EPIC

EFFICIENT TREATMENT OF PHARMACEUTICAL RESIDUE AT SOURCE - EPIC

BIOTRANSFORMATION OF DRUGS

**How to perceive the human elimination products when assessing
the efficiency of waste water purification and the environmental impacts of drugs?**

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SYKE

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- Most therapeutic drugs pass waste water purification

- Lots of evidence exists on bioaccumulation
  of drugs in non-target species
  - Especially in fish Þ Risk for secondary
    poisoning along the food chain

- Many drug target receptors are known to conserve
  across taxonomic groups (e.g., www.ecodrug.org)

  Þ Similar effects (as in man) are expected in other species as well

TIINA SIKANEN, UH   17.5.2019

SYKE

What we eat is not what we excrete
- Monitoring only the API form may lead us wrong!

Many Active Pharmaceutical Ingredients (APIs) are:

- Lipophilic
- Chemically stable

Þ The human body cannot eliminate APIs in their original form

Þ Before elimination, most APIs undergo significant enzymatic conversion (metabolism) to become more water-soluble and thus excretable

Picture: Wikimedia Commons

Lipophilic drug

Water-soluble metabolite
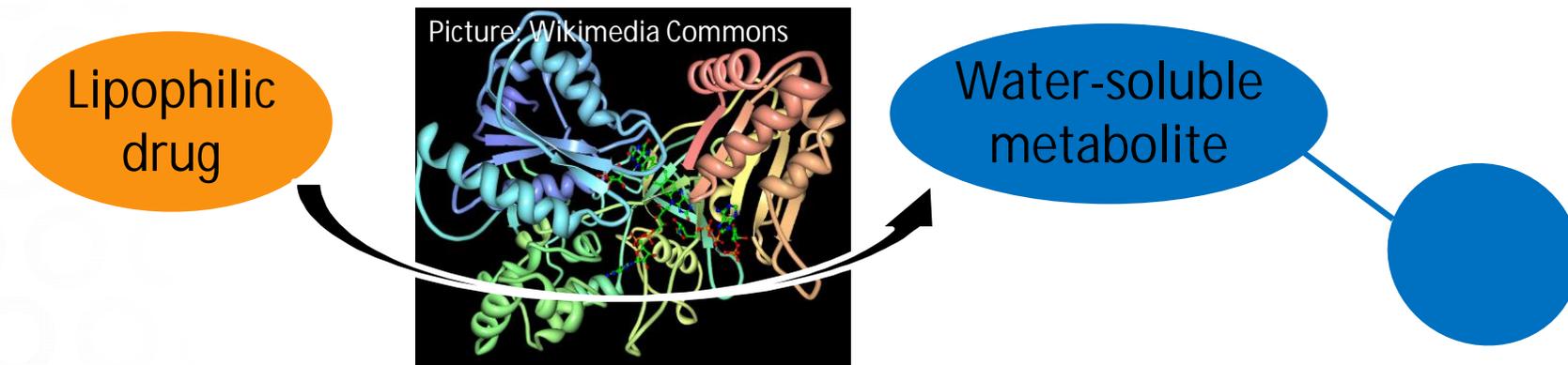
The high analytical sensitivity required for monitoring of trace-level concentrations necessitates compound-selective methods

Þ Monitoring of all metabolite forms along with the API is not feasible (time, cost)

Þ Selection of the most relevant form for monitoring depends on the API

Example: Human metabolites of ibuprofen
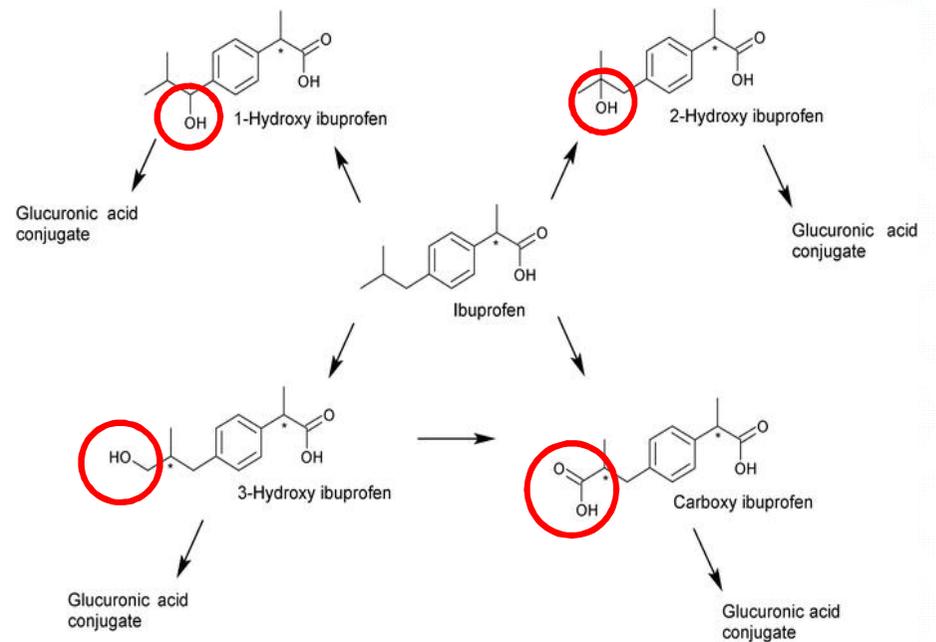
- Many clinically critical parameters *with respect to human safety and efficacy of an API* could help judge which is the most abundant eliminated form

Excreted unchanged (urine, faeces)
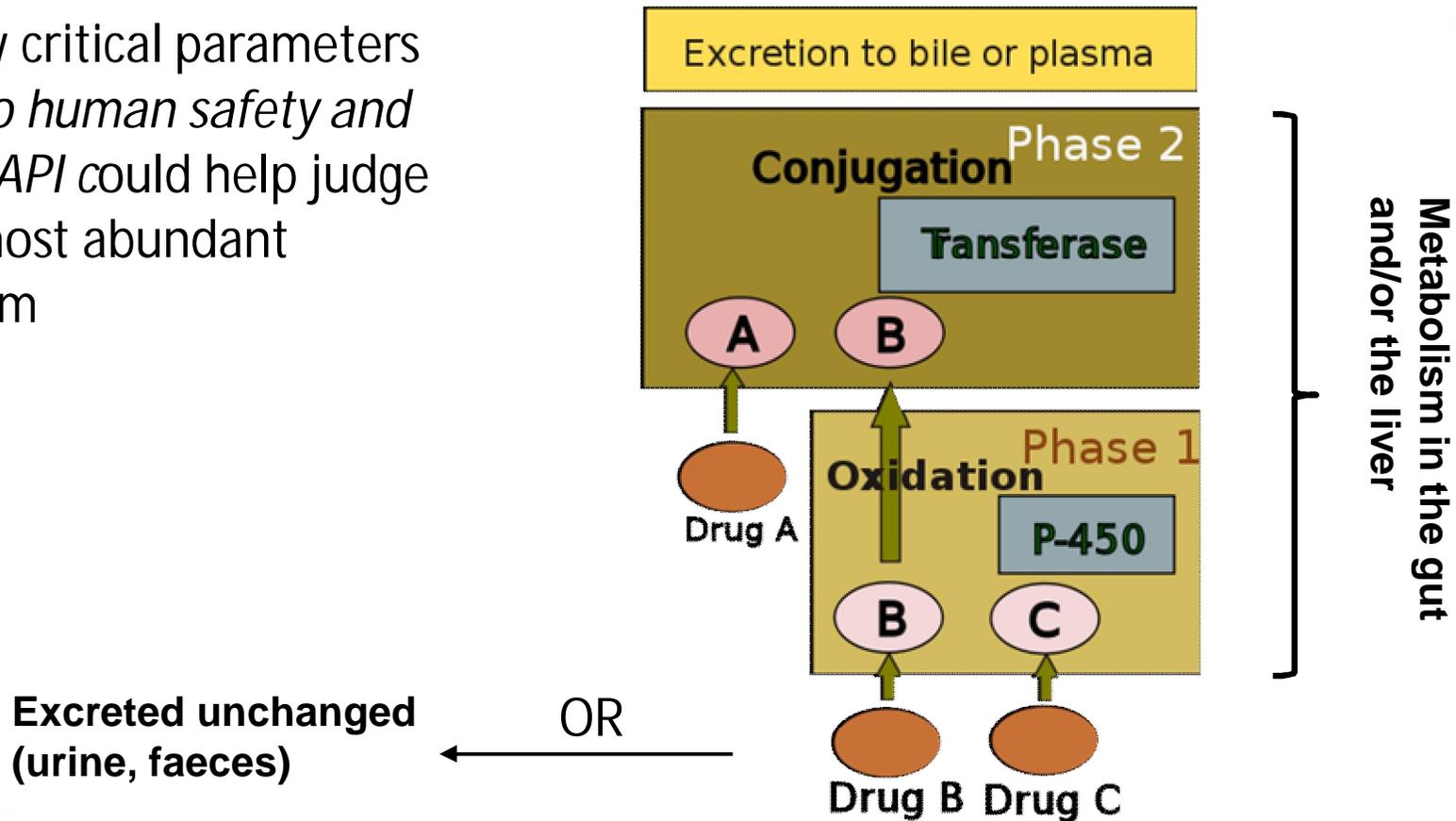
Picture from: Wikimedia commons

● A feasible approach to identification of the most relevant drug elimination products

- Step 1: The percentage of 'Excreted unchanged' <50%
Þ Indicates need for more-detailed inspection of metabolite forms

- Step 2: 'Metabolism' proceeds in two phases
  - *Phase I*: Minor oxidation/reduction   Þ Typically chemically stable forms
  - *Phase II*: Conjugation reactions   Þ Typically less stable forms
    Þ Degradation products?

Example APIs	Purpose of use	Excretion profile
Hydrochlorothiazide	Diuretic	100% unchanged
Tetracycline	Antibiotic	100% unchanged
Carbamazepine	Antidepressant	2-13% unchanged, mainly Phase I metabolites
Ibuprofen	Anti-inflammatory	1-15% unchanged, mainly Phase II metabolites

Combining pharmacokinetic data with environmental monitoring

Karlsson, S., Äystö, L., Nysten, T., Vieno, N., Yli-Kauhaluoma, J., Sikanen, T., "The impact of human drug metabolism and disposition on the occurrence of pharmaceuticals in wastewaters - A case study on Finnish influent wastewater", SETAC Europe 29th Annual Meeting, Helsinki, Finland, 26-30 May 2019.

A validation study with 32 APIs confirms the apparent correlation

- between the environmental load

- and the pharmacokinetic data
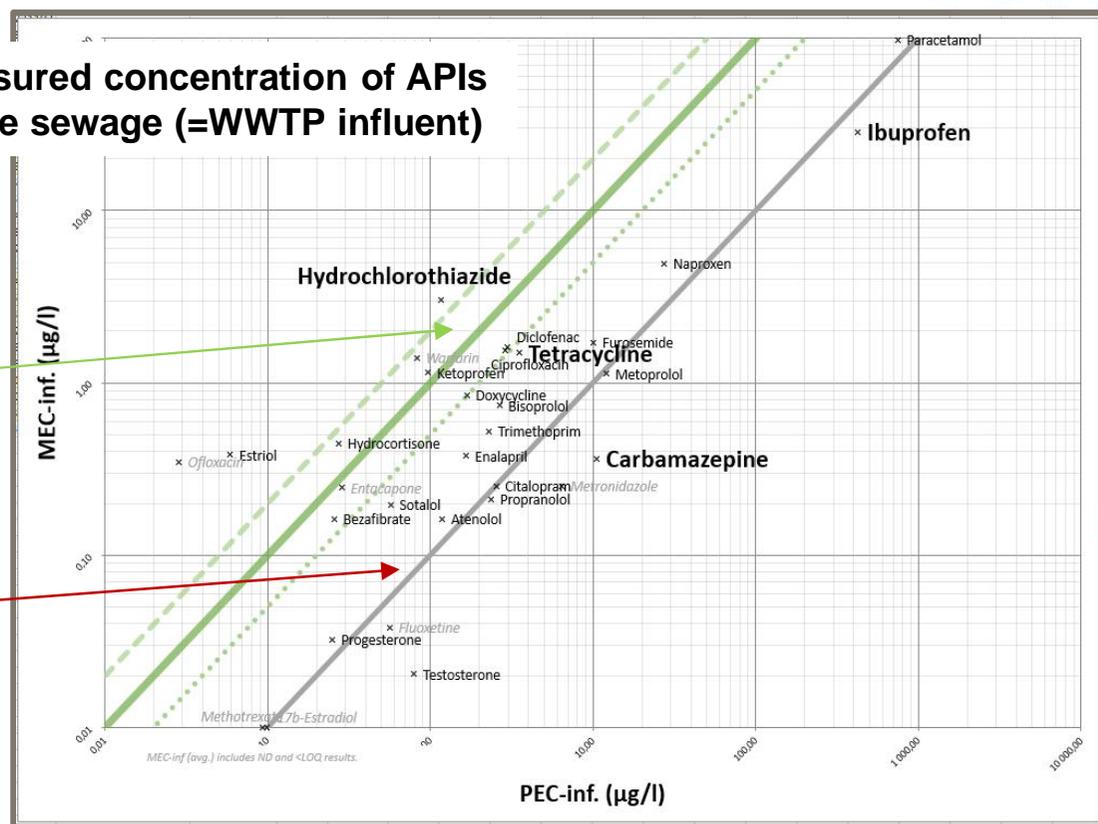
Good correlation
(max 2-fold difference, green range)
- Mainly APIs that excrete unchange or which metabolite degrades easily

Threshold for very poor correlation
= measured conc. >10% of the predicted, grey line
- Mainly APIs that excrete as stable metabolites

Measured concentration of APIs in the sewage (=WWTP influent)

Predicted concentration of APIs (based on consumption statistics & population-normalized flux)

- Metabolites - Why care?

  - Most metabolites are pharmacologically inactive, but not all!
    - E.g., the metabolites of many cancer medicines are (cardio)toxic
    - The metabolites of some antibiotics (e.g., ciprofloxacin) show substantial antimicrobial potency as well

  - The pharmacologically inactive metabolites may degrade back to the original form
    - E.g., many steroids and antibiotics are excreted as glucuronide conjugates
      which are likely to returnto the original pharmacologically active form
      upon degdaration in the sewage, at the WWTP or in the environment

  - Drug targets conserve across taxa Þ The full picture must be understood!
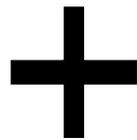
S Y K E

COLLABORATION

A lot of environmentally relevant information on APIs' fate exists in the pharmaceutical dossiers and literature/databanks

- Pharmacokinetic data (metabolism)
  - Þ Identification of the most relevant forms for environmental monitoring
    - E.g., databases: https://www.drugbank.ca/, https://www.pharmgkb.org/

- Degradation of APIs upon storage (humidity, UV)
  - Þ Identification of the common degradation products under stressed conditions (at WWTP, sewage sludge, waterways/environment)

Monitoring Þ   Wastewater purification Þ   Prediction of environmental impacts

Thank you!

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