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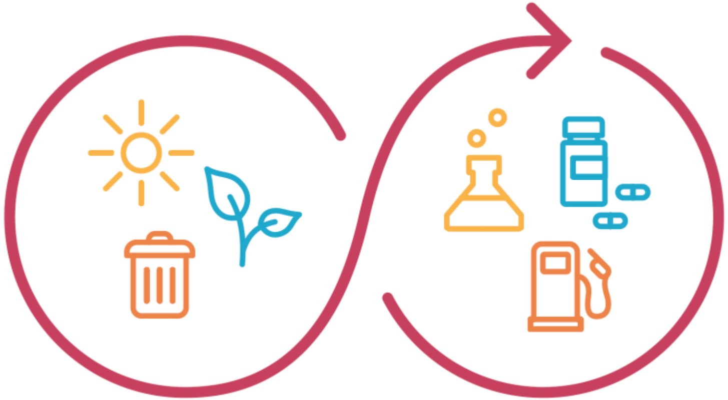
Pharmaceuticals in the aquatic environment



Group 6

Pharmaceutical Pollution: an Invisible but Widespread Issue

- Pharmaceuticals: concern when **residues enter water systems**
- APIs in soils, water, sediments, organisms, **drinking water**
- Main source: urban wastewater effluent
- Cause **harm to aquatic life** and raise concerns about **long-term human health & antimicrobial resistance**

Table 1.3. Pharmaceuticals found in surface, ground and drinking waters in all regions of the world

Global average and maximum concentration for surface water

Pharmaceutical compound	Theraputic group	Number of countries[1]	Average (µg/L)[2]	Maximum (µg/L)[2]
diclofenac	Analgesic	50	0.032	18.74
carbamazepine	Anticonvulsant	48	0.187	8.05
ibuprofen	Analgesic	47	0.108	303.0
sulfamethoxazole	Antibiotics	47	0.095	29.0
naproxen	Analgesic	45	0.050	32.0
oestrone (E1)	Oestrogens	35	0.016	5.0
oestradiol (E2)	Oestrogens	34	0.003	0.012
ethinylestradiol (EE2)	Oestrogens	31	0.043	5.9
trimethoprim	Antibiotics	29	0.037	13.6
paracetamol	Analgesic	29	0.161	230.0
clofibric acid	Blood lipid modifying agents	23	0.022	7.91
ciprofloxacin	Antibiotics	20	18.99	6500
ofloxacin	Antibiotics	16	0.278	17.7
oestriol	Oestrogens	15	0.009	0.48
norfloxacin	Antibiotics	15	3.457	520.0
acetylsalicylic acid	Analgesic	15	0.922	20.96

1. Number of countries: countries worldwide with positive detection of pharmaceuticals in surface water, groundwater or drinking water.
2. Average and maximum concentrations are of measured surface water concentrations.
Source: (aus der Beek et al., 2016[5]).

Source: aus der Beek, T. et al. (2016), "Pharmaceuticals in the environment-Global occurrences and perspectives", *Environmental Toxicology and Chemistry*, Vol. 35/4, pp. 823-835, http://dx.doi.org/10.1002/etc.3339

Pharmaceutical Pollution: an Invisible but Widespread Issue

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⚠ APIs are a **challenge to manage**:

- Potent at low doses → harmful even in tiny amounts
- Designed to be persistent → slow to degrade
- Continuously released → faster than they break down
- Not removed by standard wastewater treatment

→ What are the **risks**?

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Environmental Impact: Aquatic Life Disruption

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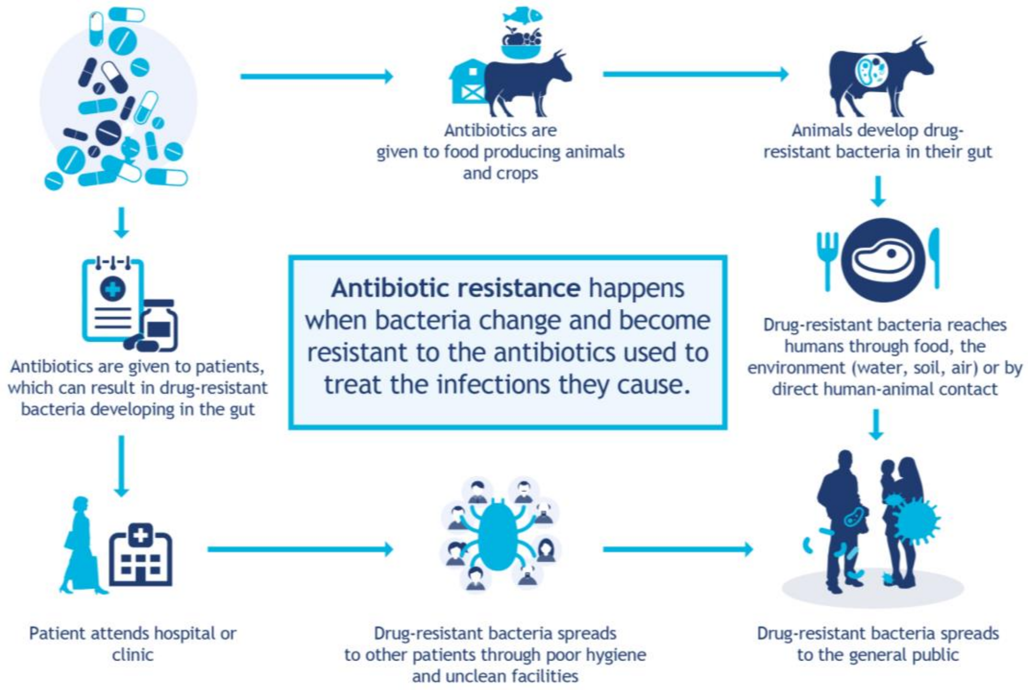
Table 1.4 Examples of measured effects of certain pharmaceutical residues on aquatic organisms in laboratory studies

Therapeutic group	Examples of Pharmaceutical	Impact and effected organisms	Examples of studies
Analgesics	Diclofenac, Ibuprofen	Organ damage, reduced hatching success (fish) Genotoxicity, neurotoxicity and oxidative stress (mollusk) Disruption with hormones (frog)	(Näslund et al., 2017[125]) (Mathias et al., 2018[126]) (Xia, Zheng and Zhou, 2017[127]) (Mezzelani et al., 2016[128]) (Efosa et al., 2017[129])
Antibiotics	-	Reduced growth (environmental bacteria, algae and aquatic plants)	(Roose-Amsaleg and Laverman, 2016[130]) (Guo, Boxall and Selby, 2015[131]) (Brain et al., 2008[132])
Anti-cancer	Cyclophosphamide[1], mitomycin C, fluorouracil, cisplatin, doxorubicin	Ecotoxcity, genotoxicity	(Česen et al., 2016[133]) (Zounková et al., 2007[134]) (Araújo et al., 2019[135]) (EC, 2016[136])
Antidiabetics	Metformin	Potential endocrine-disrupting effects (fish)	(Niemuth et al., 2015[137]; Crago et al., 2016[138])[2]
Anti-convulsants	Carbamazepine, phenytoin, valproic acid	Reproduction toxicity (invertebrates), development delay (fish)	(Ferrari et al., 2003[139]) (Martinez et al., 2018[140])
Antifungals	Ketoconazole, clotrimazole triclosan	Reduced growth (algae, fish), reduced algae community growth, disruption of hormones (rats)	(Vestel et al., 2016[141]) (Porsbring et al., 2009[142]) (Stoker, Gibson and Zorrilla, 2010[143])
Antihistamines	Hydroxyzine, fexofenadine, diphenhydramine	Behaviour changes, growth and feeding rate (fish) Behaviour changes and reproduction toxicity (invertebrates)	(Berninger et al., 2011[144]) (Kristofco et al., 2016[145]) (Jonsson et al., 2014[146]; Meinertz et al., 2010[147])
Antiparasitics	Ivermectin	Growth and reduced reproduction (invertebrates)	(Garric et al., 2007[148])
Beta blockers	Propranolol	Reproduction behaviour (fish), reproduction toxicity (invertebrates)	(Giltrow et al., 2009[149]) (de Oliveira et al., 2016[150])
Endocrine active pharmaceuticals	E2, EE2, levonorgestrel	Disruption with hormones causing reproduction toxicity (fish, frogs)	(Kidd et al., 2007[116]) (Kvarnryd et al., 2011[120]) (Gyllenhammar et al., 2009[121]) (Armstrong et al., 2016[151]) (Moore et al., 2016[122]) (Nelles, Hu and Prins, 2011[123])
Psychiatric dugs	Fluoxetine, sertraline, oxazepam, citalopram, chlorpromazine	Behaviour changes - feeding, boldness, activity, sociality (fish) Disruption with hormones (fish) Behaviour changes - swimming and cryptic (invertebrates) Reproduction toxicity and disruption with hormones (invertebrates)	(Brodin et al., 2013[152]; Brodin et al., 2014[113]) (Kellner et al., 2016[114]) (Schultz et al., 2011[153]) (De Castro-Català et al., 2017[154]) (Di Poi et al., 2014[155]) (Campos et al., 2016[156]) (Lazzara et al., 2012[157])

Source: OECD (2019), *Pharmaceutical Residues in Freshwater: Hazards and Policy Responses*, OECD Studies on Water, OECD Publishing, Paris, https://doi.org/10.1787/c936f42d-en.

- **Hormones** (e.g. from birth control) cause feminization of male fish → collapse of fish populations
- **Psychiatric drugs** alter fish behaviour (e.g. more aggression, less caution) → disrupted food webs & biodiversity loss
- **Bioaccumulation & trophic transfer**: drug residues move up the food chain → exposes predators (and humans) to harmful residues

Human Health Concerns : Antimicrobial Resistance (AMR)



Source: Antibiotic Resistance – How It Spreads, World Health Organization (WHO)

- **Antimicrobials** (antibiotics, antifungals, antivirals) enter water through wastewater, excretion, and agriculture.
- Microorganisms exposed to low concentrations develop resistance.
- **Resistant strains** spread through water, food, or contact, reaching humans.

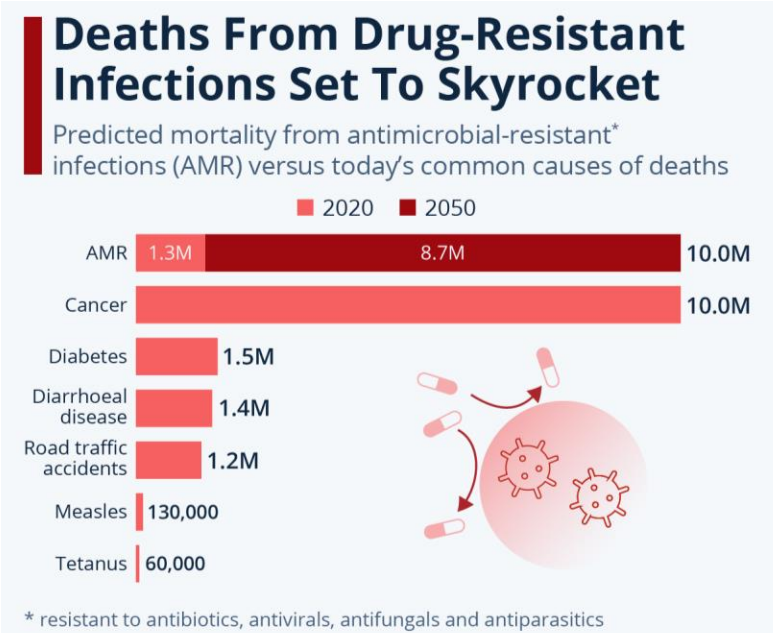
Human Health Concerns : Antimicrobial Resistance (AMR)

Current Situation :

- 700,000-1.3 million deaths globally per year (WHO, UN Environmental Programme).
- Increasing difficulty treating previously manageable infections.

Projected Health Crisis by 2050 :

- Deaths from AMR may surpass those from cancer (up to 10 million/year).
- Routine procedures (e.g., surgeries, childbirth, chemotherapy) become higher-risk.



Source: Bracing for Superbugs 2023 (UN Environmental Programme)

Human Health Concerns : Endocrine Disruptors & Antidepressants in Water

Endocrine Disruption

- Hormone-like pharmaceuticals (e.g., synthetic estrogens) disrupt hormonal balance, even at low doses.
- Associated with **infertility**, **early puberty**, **breast and prostate cancers**.
- Particularly harmful to **fetuses**, **infants**, and **reproductive health**.

Antidepressants in Water

- Trace levels (e.g., fluoxetine) have been detected in drinking water.
- May influence **mood, behavior, and neurodevelopment**, especially in children.
- **Long-term effects remain uncertain**, but growing evidence raises concern.

Economic & Social Costs

- **Healthcare** costs rise due to longer hospital stays and resistant infections.
- **Water treatment** upgrades to remove pharmaceutical residues become costly for cities and taxpayers.
- **Agriculture and fishing** are impacted when drug residues contaminate food and disrupt ecosystems.

The Cost of Inaction:

- Billions more spent on treatments and infrastructure.
- Drinking water may become unaffordable for vulnerable groups.
- Food supply chains and rural economies at risk.

Progress in Assessing Pharmaceutical Pollution

Improved Analytical Methods:

- Highly sensitive techniques now identify extremely low pharmaceutical concentrations.
- Enable precise tracking of environmental pollution levels.

Predictive Models (QSARs):

- Compensate for data gaps regarding pharmaceutical persistence and mobility.
- Inform regulatory prioritization and safer chemical development.

Progress in Assessing Pharmaceutical Pollution

Detection: using instruments (e.g., mass spectrometry) to sense the presence of pharmaceuticals in environmental samples

Identification: pinpointing specific compounds and their transformation products within the detected signals

Quantification: Measuring the concentrations of these compounds, even at trace levels, to assess exposure risks and treatment effectiveness

Technological Solutions to Mitigate Pollution

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Advanced Wastewater Treatment Technologies:

- Ozonation, activated carbon adsorption, ultrafiltration.
- Full-scale post-ozonation combined with powdered activated carbon effectively reduces micropollutants.

Bioremediation Approaches:

- Microbial degradation as a complementary, sustainable option.

Industry Initiatives:

- Advanced on-site wastewater treatment solutions reducing pharmaceutical emissions.

Table 3.1. Source-directed policy instruments to prevent the release of pharmaceutical residues to water bodies

Policy instrument type	Policy instrument	Description
Regulatory	Substance bans	Complete prohibition of non-essential use of problematic pharmaceuticals
	Marketing authorisation	Evaluation-dependent authorisation of pharmaceuticals based on their predicted risks to human health and the environment. Such evaluations can also take into account principles of green chemistry such as "rational design" or "benign by design". Incentives can be used for green pharmaceuticals, such as fast-track marketing authorisation, reimbursement for greener APIs or longer exclusivity.
	Environmental quality norms and water quality standards	EQNs and water quality standards for harmful substances in water bodies. Detection above safe levels (or PNEC) can require action upstream to protect water bodies from harmful effects.
	Green public procurement	Clear and shared environmental criteria (and performance indicators) to pre-qualify pharmaceuticals for public procurement. Added advantage of impacting trade of pharmaceutical products across country borders.
	Good manufacturing practices and audits	Mandatory codes of conduct to reduce emissions from pharmaceutical manufacturing plants, as part of good manufacturing practice audits. Alternatively, environmental criteria for green public procurement could incorporate good manufacturing practices.
	Effluent discharge permits	Effluent discharge permits issued to pharmaceutical manufacturing plants with conditions for protection of drinking water sources and freshwater ecosystems. Non-compliance may lead to fines or withdrawal of operation permits.
	Best available techniques	Guidance documents that assist industrial operators with the design, operation, maintenance and decommission of manufacturing plants in compliance with environmental quality standards and discharge permit conditions (i.e. based on the PNEC or safe level of discharge). A BAT-based approach can be used to help set emission limit values as part of discharge permit conditions.
	Drinking water quality standards and water safety planning	Preventive measures to identify and address the source of risks to drinking water.
Economic	Subsidies for "green" action	Financial support from governments in return for environmental commitments by the private sector, such as reduced pollution from pharmaceutical manufacturing facilities.
	Subsidies for green pharmacy innovation	Subsidies or tax incentives for innovations green pharmacy, biological therapies, personalised or precision medicines to improve the business case for industry.
	Pollution charges	Charges to pharmaceutical manufacturing plants for discharging toxic effluent to water bodies.
Voluntary	Information campaigns	Transfer of knowledge or persuasive reasoning to industry on how to avoid water pollution.
	Voluntary agreements between private and public sectors	Non-legally binding agreements negotiated on a case-by-case basis between industry and public authorities fixing environmental targets or specific mitigation measures (e.g. changes in the production chain).

Source: OECD studies on water - 2019

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Policy Developments and Collaborative Stewardship

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- **EU Regulatory Actions:**
  - Environmental Risk Assessments (ERA) for APIs mandatory since 2005.
  - EU Chemicals Strategy for Sustainability (CSS) targeting PMT/vPvM substances.
- **Safe and Sustainable by Design (SSbD):**
  - Pharmaceutical industry's proactive approach to reducing environmental harm from the design phase.
  - Eco-Pharmaco Stewardship (EFPIA) as a model for industry collaboration.
- **Disposal and Application Guidelines:**
  - National return programs for unused medications.
  - Guidelines for manure and biosolids application to reduce agricultural pollution.

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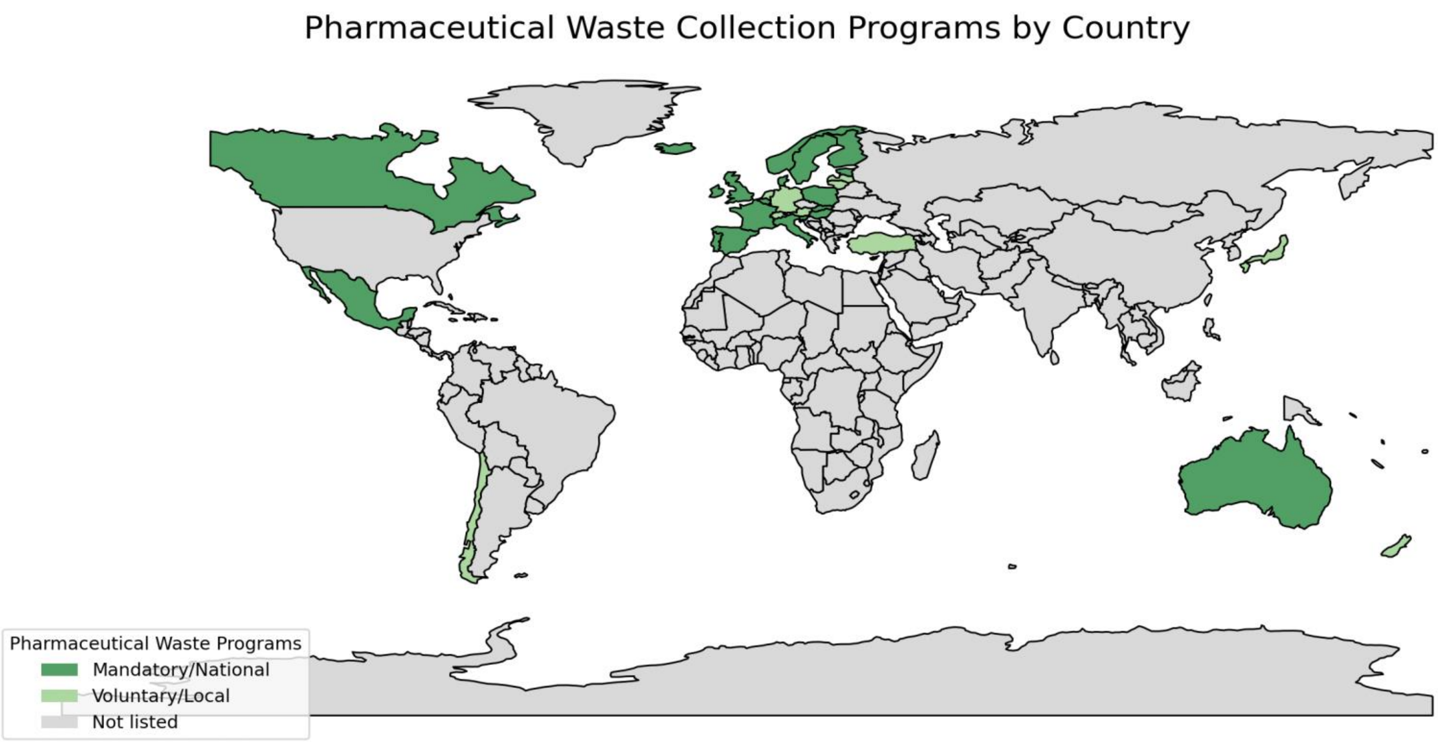
Achievements, Remaining Challenges, and Future Directions



Source: OECD studies on water 2022

Map generated on VS code

What obstacles are preventing further progress

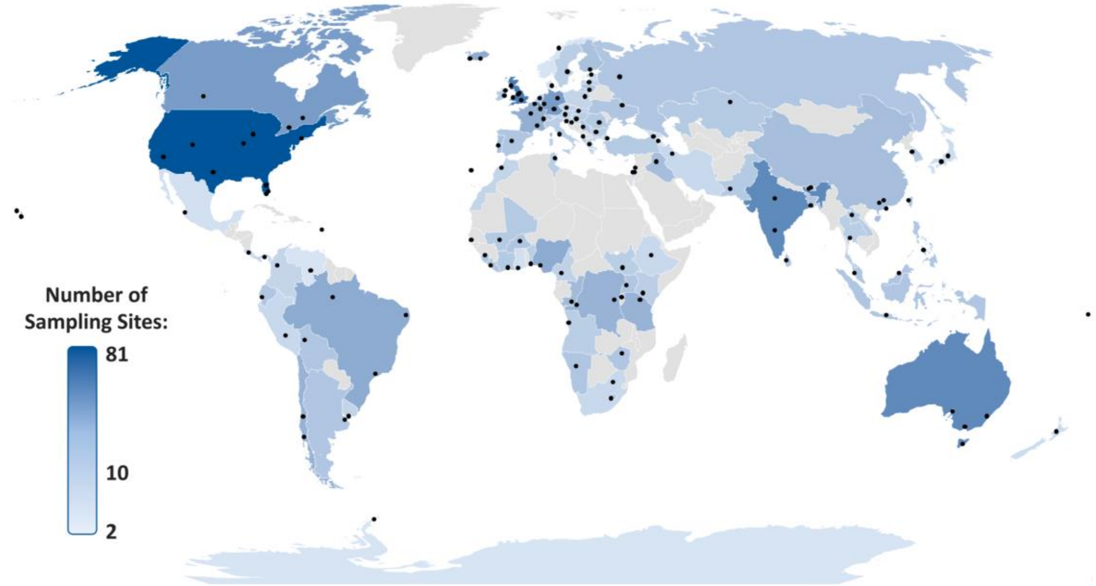


Fig. 1. Locations of studied rivers/catchments (n = 137) for our global study (Dataset S2). Points indicate groups of sampling sites across respective river catchments and countries are shaded based upon the total number of sampling sites.

Source: Wilkinson JL, Boxall ABA, Kolpin DW, Leung KMY, Lai RWS, Galbán-Malagón C et al. Pollution pharmaceutique des rivières du monde. Proc Natl Acad Sci USA

- **Incomplete and Uneven Regulations:**
  - Lack of data from certain countries
  - Lack of strict and harmonized regulation
  - Sometimes difficult to track the active ingredients of compounds

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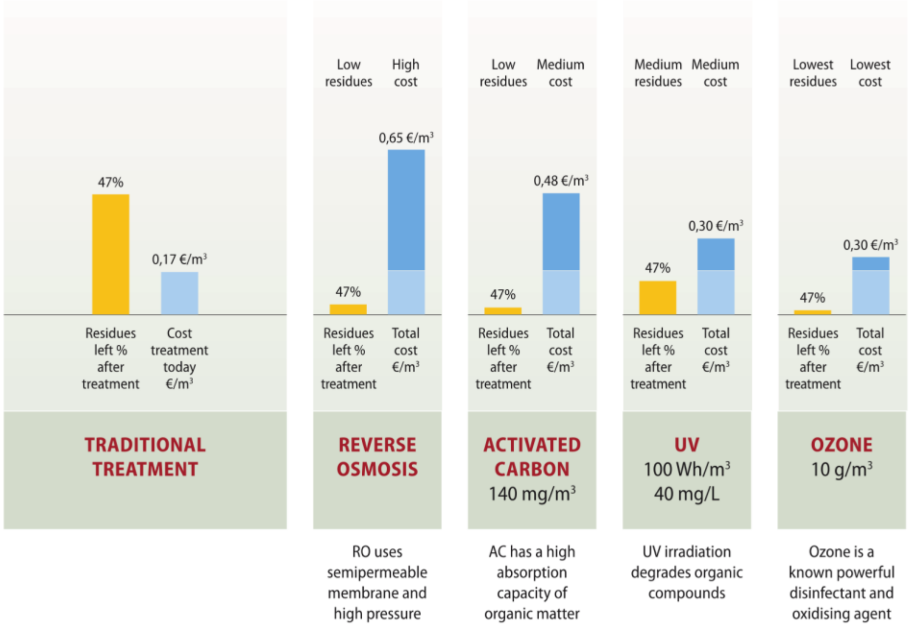
What obstacles are preventing further progress

- **Inadequate Wastewater Treatment Plants:**

  - Lack of economics resources in developing countries
  - Only a few countries use advanced technologies

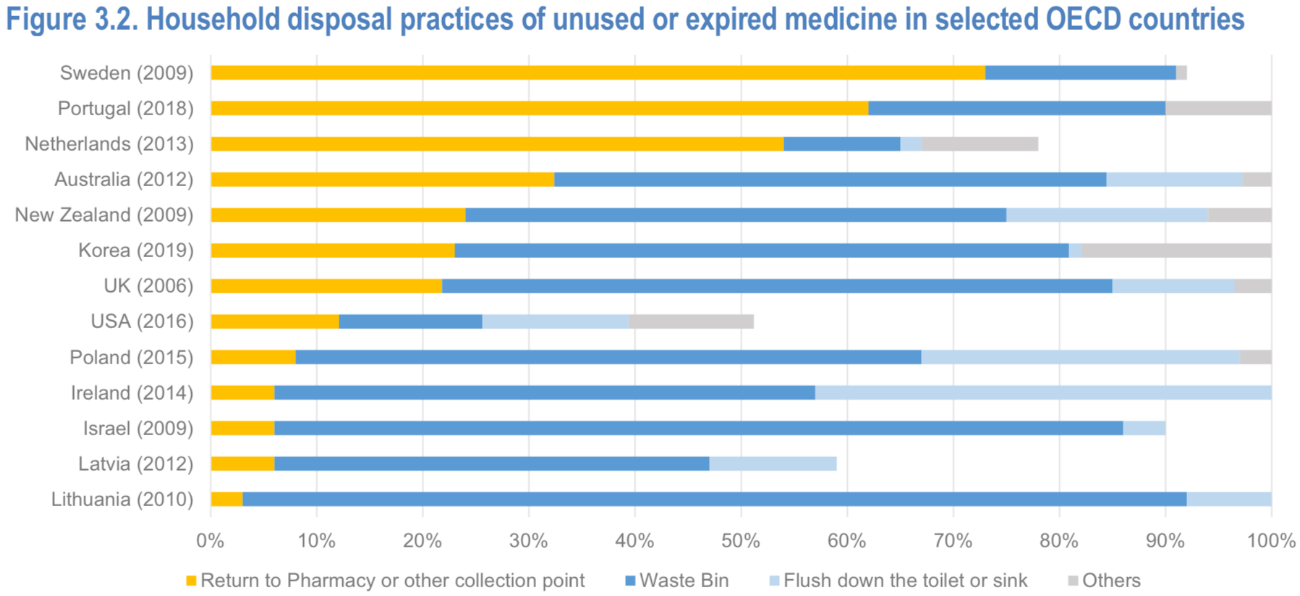
Figure 3.1. Relative reduction efficiency to remove pharmaceuticals and cost comparison between different advanced wastewater treatment methods



Source: OECD (2019), *Pharmaceutical Residues in Freshwater: Hazards and Policy Responses*, OECD Studies on Water, OECD Publishing, Paris

What obstacles are preventing further progress

- Insufficient awareness and waste management



Source: OECD (2022), *Pharmaceutical Residues in Freshwater: Hazards and Policy Responses*, OECD Studies on Water, OECD Publishing, Paris

What solutions can overcome these challenges?

Act across the full life cycle: green design, LCA, regulation

Improve treatment: activated carbon, wetlands, ozonation

Enhance monitoring: sensors, modelling, biomonitoring

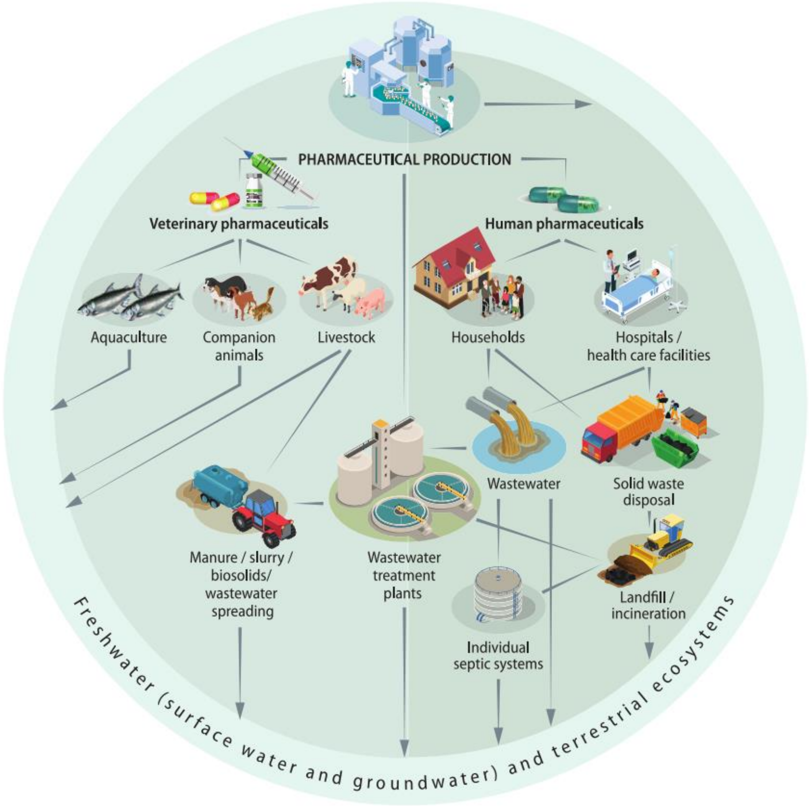
Make ERA mandatory — even for legacy substances

Engage stakeholders: health professionals, industry, citizens

Support take-back systems and green procurement

What solutions can overcome these challenges?

- Visual overview of the main emission pathways — a reminder that environmental solutions must address the entire pharmaceutical chain.



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Achievements, Remaining Challenges, and Future Directions

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Achievements:

- Improved international awareness and regulatory responses.
- Technological advancements reducing pharmaceutical residues significantly.

Remaining Challenges:

- Need for broader global participation and harmonization of regulations.
- Addressing complexities in global pharmaceutical production and environmental impact.

Future Directions:

- Further integration of Safe and Sustainable by Design principles.
- Ongoing development and refinement of predictive and detection methodologies.

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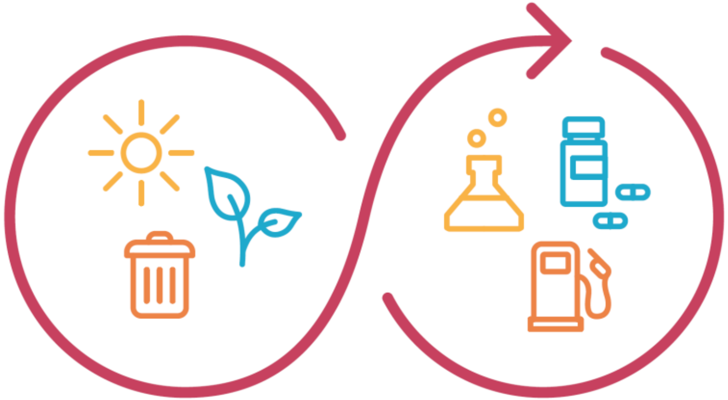
Thank you for your attention!



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