Assessing the Environmental Risk of Pharmaceuticals following Patient Use

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ACT Webinar

Outline

- Pharmaceuticals in the Environment (PIE)
- Hazard versus Risk
- Environmental Risk Assessment (ERA)
- Current State—Regulatory ERAs
- Industry Response to PIE

Pharmaceuticals in the Environment (PIE)

c&en CHEMICAL & ENGINEERING NEWS
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Side Effects
Pharmaceuticals have been finding their way into our environment for a long time, but just what are they doing there?

A Complex System
Fish, plants, and other aquatic life are feeling the effects of pharmaceuticals in the environment. Credit: EPA

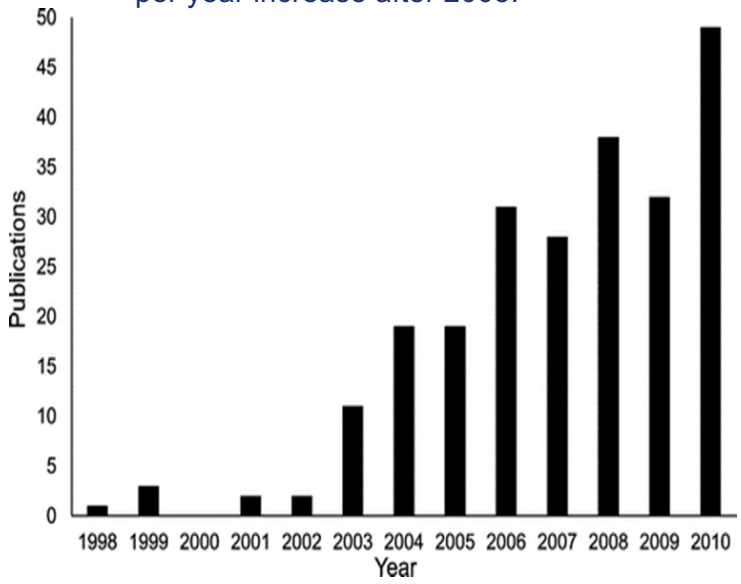
BBC NEWS

Sunday, 17 March, 2002, 03:06 GMT

River 'pollution' sparks fertility fears

Chemical could be flushed via sewage works into rivers
http://news.bbc.co.uk/2/hi/uk_news/1877162.stm

Database of 236 publications shows rapid per year increase after 2003.



https://pubs.acs.org/doi/10.1021/es3030148

Pharmaceuticals in the Environment (PIE)

Hughes *et al* (2013) conducted a "global-scale analysis of the presence of 203 pharmaceuticals across 41 countries and show that contamination is extensive due to widespread consumption and subsequent disposal to rivers." [1]

Do the presence of pharmaceuticals in surface water, ground water, and drinking water pose a risk to human health? To the environment?

[1] https://doi.org/10.1021/es3030148

Properties of Pharmaceuticals

Designed to elicit a biological response

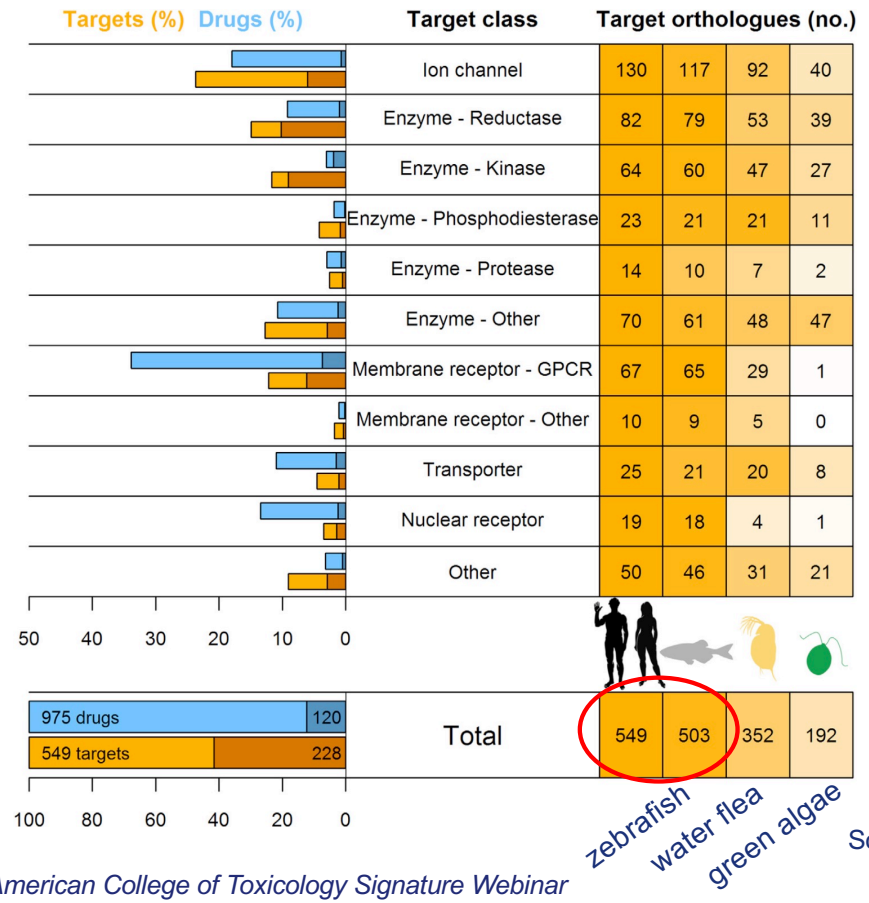
Various mechanisms of action result in pharmacological effect:

- Binding to specific molecular targets—enzymes, receptors
- Interacting with chemical/physical properties in body

Presence of pharmaceuticals in environment + biological response by design

Hazard

Drug Target Conservation across Species



Orthologues:

- Genes in different species that evolved from a common ancestral gene
- Retain the same function during the course of evolution

Number of small molecule drugs (blue)

Corresponding human protein targets (orange)

Inlaid darker colors—drugs available in DrugBank.ca with full set of aquatic environmental effects data (120)

Target orthologues:

Number of human drug targets with orthologues in zebrafish, water flea, green algae for each protein class

Source: L Gunnarsson *et al.*, *Environ. International* 129 (2019) P323, Fig. 1

Hazard versus Risk

Source: https://scimoms.com/hazard-risk/

Human Risk—Pharmaceuticals in the Environment

2 liters of water per day for over 100,000 years

one 200 mg tablet of ibuprofen

Trace concentrations of drugs found in drinking water:

- Ibuprofen—"one of the most common drugs (in trace amounts) found in drinking water across the world"
- "Drink two liters of water per day for over 100,000 years to consume the equivalent of one 200 mg tablet of ibuprofen"[1]

"Existing research indicates that pharmaceuticals are generally present in freshwaters within the ng L^{-1} range and, at these subtherapeutic levels, the risk of acute toxicity is thought to be negligible."[2]

[1] Pfizer (May 14, 2014). Drug Watch. https://dualdiagnosis.org/the-environmental-impact-of-growing-drugs/

[2] https://pubs.acs.org/doi/10.1021/es3030148. Iburprofen: This Photo by Unknown Author is licensed under CC BY-ND

Early Findings—Environmental Effects

Diclofenac

- An anti-inflammatory drug administered to cattle to ease pain
- Vultures in India near extinction due to kidney failure from eating carcasses of diclofenac-treated cattle
- Veterinary use of diclofenac banned in 2006

Estrogenic compounds

- Reported feminization of fish in UK rivers following exposure to effluent discharges containing ethinylestradiol (contraceptive) and natural/synthetic estrogens

Fluoxetine

- Selective serotonin reuptake inhibitor for treatment of depression
- Altered levels of neurotransmitters (dopamine and norepinephrine) in brain tissue of fish exposed to fluoxetine

What do these findings mean in terms of environmental risk?

Assessment of Environmental Risk—Drug Application Process

Assessment of environmental risk—a component in all drug applications

US

- National Environmental Policy Act of 1969 (NEPA): all federal agencies to assess the environmental impact of their actions (FDA - EA Guidance, 1998)

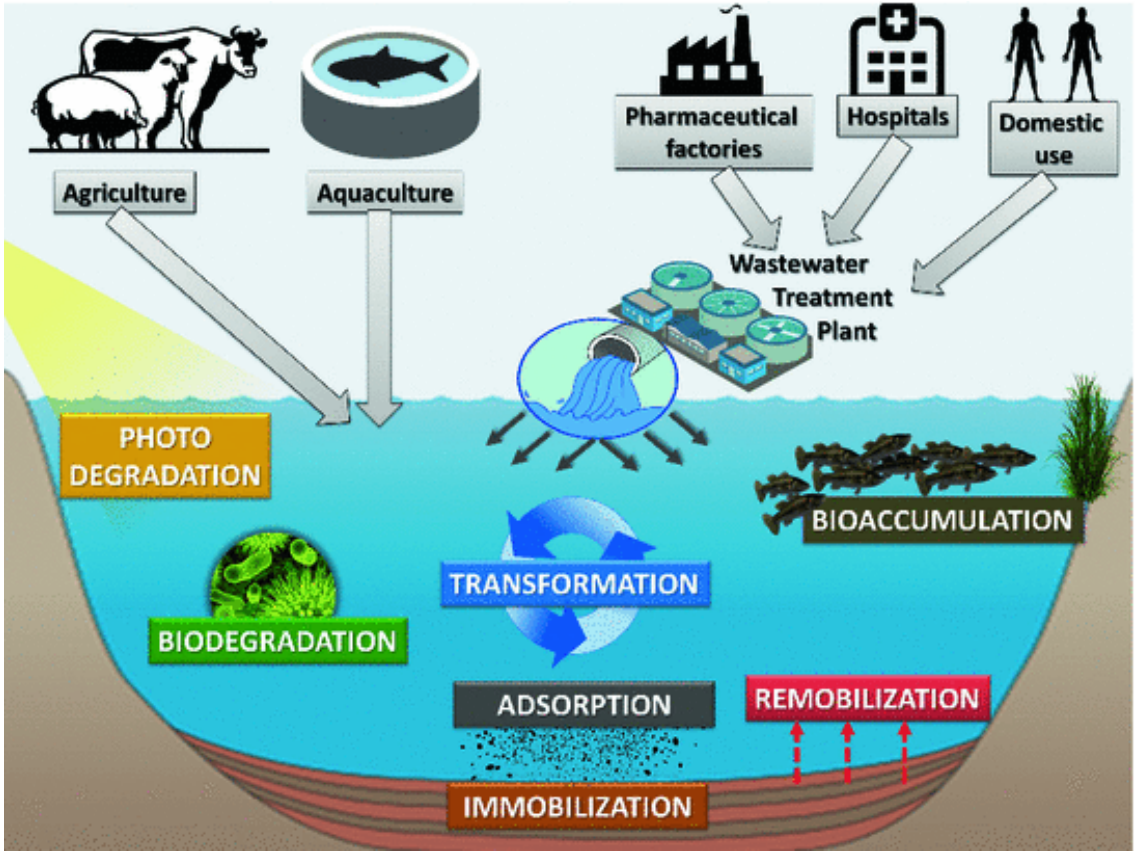
EU

- Council Directive 2001/83/EC, Article 8, 3. (g) application for the marketing authorization (MAA) for a medicinal product for human use shall be accompanied by an environmental risk assessment (EMA – ERA Guideline, 2006)

Canada

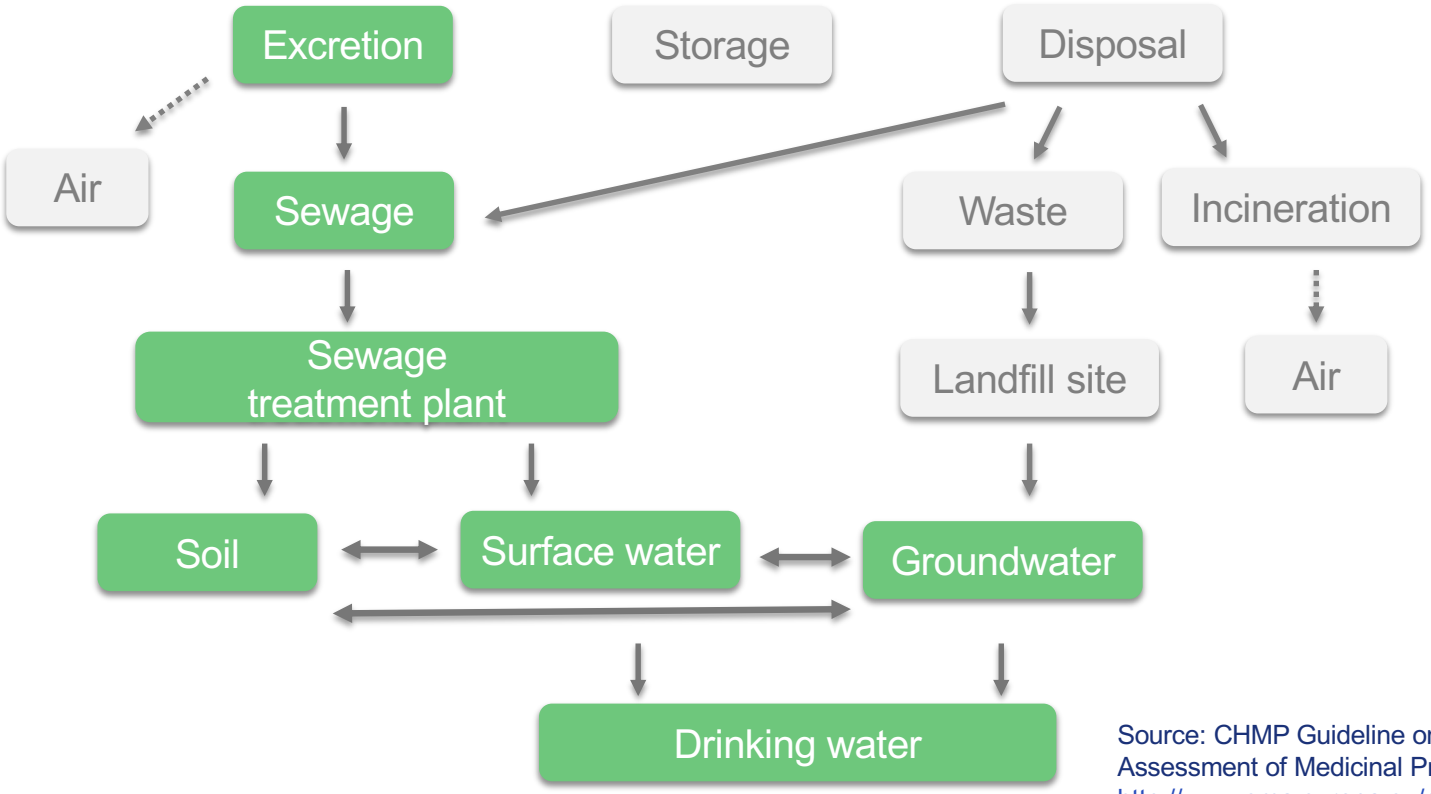
- Canada New Substance Notification Regulations (NSNR) under subsection 81 (1) of CEPA 1999 (New ERA Framework pending)

Sources and Fate of Pharmaceuticals in the Environment



Source: Klimaszyk P., Rzymski P. (2018) Water and Aquatic Fauna on Drugs: What are the Impacts of Pharmaceutical Pollution?. In: Zelenakova M. (eds) Water Management and the Environment: Case Studies. WINEC 2017. Water Science and Technology Library, vol 86. Springer, Cham

Pathways for Pharmaceuticals Entering in the Environment

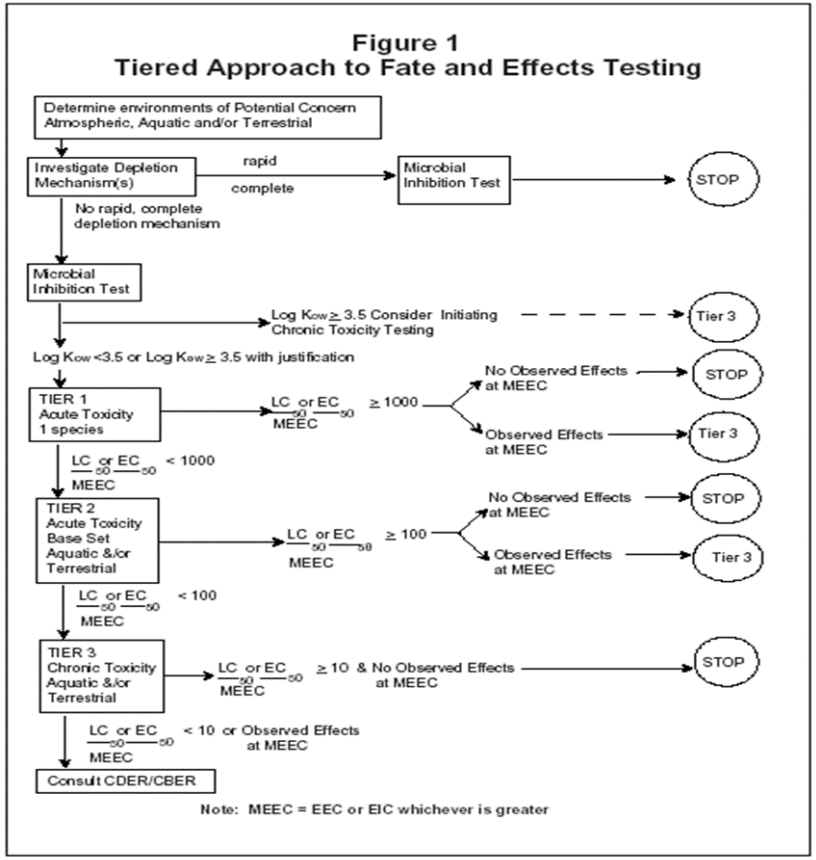


Source: CHMP Guideline on the Environmental Risk Assessment of Medicinal Products
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf

Anatomy of an ERA

Define Environmentally Relevant Components	• Consider API, human metabolism, and excretion to define environmentally relevant component(s).
Regulatory and Testing Strategy	• Physicochemical properties (log Kow, sorption), MOA, daily dose (EU), market volume (US, Canada)
Environmental Fate	• Where do APIs/metabolites reside after excretion (post consumer fate)? How do they behave in various environmental compartments (i.e. *biomass, water, soil, sediment*)?
Ecotoxicity	• Impact on environmental species following exposure to compounds (i.e. *fish, algae, daphnia* [aquatic]; *microorganisms* [sludge]; *chironomid* [sediment]; *earthworm, plants, collembola* [soil]).
Environmental Risk Assessment Outcome	• Present data and scientific assessment of risk to the environment following patient use.

US FDA EA Guidance



Trigger for full EA:
≥ 44,000 kg API/annum
(PEC ≥ 1 ppb)

Guidance for Industry: Environmental Assessment of Human and Biologics Applications: https://www.fda.gov/downloads/Drugs/Guidances/ucm070561.pdf

EU, ERA Tiered Approach Guidance

Stage in Regulatory Evaluation	Stage in Risk Assessment	Objective	Method	Test/Data Requirement
Phase I	Pre-screening	Estimation of exposure	Action limit	Consumption data, log Kow
Phase II Tier A	Screening	Initial prediction of risk	Risk assessment	Base set aquatic toxicology and fate
Phase II Tier B	Extended	Substance and compartment specific refinement and risk assessment	Risk assessment	Extended data set on emission, fate, and effects

Source: Section 3, Table 1 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf

EU, ERA Tiered Testing Requirements

Regulatory Evaluation Stage (approximate timeline)	Test	Recommended Protocol	Data Application in ERA
Phase I (4 months)	Log Kow - partition coefficient at pH 4-5, 7, 9	**OECD 107**	PBT assessment, fish bioaccumulation potential
Phase II Tier A (18 months)	Ready Biodegradation or sludge die-away	**OECD 301 or 314b**	Fate/biodegradation in sludge during wastewater treatment
	Sorption/desorption in sludge, sediment, soil	**OECD 106**	Sorption to sludge/land applied → terrestrial compartment binding to sediment and/or soil
	Aerobic Transformation in water/sediment	**OECD 308**	Transformation rate, reside in water and/or sediment compartment
	Sludge respiration inhibition	**OECD 209**	Inhibition of sludge micro-organisms, PNEC micro-organisms [EC15]
	Toxicity to algae	**OECD 201**	PNEC—surfacewater & groundwater (*daphnia*) [NOEC, EC10, EC50] (growth, development, and reproduction)
	Life cycle toxicity—*Daphnia magna* (water flea)	**OECD 211**	
	Fish early life stage test	**OECD 210**	
	Bioconcentration in fish (APIs log Kow > 3.0)	**OECD 305**	Bioconcentration factor
	Toxicity to Chironomid (sediment organism)	**OECD 218**	PNEC sediment [NOEC, EC10, LOEC]

PBT—persistent, bioaccumulative, and toxic

EU, ERA Tiered Testing Requirements

Regulatory Evaluation Stage	Test	Recommended Protocol	Data Application in ERA
Phase II Tier B terrestrial* (6 months)	Acute toxicity to earthworm	**OECD 207**	PNEC—soil [NOEC, LOEC, EC50]
	Collembola, Reproduction test	**ISO 11267**	
	Terrestrial plants, growth test	**OECD 208**	
	Soil Microorganisms: Nitrogen transformation test	**OECD 216**	
	Aerobic and anaerobic transformation in soil	**OECD 307**	Fate/transformation in soil

* Triggered by high sorption to sludge which is applied to land.

ERA Outcome:

What drug or drug-related residues will reside in environment, in what compartment(s), and for how long?
What are the effects, if any, on environmental organisms at environmentally relevant concentrations (PEC)?

- Risk assessed using PEC/PNEC ratio for sludge, surface water, ground water, water-sediment, and soil
- Labeling for persistence, bioaccumulation, and toxicity (PBT, vPvB), as applicable

Predicted Environmental Concentration (PEC)

EU-Phase I: *standard equation based on maximum daily dose*

$$PECsw\ [mg/L] = \frac{DOSEai \times Fpen}{WASTEWinhab \times Dilution}$$

PECsw action limit ≥ 0.01 µg/L
(dose ≥ 2 mg/day)

PEC_{SW}	Predicted environmental concentration in surface water	-- mg/L
DOSEai	Maximum daily dose applied per inhabitant	mg/(inh·d)
Fpen	Market penetration	0.01 [Default]
WASTEWinhab	Amount of wastewater per inhabitant per day	200 L/(inh·d) [Default]
DILUTION	Dilution factor	10 [Default]

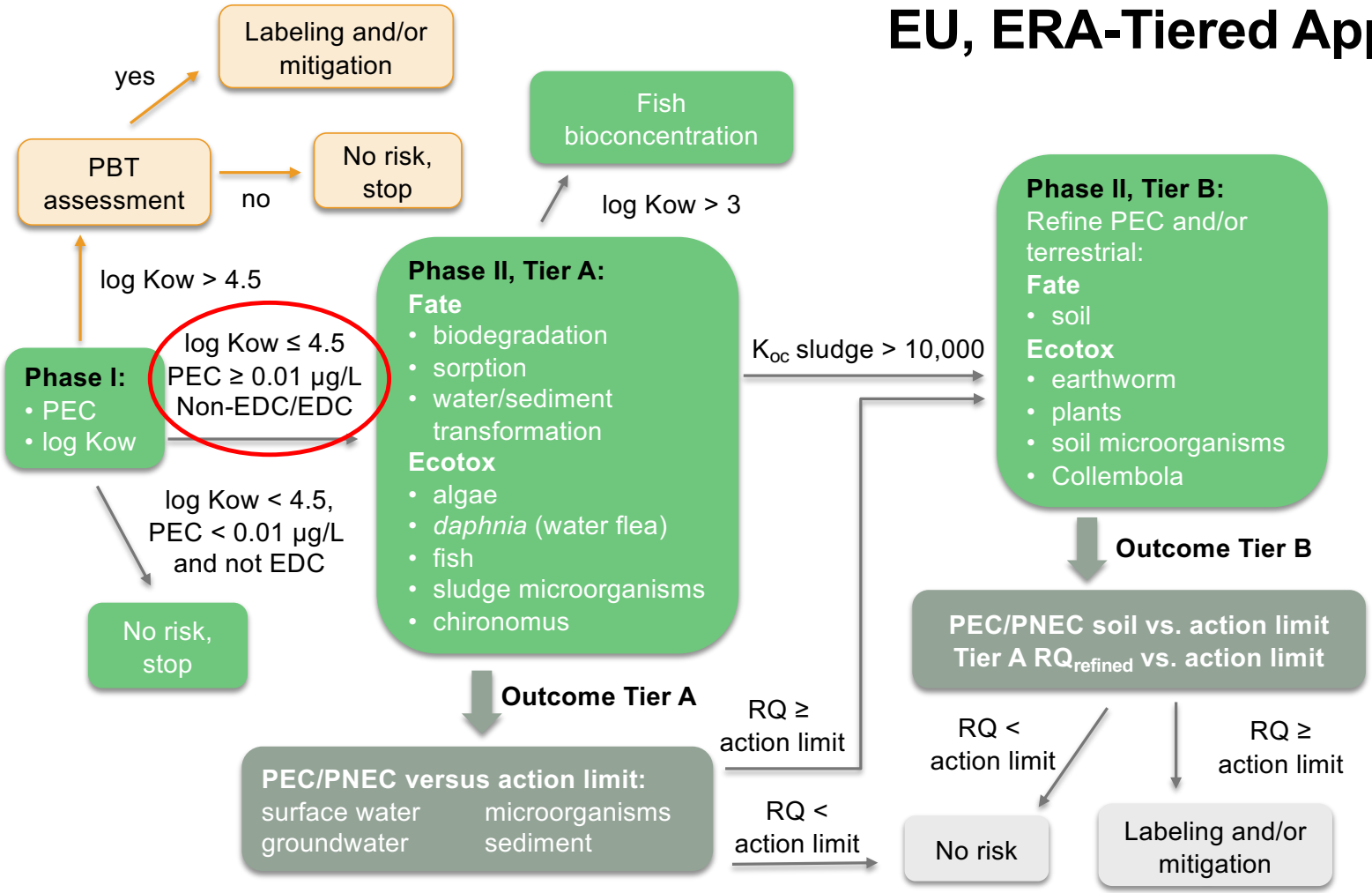
US: *standard equation based on kg/year market forecast*

$$EIC_{aquatic}\ (ppm) = A \times B \times C \times D$$
$$EEC\ or\ PEC = EIC_{aquatic} / 10$$

PECsw action limit ≥ 1.0 µg/L
(≥ 44,000 kg API/year)

$EIC_{aquatic}$ EEC or PEC	Expected Introductory Concentration Expected Environmental Concentration	-- mg/L
A	Usage ~5 years post filing	kg API/year
B	Amount of wastewater entering public treatment works/day	$1/1.22 \times 10^{11}$ [Default]
C	Conversion factor per day to per year	1/365
D	mg/kg conversion factor	1×10^{6}

EU, ERA-Tiered Approach



Current State—Regulatory ERAs

EU ERAs learnings - 2006 to present:

- > 90% of human medicinal products pose no risk to the environment.

- Fish bioconcentration data set: 3 of 54 APIs were classified as bioaccumulative ('B') according to REACH criteria (BCF > 2000). All 'B' APIs have log Kow value > 4. Industry proposal to EMA - increase current BCF testing trigger (log Kow > 3) to log Kow > 4.

Draft EMA ERA guidelines proposed Nov. 2018; update expected 2021.

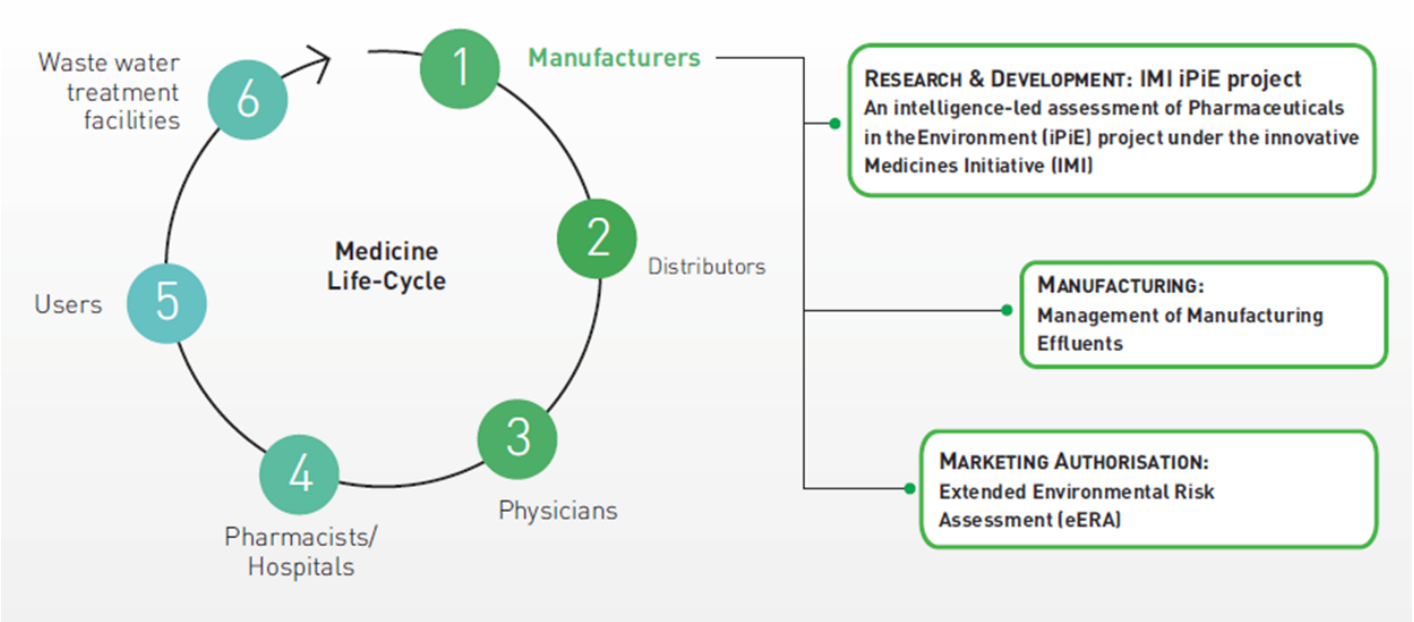
Canada and Japan:

Guidelines to be developed.

Industry Response to PIE

Eco-Pharmaco-Stewardship (EPS): A Lifecycle Approach

Objective: Providing knowledge and data enabling assessments of sustainability of pharmaceuticals



AESGP

Official representation of manufacturers of non-prescription medicines, food supplements, and self-care medical devices in Europe

efpia

European Federation of Pharmaceutical Industries and Associations

Represents research-based pharmaceutical industry operating in Europe.

medicines for europe

better access. better health.

Official representative body of the European generic and biosimilar pharmaceutical industry.

https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/pharmaceuticals-in-the-environment-pie/

Industry Response to PIE

Anti-microbial Resistance (AMR) Industry Alliance:

120+ members representing biotech, diagnostics, generics, and R&D pharma

In 2016, United Nations called for concerted action from governments and various sectors to address the implications of AMR in a comprehensive manner and implement strategies at national level. "The AMR Industry Alliance is the life-sciences industry response to the call for action."

Signatory Commitments:

- Work to reduce the development of AMR
- Invest in R&D that meets global public health needs with new innovative diagnostics and treatments
- Improve access to high-quality antibiotics and ensuring that new ones are available to all

Source: https://www.amrindustryalliance.org/

Summary

- For decades, academia, industry, regulators, governmental organizations, and non-governmental organizations alike have recognized the need to understand potential risks of PIE, which has resulted in legislative and regulatory action, ongoing research and testing initiatives, and various PIE-related programs.
- Pharmaceuticals enter the environment via multiple pathways, with the greatest contribution resulting from patient use.
- To date, the majority (>90%) of pharmaceuticals evaluated to support drug approval do not present a risk to the environment following patient use. Hazard does not necessarily indicate a risk at environmentally relevant concentrations.
- Patient benefit outweighs environmental risk concerns - environmental profile will not impact approval of human medicinal products.
- Research and collaborative efforts among industry, academia, and governmental agencies worldwide continue to enhance our knowledge and understanding of the hazards and risks associated with PIE.

Acronyms

AESGP - Association of the European Self-Medication Industry

AMR – Anti-microbial Resistance

API – Active Pharmaceutical Ingredient

BCF – bioconcentration factor

EA – Environmental Assessment (US FDA term)

ECx – Effect Concentration on x% of population

EDC – endocrine disrupting compound

EEC – Expected Environmental Concentration (or PEC)

EFPIA- European Federation of Pharmaceutical Industries and Associations

EIC – Expected Introductory Concentration

EMA – European Medicines Agency

EPS – Eco-Pharmaco Stewardship

ERA – Environmental Risk Assessment (EU EMA term)

EU – European Union

FDA – Food and Drug Administration (United States)

IMI-iPiE – Innovative Medicines Initiative-Intelligence-led assessment of Pharmaceuticals in the Environment

Acronyms, continued

ISO - International Organization for Standardization

Koc – sorption coefficient corrected for organic carbon content of matrix (i.e., sludge, sediment, soil)

LOEC – lowest observed effect concentration

log Kow – octanol-water partition coefficient

MAA – Marketing Authorization (EU)

MOA – Mechanism of Action

NOEC – no-observed effect concentration

OECD – Organization for Economic Co-operation and Development

PEC – Predicted Environmental Concentration

PECsw – Predicted Environmental Concentration in surface water

PBT – Persistent, Bioaccumulative and Toxic

PIE – pharmaceuticals in the environment

PNEC – predicted no effect concentration

ppb – parts per billion

REACH – Registration, Evaluation, Authorisation and Restriction of Chemicals, an EU Regulation

RQ – risk quotient (i.e., PEC/PNEC)

vPvB – very persistent, very bioaccumulative

US Regulations, information

- Basis:
  - **National Environmental Policy Act of 1969 (NEPA): all federal agencies to assess the environmental impact of their actions**
- Links to Guidance:
  - Guidance for Industry: Environmental Assessment of Human and Biologics Applications: https://www.fda.gov/downloads/Drugs/Guidances/ucm070561.pdf
  - MAPP Environmental Assessments and Claims of Categorical Exclusion: https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM079568.pdf
  - Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity Guidance for Industry: https://www.fda.gov/downloads/Drugs/Guidances/UCM444658.pdf
  - Environmental Assessment Technical Handbook (NTIS Publication Number PB 87175345/AS):https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB87175345.xhtml

- US FDA pharmaceutical disposal recommendations: https://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know

EU Regulations

- Basis
  - **Council Directive 2001/83/EC, Article 8, 3. (g) application for the marketing authorization (MAA) for a medicinal product for human use shall be accompanied by an environmental risk assessment (ERA)**
- Link to Guidance:
  - CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf
  - EMA Questions and Answers on the 'Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use': http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/06/WC500207858.pdf