A strategy to prioritize human pharmaceuticals in French aquatic ecosystems

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Context

High consumption of human pharmaceuticals in France:

First European consumer of pharmaceuticals.

High number of active molecules.

Growing concern to monitor pharmaceuticals in waters

Priority list needed **prior to start** any monitoring program.

Prioritization regarding the environmental risk in surface waters.

Financial support from the *Agence de l'Eau Rhône-Méditerranée & Corse*.

Candidate list and strategy

Prioritization candidate list: Based on AFSSAPS data

Top 100 pharmaceuticals used in France

Range from 3000 tons / year for paracetamol to 20 kgs / year for escitalopram.

Excluding hormones and cytotoxic compounds.

120 Active Pharmaceutical Ingredients (APIs).

Prioritization strategy:

Exposure assessment adapted from EMEA 2006

Identification of environmentally relevant **metabolites.**

Effect assessment based on available data

Exploitation of **human pharmacological** data.

Besse and Garric. Toxicology Letters, 2007.

Tier 1: Exposure assessment

PEC calculation (adapted from EMEA 2006)

$$PEC = \frac{amount \times Fexcreta}{Qeffluent \times hab \times Dilution \times 365}$$

Consumption amount (mg.year^{-1}) **including OTC drugs**

Excretion fraction of the active ingredient

hab : number of inhabitants of a country (set at 60 millions for France).

dilution : dilution from WWTP effluents to surface waters (default value: 10).

Qeffluent : amount of wastewater per inhabitant per day (default value: 200 l.inhab^{-1}day^{-1}).

365 : 365 days per year.

Tier 1: Exposure assessment

Fexcreta parameter

Importance in PEC calculation:

Human metabolism is the first mechanism that can limit the **the amount** of pharmaceuticals reaching the environment.

Importance in prioritization strategy:

Metabolism can lead to **metabolites structurally different** from the parent drug.

Allow to **target** metabolites of concern for the aquatic environment.

Tier 1: Exposure assessment

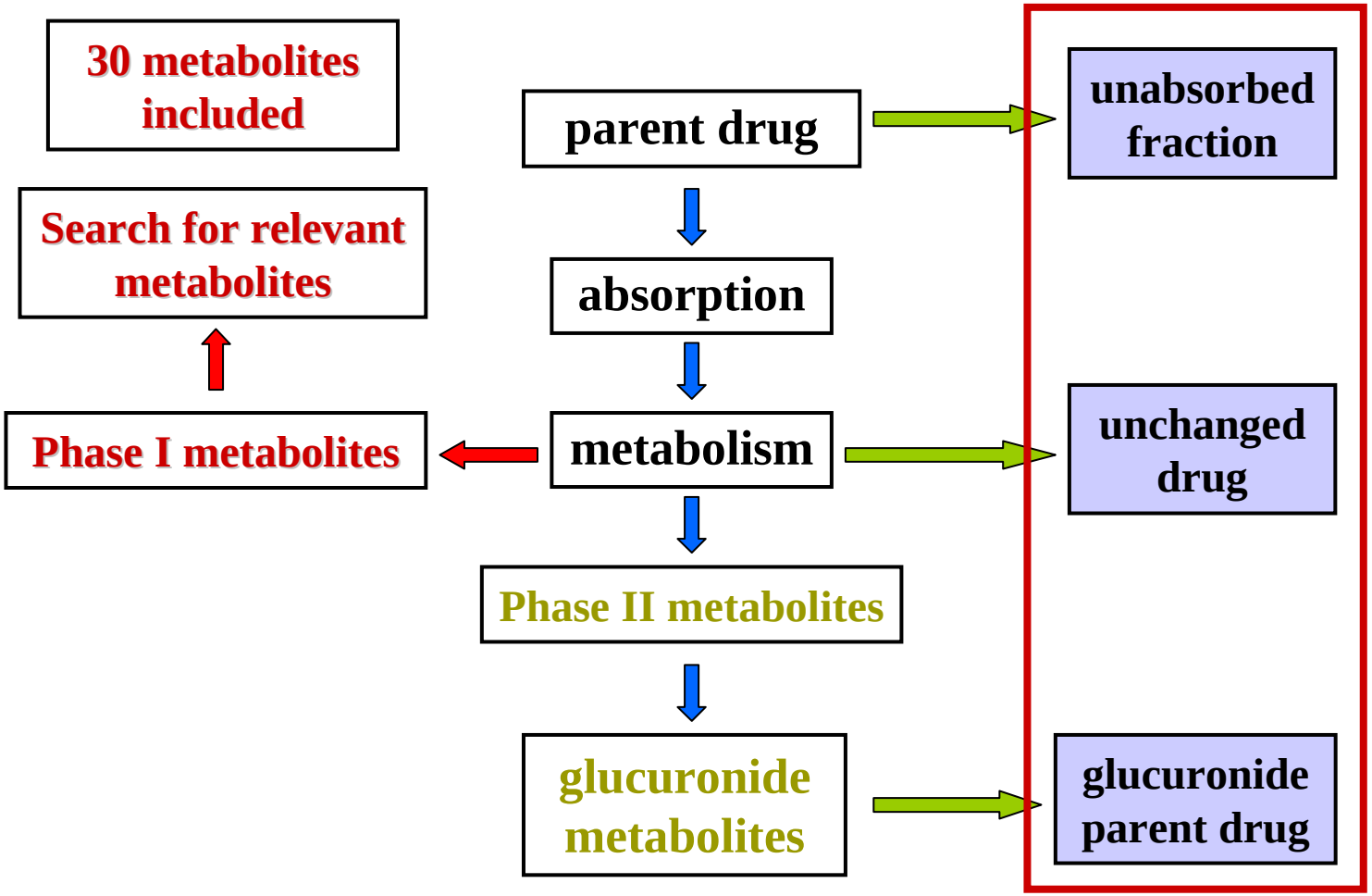
Determination of Fexcreta

Banque Claude Bernard, (www.resip.fr),

Drugs.com database (www.drugs.com),

Micromedex Drugdex® databank

Martindale compendium



Fexcreta for parent compound

For 80% of selected pharmaceuticals

Besse et al., Human and Ecological risk assessment, in press

Tier 1: Exposure assessment

Exposure classification

$$PEC = \frac{amount \times Fexcreta}{Qeffluent \times hab \times Dilution \times 365}$$

Calculation of two PEC values

PECa: conservative PEC assuming no metabolism

PECb: PECa refined with Fexcreta

Comparison of PECa and PECb with two threshold values

Threshold value of the FDA guideline, value of 100 ng.l^{-1}

Threshold value of the EMEA guideline, value of 10 ng.l^{-1}

Ranking of pharmaceuticals in 6 exposure classes

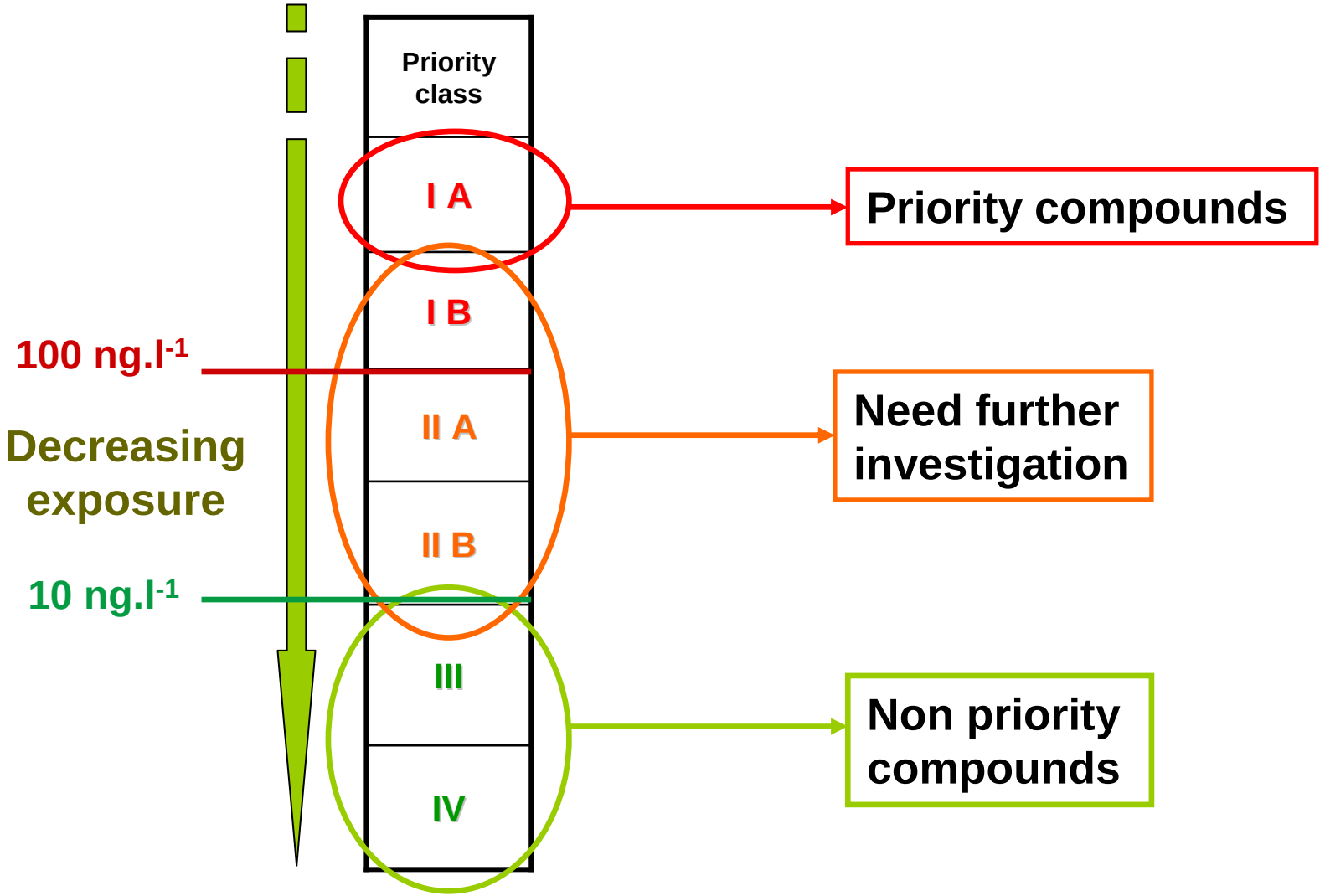
Tier 1: Exposure assessment

Results

Priority class	Priority rank according to the exposure criteria	Comments
I A	**highest risk compounds**	PECa and PECb higher than 100 ng.l^{-1}. **High consumption and limited metabolism.**
I B	**potentially hazardous compounds but limited data**	PECa higher than 100 ng.l^{-1}. **High consumption. No data on metabolism.**
II A	**potentially hazardous compounds**	PECa higher than 100 ng.l^{-1} PECb higher than 10 ng.l^{-1}. **High consumption and intermediate metabolism.**
II B	**unclassified priority risk**	PECa lower than 100 ng.l^{-1} but higher than 10 ng.l^{-1}. **No data on metabolism.** **No definitive conclusion, need further investigation.**
III	**very low risk for the environment (extensive metabolism)**	PECa higher than 100 ng.l^{-1} PECb lower than 10 ng.l^{-1}. **High consumption but extensive metabolism.**
IV	**very low risk for the environment (low consumption amount)**	PECa lower than 10 ng.l^{-1}. **Low consumption amount.**

Tier 1: Exposure assessment

Results (II)



Tier 2: Effect assessment

➡ As a precaution, all pharmaceuticals, whatever exposure class, were submitted to the effect assessment.

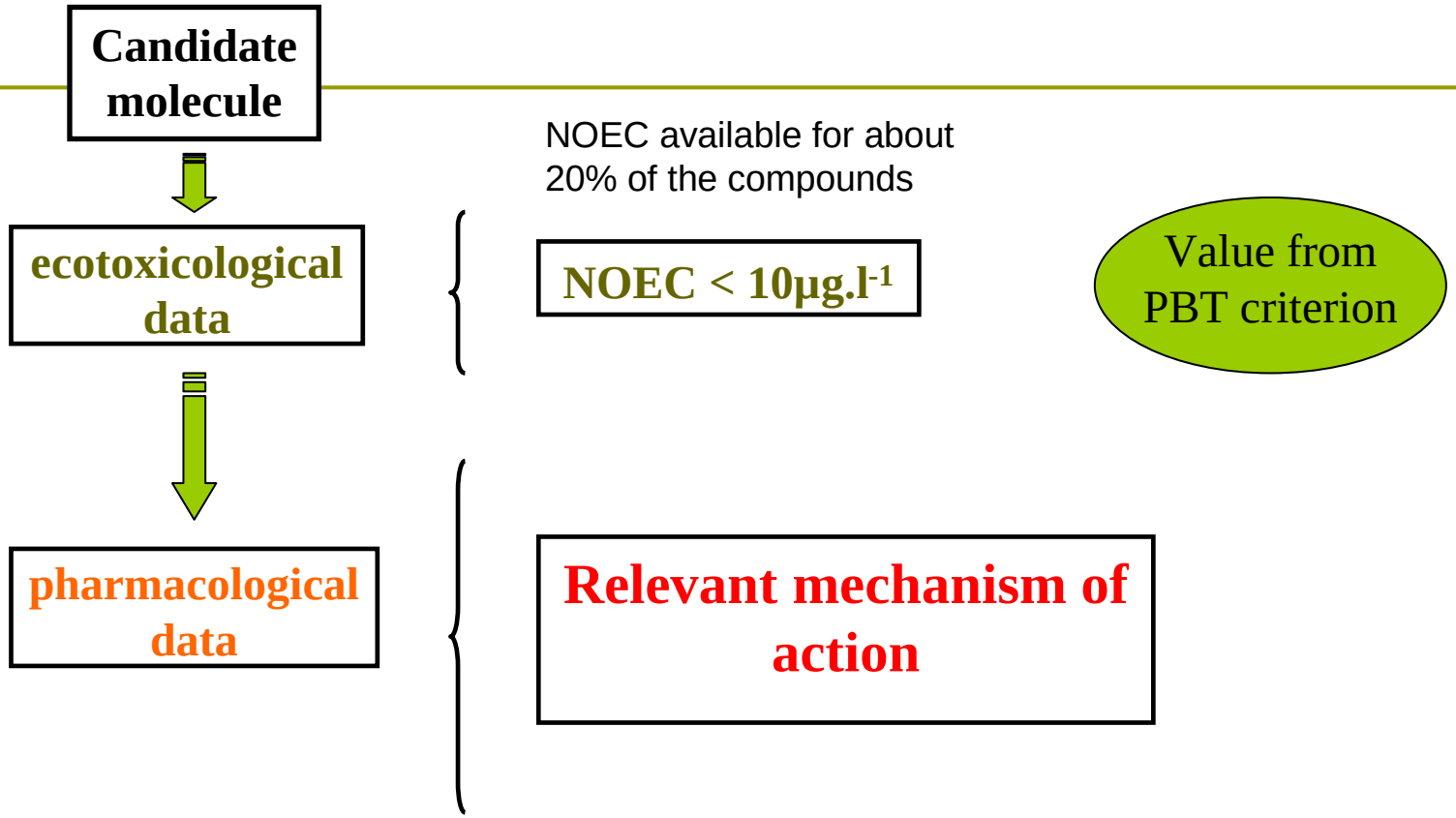
➡ Implementation of a pragmatic approach:

Available chronic NOEC values.

Investigation of human pharmacological data.

Physico-chemical data (Log Kow).

Tier 2: Effect assessment



Tier 2: Effect assessment

Mechanism of action

➡ Pharmaceuticals are designed to have specific MoAs.

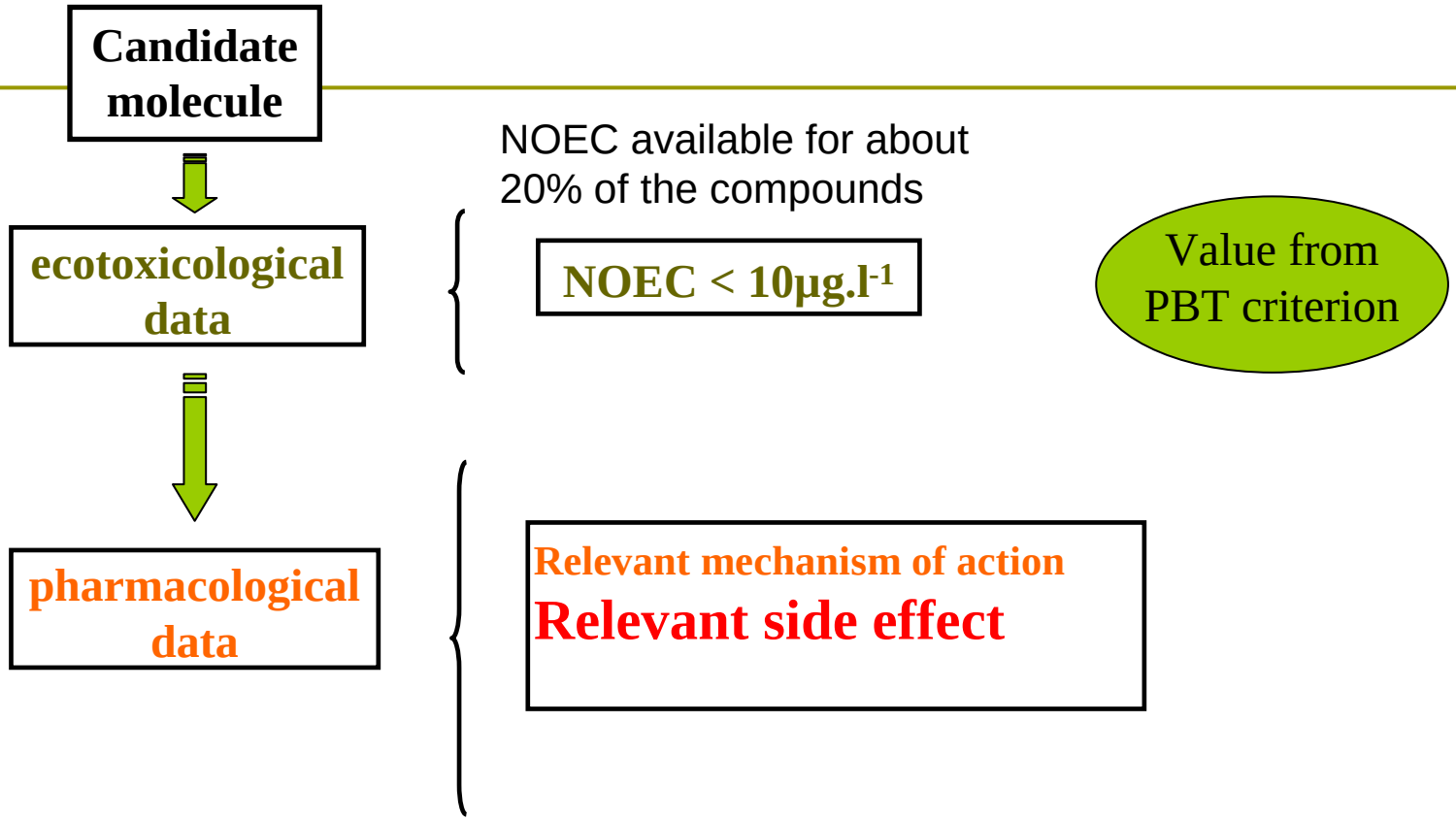
For non-mammalian animals with **targets similar** to those of mammals, **biological effects** may occur.

➡ Example:

Anti-inflammatories ⟶ Cyclooxygenase inhibition

Similar targets in human and fish and enzyme cox-like in lower invertebrates.

Tier 2: Effect assessment



Tier 2: Effect assessment

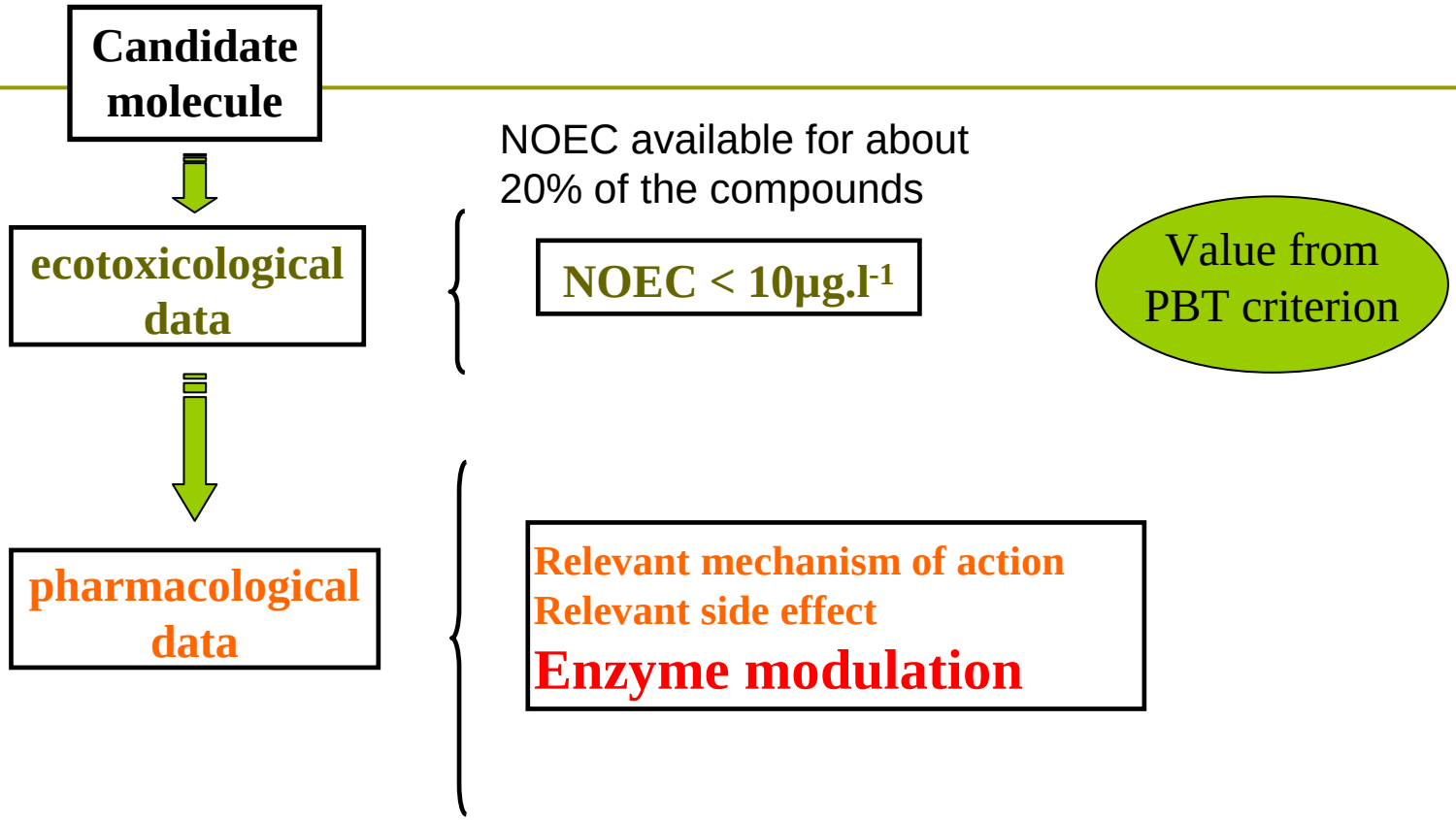
Adverse effects

- Known adverse **human side effects** of pharmaceuticals may also be valuable to indicate **potential harmful effects** on non-target organisms.

- Examples:

SSRIs	Sexual dysfunction in human	Alters estradiol levels in fish
NSAIDs (diclofenac)	Kidney toxicity in human	Renal impairment in fish and birds

Tier 2: Effect assessment



Tier 2: Effect assessment

Enzyme modulation

➡ Several APIs are known to interact with Cytochrome P-450

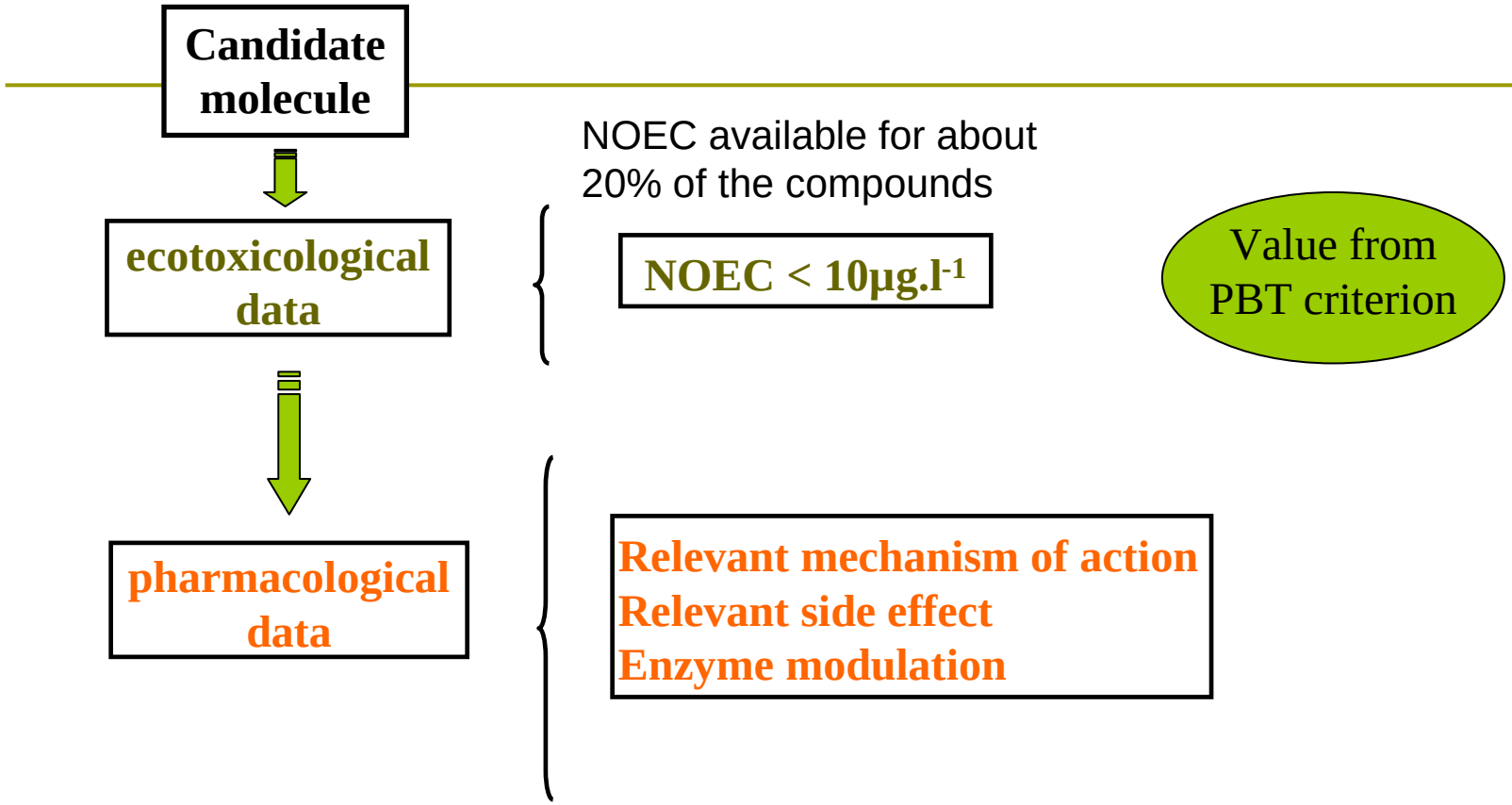
Potential risk of **disruption in the homeostasis** of non-target organisms.

➡ Several pharmaceuticals are known to interact with Glycoprotein-P (P-gp)

Multidrug transporter that actively transports xenobiotics out of the cell, preventing the accumulation of toxic compounds.

Inhibition of its expression by a specific drug could result in **enhancing the sensitivity** of organisms to environmental pollutants.

Tier 2: Effect assessment



Scoring of pharmaceuticals using pharmacological data

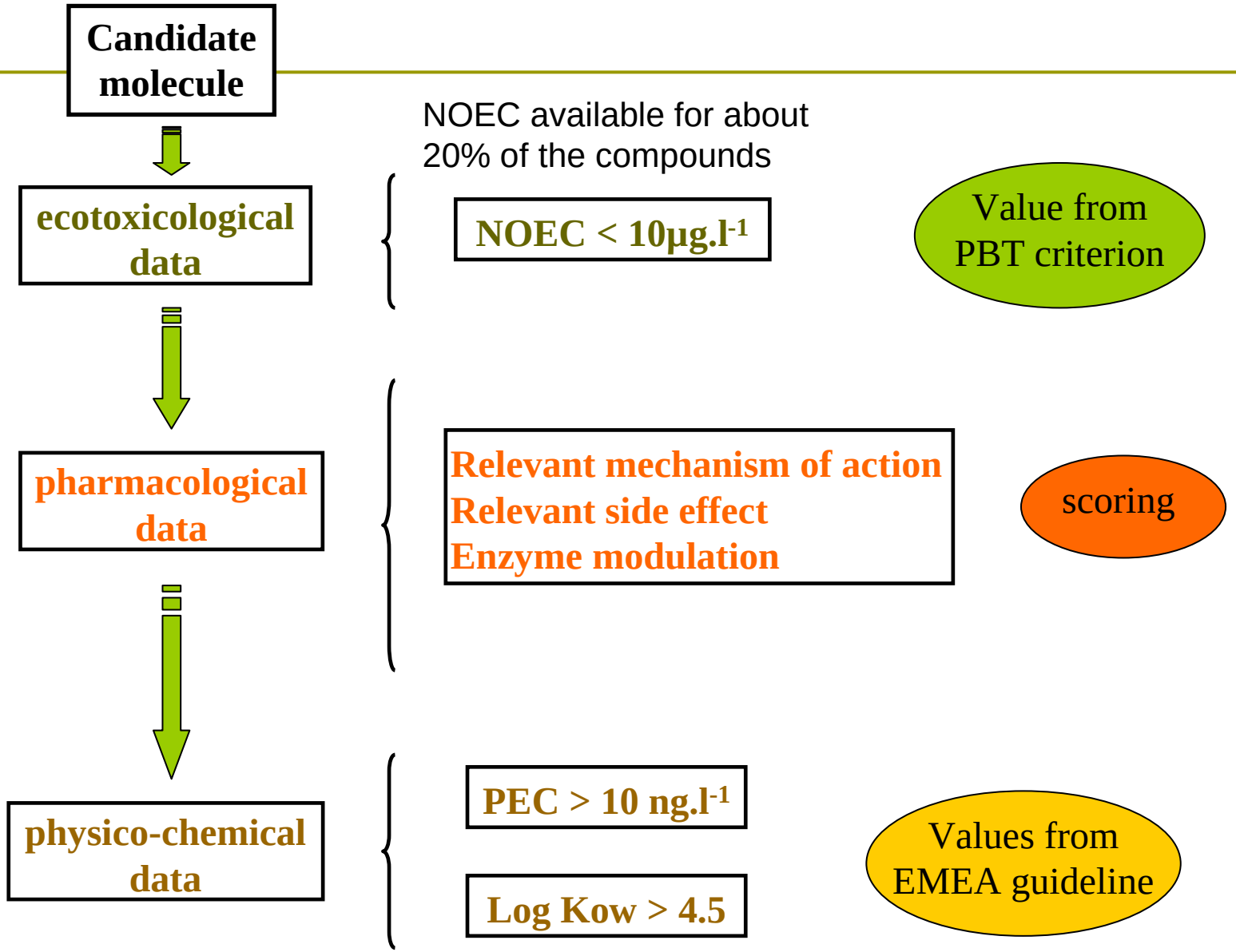
Relevant MoA: 2

Relevant side effect: 1

Enzyme modulation: 1

Score ≥ 2 indicate a priority compound

Tier 2: Effect assessment



Conclusion (I): Final priority list

Prioritisation strategy:

Exposure assessment adapted from EMEA 2006.

Effect assessment based on ecotoxicological, pharmacological and physico-chemical data.

➡ Final list of 40 parent compounds and 14 metabolites

Several therapeutic and chemical classes represented:

Antibiotics, anti-inflammatories, various anti-hypertensive classes, blood lipid lowering agents, anti-ischemics, psychiatric drugs…

Large screening of compounds.

Conclusion (II): Approach validation (Exposure)

➡ **21 parent compounds already detected** in surface waters (mainly β-blockers, anti-inflammatories and antibiotics).

5 metabolites already detected in surface waters, other metabolites have not been searched yet.

➡ PEC values refined by WWTPs plants removal rates are in **good agreement** with field measurements.

(Besse et al., Human and Ecological risk assessment, in press)

Conclusion (III): Approach improvement

- Include **WWTP removal rates** in the PEC calculation, when available.
- Include **fate data** (biodegradation, photodegradation and hydrolysis time) and take into account **degradation byproducts** of APIs.
- Use **Log Dow** rather Log Kow to describe environmental behavior.
  Most of pharmaceuticals are **polar ionisable** compounds.

Conclusion (IV) Research perspectives

Investigate the use of pharmacological data to assess the environmental risk for pharmaceuticals:

- Direct extrapolation of pharmacological data may not be relevant for the characterization of environmental hazard because of differences in physiology and target receptors in aquatic organisms.

- MoA, side effects and enzyme modulation give an **overview of the biological effects** of pharmaceuticals and can be considered as **valuable indicators** of their potential toxicity.

Build ecotoxicological data to compare with the result of the pharmacological based approach.


Thank you for your
attention