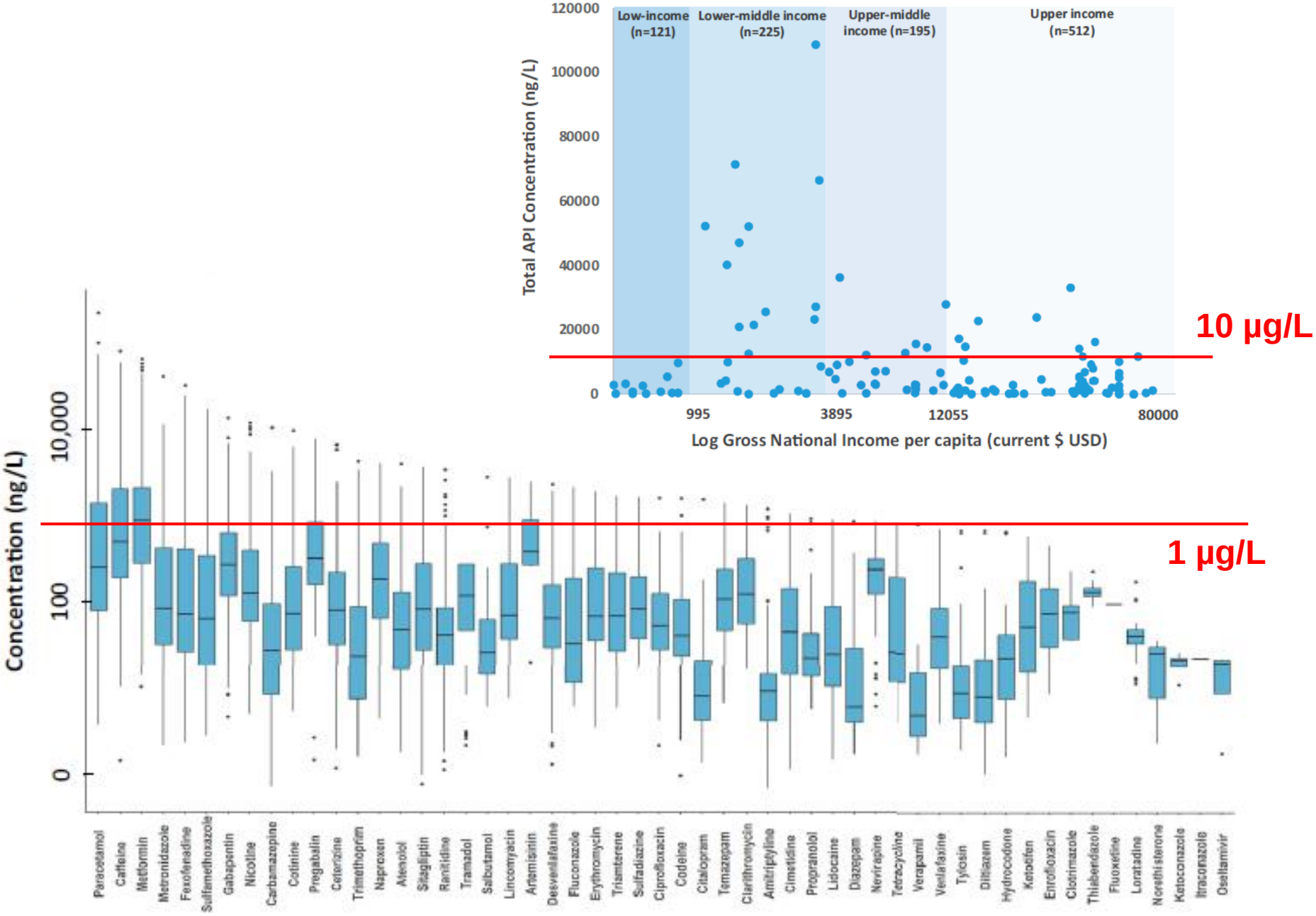
Patel et al; Chem. Rev. 2019

Pharmaceutical pollution of the world's rivers

Proceedings of the National Academy of Sciences AS 2022 Vol. 119 No. 8

→ 1052 sampling sites; 258 rivers ; 104 countries ; all continents ; 471,4 M people ; 61 API




Low-income (n=121)
Lower-middle income (n=225)
Upper-middle income (n=195)
Upper income (n=512)
Total API Concentration (ng/L)
120000
100000
80000
60000
40000
20000
0
995
3895
12055
80000
Log Gross National Income per capita (current $ USD)
10 µg/L
1 µg/L
Concentration (ng/L)
10,000
100
0
Paracetamol
Caffeine
Metformin
Metronidazole
Fexofenadine
Sulfamethoxazole
Gabapentin
Nicotine
Carbamazepine
Cotinine
Pregabalin
Cetirizine
Trimethoprim
Naproxen
Atenolol
Sitagliptin
Ranitidine
Tramadol
Salbutamol
Lincomycin
Artemisinin
Desvenlafaxine
Fluconazole
Erythromycin
Triamterene
Sulfadiazine
Ciprofloxacin
Codeine
Citalopram
Temazepam
Clarithromycin
Amitriptyline
Cimetidine
Propranolol
Lidocaine
Diazepam
Nevirapine
Tetracycline
Verapamil
Venlafaxine
Tylosin
Diltiazem
Hydrocodone
Ketoiofen
Enrofloxacin
Clotrimazole
Thiabendazole
Fluoxetine
Loratadine
Norethisterone
Ketoconazole
Itraconazole
Oseltamivir

Score of hazard: databases

➢ Toxicity

Toxicological data:

acute: LC50, EC50

chronic: LOEC, NOEC, ChV

Databases: https://pubchem.ncbi.nlm.nih.gov/

https://products.coastalscience.noaa.gov/peiar/

https://substances.ineris.fr/

➢ Therapeutic dosage

MRTD

https://drugcentral.org/

DDD

https://www.whocc.no/atc_ddd_index

https://www.theriaque.org/apps/contenu/accueil.php

ATC code	Name	DDD	U	Adm. R
A10BA02	metformin	2	g	O
M01AE01	ibuprofen	1.2	g	O
N03AF01	carbamazepine	1	g	O

Metformin 50 mg/kg

Ibuprofene 40 mg/kg

Carbamazepine 26,7 mg/kg

Score of hazard: prediction

ECOSAR ⇨ estimation of the water toxicity of chemicals

Acute: LC50 fish, LC50 daphnia, EC50 algae
Chronic: ChV fish, Daphnia, algae

- mathematic models (SAR)
- 40 chemical classes

Ex: acrylates log (48hLC50) = 0,00886 – 0,51136logKow (Daphnia)

- Validation with 462 chemical products

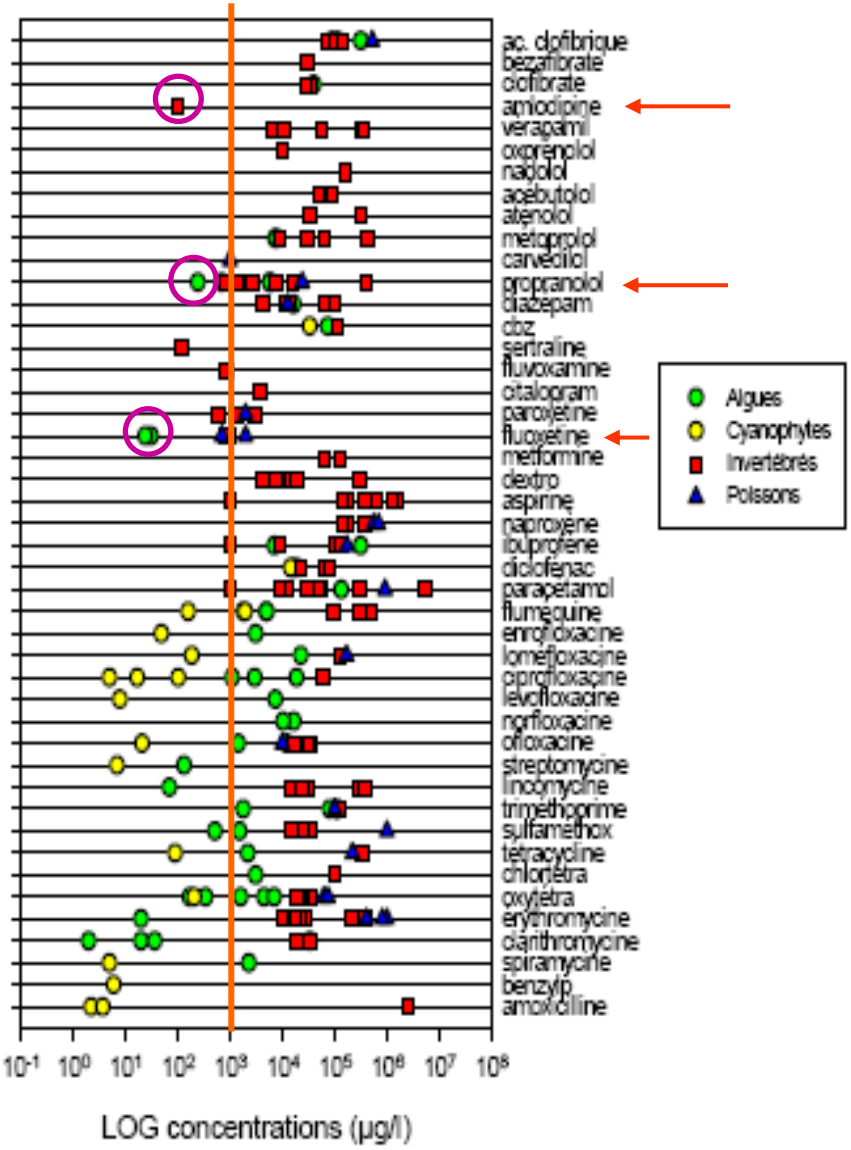
EPI suite ⇨ estimation of physicochemical properties and behavior in the environment:

- Kowwin
- Kocwin
- Hydrowin

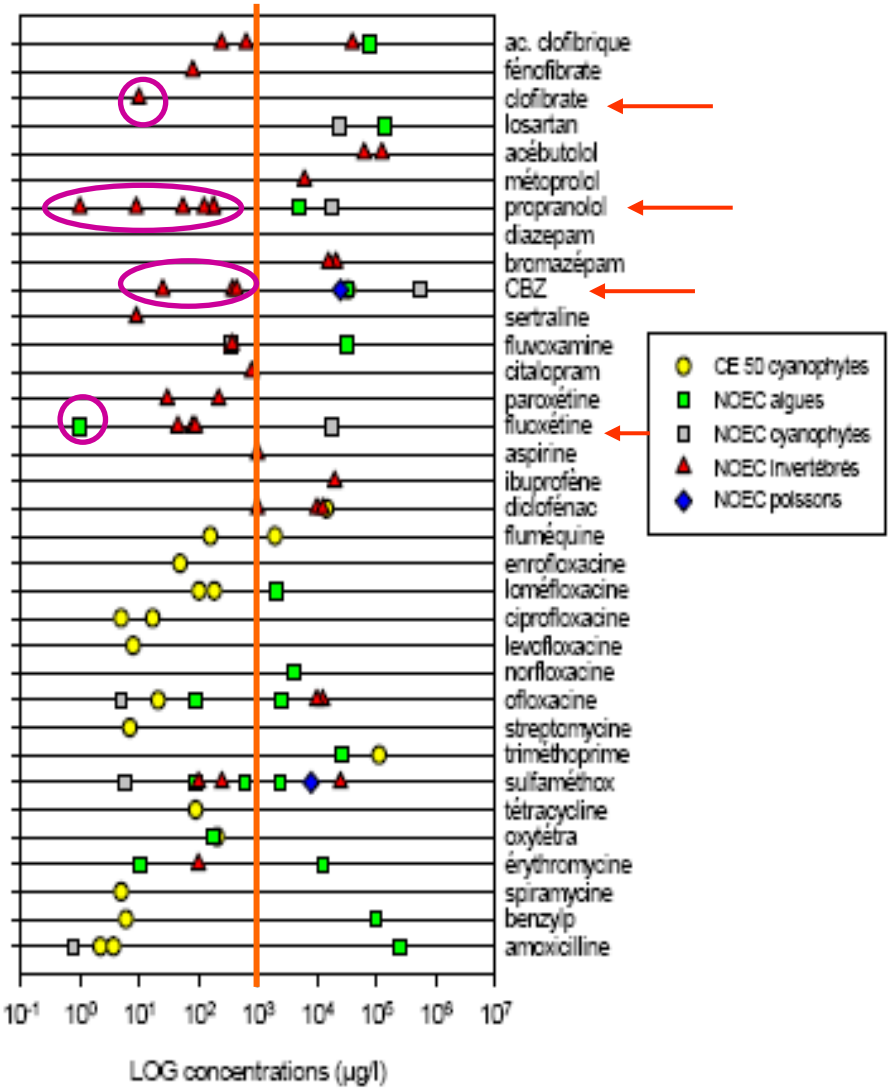
The OECD (Q)SAR Application Toolbox

	ECOSAR		NCCOS / *INERIS*
Molecule	**Acute toxicity** Fish: LC50, 4 days Daphnia: EC50 2 days Algae: LC50 4 days	**Chronic toxicity** ChV Fish ChV Daphnia ChV Algae	**Lowest toxic conc.** Fish Daphnia Algae
Metformin (aliphatic amine)	14 034 mg/L 542 mg/L 52 mg/L	163 mg/L 0,04 mg/L 70 mg/L	LC50 > 982 mg/L EC50 130 mg/L No data
Ibuprofene (organic acid)	42 mg/L 31 mg/L 32 mg/L	4,9 mg/L 4,8 mg/L 16,4 mg/L	LC50 4 days 173 mg/L EC50 2 days 108 mg/L EC50 3 days 315 mg/L
Carbamazepine (amide)	19,3 mg/L 11,8 mg/L 0,4 mg/L	0,11 mg/L 0,16 mg/L 0,40 mg/L	*EC50 4 days 35.4 mg/L* *EC50 2 Days 97,8 mg/L* *EC50 4 days 31.6mg/L*

Toxicité aiguë des composés pharmaceutiques



Toxicité chronique des pharmaceutiques



Référence à citer :

Besse J.P.; Garric J. (2007) *Médicaments à usage humain: risque d'exposition et effets sur les milieux récepteurs. Proposition d'une liste de médicaments à usage humain à surveiller dans les eaux de surface continentales.* Agence de l'Eau R.M.C., Lyon, 241 p.

Effects of mixtures

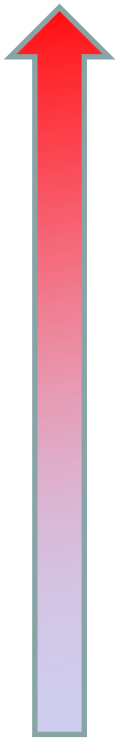
Daphnia immobilization test:
- clofibric acid → 1% immobilization
- CBZ → 16% immobilisation
- clofibrique acid + CBZ: → 95% immobilization

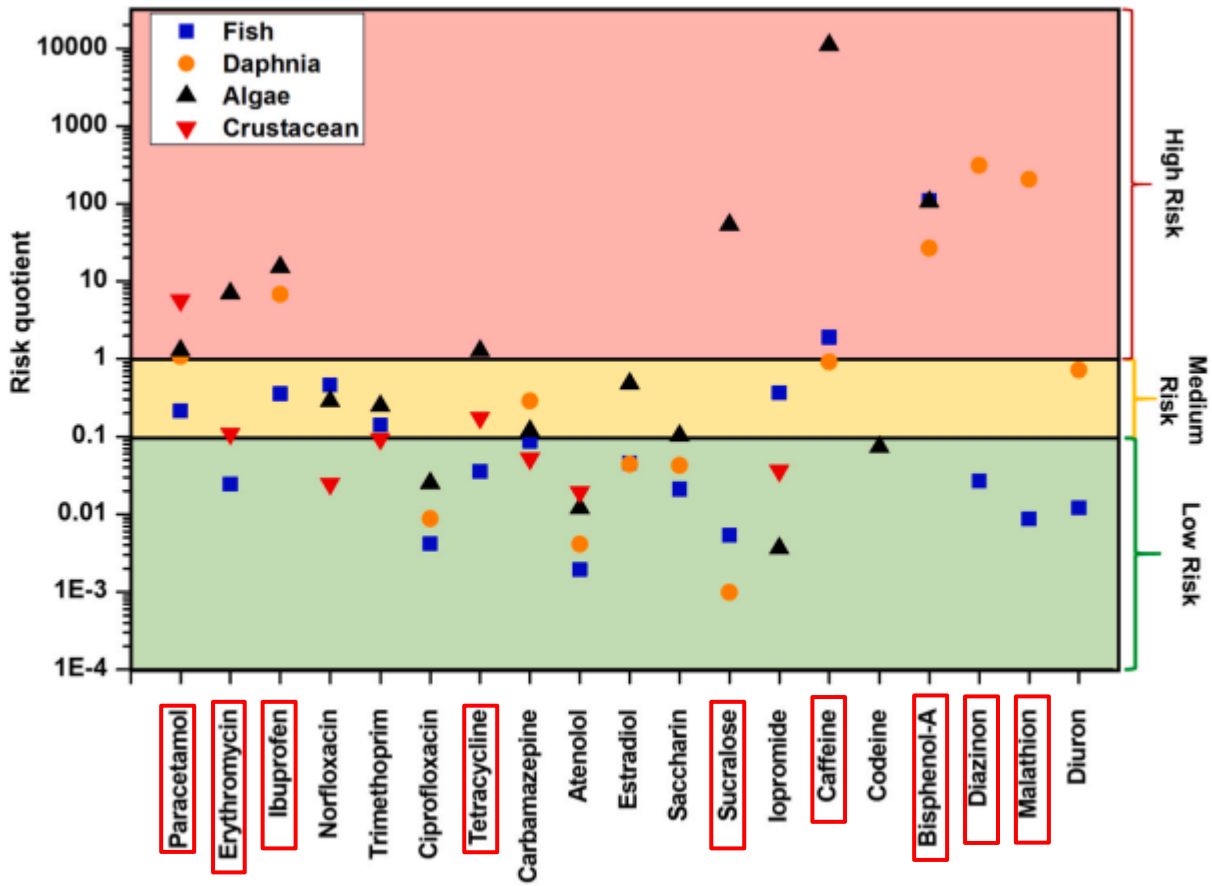
NOEC algae:
- Triméthoprime: 25,5 mg/L
- SMX: 0,6 mg/L
- SMX + TMP: 0,2 mg/L

Test variability

- D. Magna, CE50, 48 h erythromycine: 22,4 or 211 mg/L
- D. Magna, CE50, 48 h ibuprofene: 9 to 1326 mg/L
- D. Magna, CE50, 24 h aspirine: 168 to 1468 mg/L

Toxicity assessment of 19 substances over 4 species





RQ > 1

0,1 < RQ < 1

RQ < 0,1

$$RQ = \frac{MEC}{PNEC}$$

Parida et al., Journal of Environmental Chemical Engineering 9 (2021)

MEC: Environmental concentration
PNEC: Predicted No Effect Concentration

Science of the Total Environment 490 (2014) 889–898
Contents lists available at ScienceDirect
Science of the Total Environment
journal homepage: www.elsevier.com/locate/scitotenv

Occurrence and ecological potential of pharmaceuticals and personal care products in groundwater and reservoirs in the vicinity of municipal landfills in China

Science of the Total Environment 639 (2018) 1334–1348
Contents lists available at ScienceDirect
Science of the Total Environment

nt of pharmaceuticals: Is there
onment?

PERGAMON
Water Research 36 (2002) 5013–5022
WATER RESEARCH
www.elsevier.com/locate/watres

Aquatic environmental assessment of the top 25 English prescription pharmaceuticals

O.A.H. Jones, N. Voulvoulis, J.N. Lester*

PERGAMON
Chemosphere 40 (2000) 783–793
CHEMOSPHERE

Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use

F. Stuer-Lauridsen[a,*], M. Birkved[a], L.P. Hansen[a], H.-C. Holten Lützhøft[b], B. Halling-Sørensen[b]

Chemosphere 74 (2008) 131–141
Contents lists available at ScienceDirect
Chemosphere
journal homepage: www.elsevier.com/locate/chemosphere

Pharmaceutical contamination in residential, industrial, and agricultural waste streams: Risk to aqueous environments in Taiwan

Available online at www.sciencedirect.com
SCIENCE DIRECT
Science of the Total Environment 364 (2006) 67–87

Are pharmaceuticals potent environmental pollutants? Part I: Environmental risk assessments of selected active pharmaceutical ingredients

Carina Carlsson *, Anna-Karin Johansson, Gunnar Alvan, Kerstin Bergman, Thomas Kühler

ble online at www.sciencedirect.com
ScienceDirect
Toxicology Letters 176 (2008) 104–123
Toxicology Letters
www.elsevier.com/locate/toxlet

Human pharmaceuticals in surface waters
Implementation of a prioritization methodology and application to the French situation

Jean-Philippe Besse, Jeanne Garric*

Chemosphere 84 (2011) 1336–1348
Contents lists available at ScienceDirect
Chemosphere
journal homepage: www.elsevier.com/locate/chemosphere

Detection of pharmaceutically active compounds in the rivers and tap water of the Madrid Region (Spain) and potential ecotoxicological risk

Journal of Hazardous Materials 122 (2005) 205–209
Journal of Hazardous Materials
www.elsevier.com/locate/jhazmat

Identification of the pharmaceuticals for human use contaminating the Italian aquatic environment

Ettore Zuccato[a,*], Sara Castiglioni[a,b], Roberto Fanelli[a]
[a] Department of Environmental Health Sciences, Mario Negri Institute for Pharmacological Research, via Eritrea 62, Milan 20157, Italy
[b] Department of Structural and Functional Biology, University of Insubria, Via J.H. Dunant 3, Varese 21100, Italy

Available online 19 March 2005

Second case:
Environmental risk assessment for a new molecule

Request from regulatory authorities to grant the marketing authorization

ERA guidelines EMEA and FDA

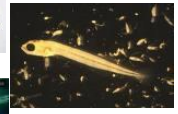
PEC / PNEC

- Quantity consumed

PEC < 10 ng/L
EIC < 100 ng/L

- Human metabolism
- WWTP efficacy
- PBT factor (log Kow)

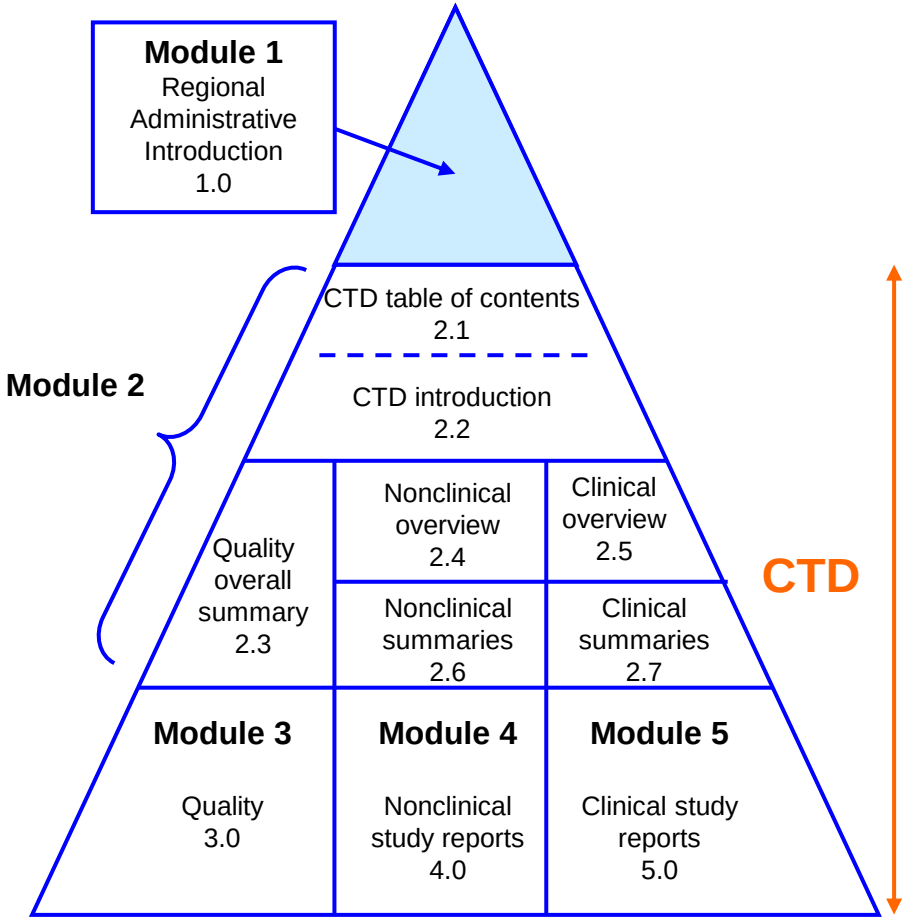
- Acute toxicity tests
  - Daphnia
  - Algaes
  - Fish



- chronic toxicity

EC50, LC50, NOEC

PNEC



Module 1 Table of Content

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- 1.3.5 Product Information already approved in the Member States
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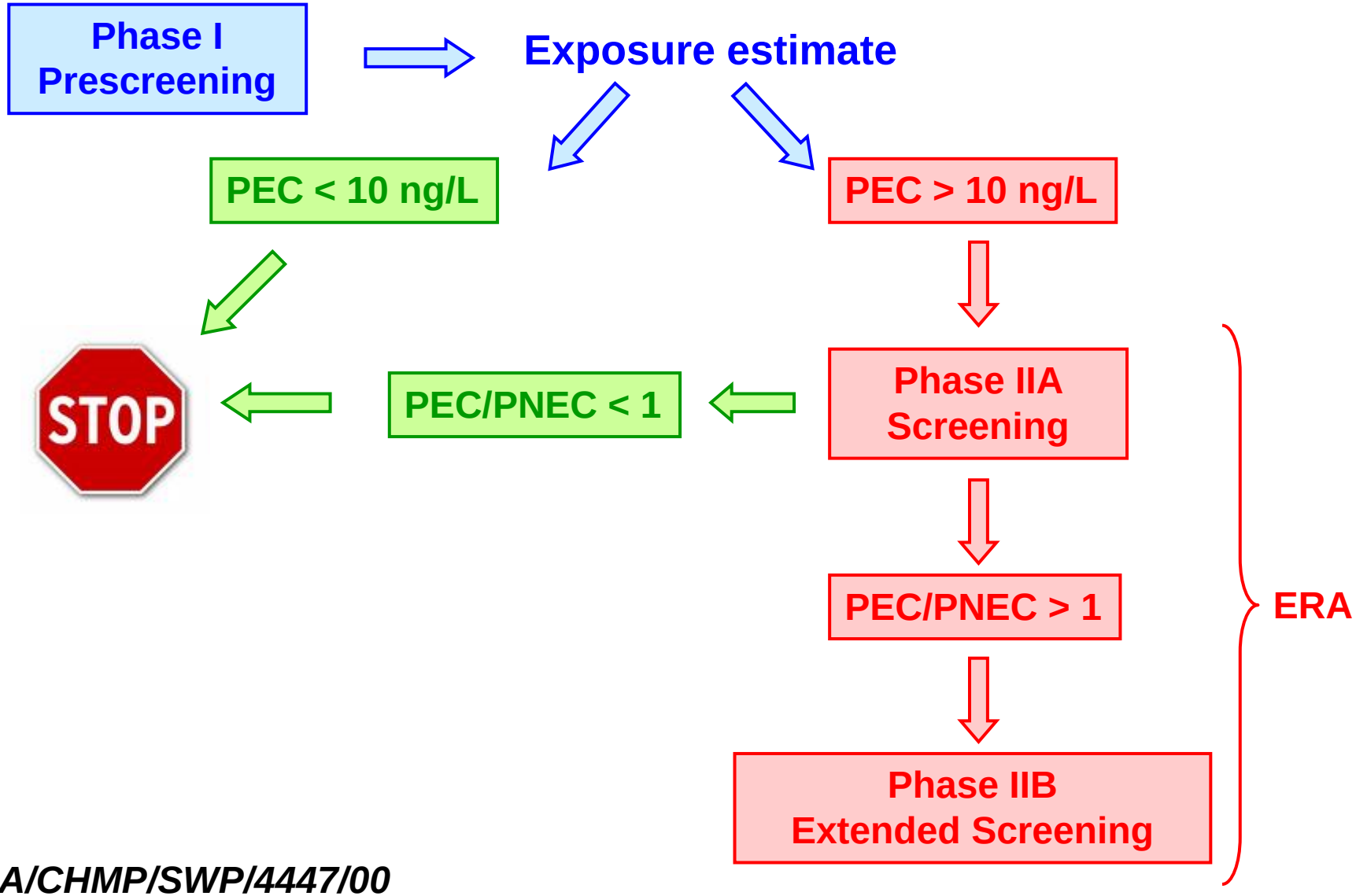
Please also refer to the "Guideline on the environmental risk assessment of medicinal products for human use" 22 August 2024 EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*- published on the EMEA website: (http://www.emea.europa.eu/pdfs/human/swp/444700en.pdf).

General procedure



EMEA/CHMP/SWP/4447/00

Phase I: Pre-screening

Log Kow > 4,5 → PBT study

Persistance	Half-life in water or soil > 182 days Half-life in sediment > 365 jours
Bioaccumulation	Log Kow > 5
Toxicity	EC 50 or LC 50 < 1 mg/L NOEC < 0,1 mg/L

Calculation of PEC

Aquatic compartment only

$$PEC_{SW} = \frac{Dose_{ai} \times F_{pen}}{Wastew_{inhab} \times Dilution}$$

$$PEC_{GW} = 0{,}25 \times PEC_{SW}$$

PEC_{SW} < 0,01 µg/L

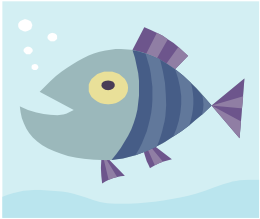
➢ **no major risk for the aquatic environment**

Fpen = 0,01 and $Wastew_{inhab}$ = 200 L/inhab and Dilution factor = 10

Phase IIA: Screening

Identification of an environmental risk

?



Fate in the environment:

- Biodegradability test (OCDE 301)
- Adsorption / desorption (OCDE 106 ou 121)
- Adsorption on WWTP sludge → Koc
- Transformation in sediment (OCDE 308)

Effects on aquatic organisms:

- Inhibition of algae growth (OCDE 201)
- Reproduction of daphnia (OCDE 211)
- Fish toxicity (OCDE 210)
- Respiration inhibition test, sludge (OCDE 209)

$PNEC_W$ → NOEC lowest
$PNEC_{GW}$ → NOEC on test daphnia
$PNEC_{\mu org}$ → NOEC for inhibition test

Safety factor of 10

Phase IIA: Screening (2)

➢ PEC / PNEC?

$PEC_{SW} / PNEC_{W} < 1$ → **No major risk for the aquatic environment**

$PEC_{SW} / PNEC_{W} > 1$

$PEC_{GW} / PNEC_{GW} > 1$

$PEC_{SW} / PNEC\mu org > 0,1$

→ **Phase IIB, with metabolites**

Kow > 1000

Koc > 10 000 L/kg

Adsorption on sediments

→ **Phase IIB, with metabolites**

Phase IIB: Extended Screening

Phase IIB
→ Refining the assessment + taking into account metabolites

Reassessment of PEC:

$$PEC_{SW} = \frac{Dose_{ai} \times F_{excreta} \times F_{pen} \times F_{stp}}{Waste_{inhab} \times Factor \times Dilution}$$

$$F_{pen} = \frac{Amount \times 100}{DDD \times Inhbts \times 365}$$ → % people treated in the population

Adsorption on suspended matter: Factor = 1 + (Foc x Koc) x MES x 10^{-6}

$F_{excreta}$: portion eliminated unmetabolized ; F_{stp} : portion eliminated by WWTP ; MES: suspended matter

Refinement of effects

Toxic effect on sediment → tests on exposed species
Additional tests on aquatic and terrestrial microorganisms

Test OCDE 307	Aerobic and anaerobic transformation of chemicals in soil
Test OCDE 216	Soil microorganisms: nitrogen transformation test
Test OCDE 208	Terrestrial plant test: seedling emergence and seedling growth test
Test OCDE 207	Earthworm, acute toxicity testing
Test ISO 11267	Soil quality -- Inhibition of reproduction of Collembola (Folsomia candida) by soil pollutants

ERA Report in CTD (Module 1.6)

- PEC estimate
- Assessment of possible risks (summary of studies)
- Precision of usage precautions to be taken (unused products)
- Suggested indication on the product packaging and in the summary of characteristics

Veterinary drugs:
Guideline on environmental impact assessment for veterinary medicinal products
EMA/CVMP/ERA/418282/2005

$$PEC_{SW} = \frac{Dose_{ai} \times F_{pen}}{Wastew_{inhab} \times Dilution}$$

(1200 x 0,01)/(200 x 10)

	Dose ai (mg)	PEC phase I (ng/L)
Metformine	3000	15 000
Ibuprofène	1200	6 000
Carbamazépine	2000	10 000

$$PEC_{SW} = \frac{Dose_{ai} \times F_{excreta} \times F_{pen} \times F_{stp}}{Waste_{inhab} \times Factor \times Dilution}$$

(5480 x 0,10 x 0,10)

	PEC adjusted consumption	$F_{excreta.}$	F_{stp}	PEC (ng/L)	Ecotoxicological data	PNEC (µg/L)	RQ
Metformine	16 367	1	?	16 367	LC50 Daphnia 64 000 µg/L **(SF 1000)**	64	0,26
Ibuprofène	5 480	0,10	0,10	55	NOEC Daphnia reproduction 20 000 µg/L **(SF 100)**	200	0,0003
CBZ	765	0,02	0,97	15	NOEC Daphnia reproduction 25 µg/L **(SF 100)**	2.5	0,006

Fpen
Data consumption

Metabolism
WWTP treatment

FDA approach:

$$\text{EIC} \quad (\mu g/L) = \frac{\text{Quantity used (kg/year)} \times 10^6}{365 \times Q_{effluent} \ (L/j)}$$

EIC < 100 ng/L

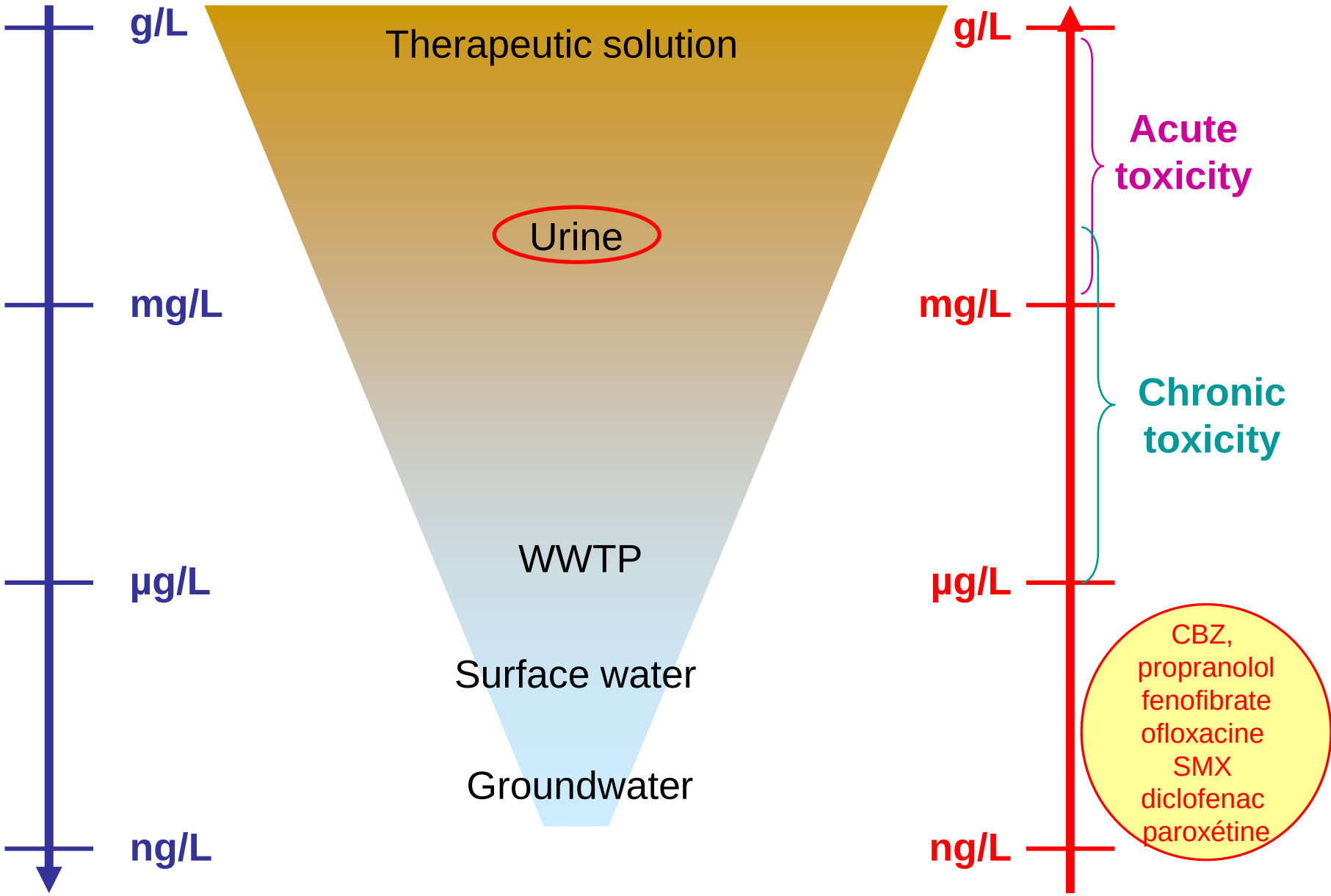
Phase I: acute toxicity on a species

CL50/MEEC > 1000

Phase II: acute toxicity « base set »

CL50/MEEC > 100

Phase III: chronic toxicity « base set »


g/L
mg/L
µg/L
ng/L
Therapeutic solution
Urine
WWTP
Surface water
Groundwater
g/L
mg/L
µg/L
ng/L
Acute toxicity
Chronic toxicity
CBZ,
propranolol
fenofibrate
ofloxacine
SMX
diclofenac
paroxétine