CWPharma

CLEAR WATERS FROM PHARMACEUTICALS

Joint Conclusions for API Emission Reductions

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Executive Summary

Elevated levels of active pharmaceutical ingredients (API) have been detected in the Baltic Sea for many years. These APIs are often discharged from hospitals, households, pharmaceutical manufacturing plants, and animal farms, among other sources. As APIs are not completely degraded in municipal wastewater treatment plants (WWTP), they are then transported to the Baltic Sea. Although research on the effects of APIs in the Baltic Sea has been ongoing, the consequences of API discharges on the environment, in terms of potentially risky ecological effects, have not yet been fully evaluated.

The European Union's Interreg Baltic Sea Region programme funded the Clear Waters from Pharmaceuticals (CWPharma) project, which quantified API loading into the Baltic Sea from six river basin districts. Seven Baltic Sea Region (BSR) countries were involved as CWPharma partners (Denmark, Estonia, Finland, Germany, Latvia, Poland and Sweden). Surface water, soil, and sediment samples were collected from coastal, rural, and agricultural locations and analysed for up to 80 APIs. By comparing the API concentrations detected in rivers with predicted no-effect levels (PNEC), the environmental risk of individual APIs was quantified. A GIS-based model was developed which allowed illustration and assessment of API loads into the Baltic Sea coming from the project partner countries, as well as evaluation of the impacts of various emission reduction scenarios.

Different types of emission reduction measures were proposed. Reductions of API emission from WWTPs through the application of advanced wastewater treatment (AWT) technologies were experimentally validated at full- and pilot-scale. AWT technologies tested in CWPharma included full-scale ozonation and various post-treatment technologies, such as moving bed bioreactors, constructed wetlands, deep bed filters using sand/anthracite, and granular activated carbon. Additionally, 21 recommendations for other reduction measures focused on improving collection and disposal of unused pharmaceuticals and pharmaceutical waste, targeting various groups and emitters, were also developed.

By simulating the variety of API reduction methods within the API loading model, the most effective measures for reducing API emissions could be determined. Similarly, both the costs and global warming potential of upgrading various classes of WWTPs with AWT in the form of ozonation or activated carbon were calculated for each CWPharma project partner country.

This report summarizes the most important recommendations elicited from the CWPharma project.

Recommendations for avoiding API emissions to the environment

To improve collection of APIs, residents should return all unused household human and veterinary medicines anonymously and free of charge to dedicated collection points within all Baltic Sea countries. Increasing the awareness of residents, medical doctors, pharmacists, veterinarians and farmers about the negative effects of pharmaceuticals in the environment should be undertaken through targeted information campaigns. Hospitals and other healthcare institutions should collect their own pharmaceutical waste and send it directly to the country-specific appropriate waste treatment facilities. Farmers should be responsible for organizing the transport of their unused veterinary medicines.

To improve the disposal of APIs, different disposal methods are recommended depending on the country regulations. If pharmaceutical wastes are separately collected, high temperature incineration (~ 1100 - 1300°C) is the recommended treatment method, unless a lower temperature is proven to irreversibly transform the active ingredients into non-hazardous substances. If unused medicines and pharmaceutical wastes are collected with mixed household waste, incineration at lower temperatures is the next best waste treatment option.

Recommendations for technical measures minimizing API emissions to the environment

To reduce emissions of environmentally risky APIs to the Baltic Sea, indirect discharges of APIs, such as those from hospitals, households, pharmaceutical manufacturing plants, and animal farms, should be controlled. Municipal WWTPs should be upgraded with AWT technologies. The suitability of AWT technologies should be determined on a site-specific basis by monitoring crucial water quality parameters and conducting lab-scale tests. When evaluating AWT technologies, in addition to the local boundary conditions, the carbon footprint of the different technologies should be considered. If ozonation is selected as the AWT technology, a biological post-treatment step is necessary. In terms of cost and technical efficiency, if AWT is implemented to reduce API loading into the Baltic Sea, upgrades should start first at larger WWTPs and then at smaller WWTPs.

To speed up WWTP upgrades and implementation of AWT technologies, national knowledge platforms for sharing technical information on API removal should be established. Depending on the local API of concern, significant reduction in API emissions will require a combination of technical and other reduction measures.

Recommendations for improving knowledge on emissions, environmental concentrations and ecotoxicity of APIs

To reduce API emissions from the pharmaceutical industry, environmental permits mandate the plants to estimate their API emissions and impacts on WWTPs and surface waters. When necessary, environmental permit requirements for pharmaceutical plants should be further supplemented with industrial wastewater contract requirements.

To improve knowledge of API emissions and consequently improve models predicting API loading into the Baltic Sea, the public availability of API consumption statistics should be improved.

To improve knowledge of the ecological effects of APIs, knowledge on the environmental risks of APIs must be improved via collection of more ecotoxicological data on single APIs and their metabolites, on mixture toxicity, on toxic effects for different trophic levels, and on chronic effects. Likewise, more studies on the use of veterinary medicines and their dispersal in the environment should be conducted. APIs should be included in regular environmental monitoring programmes, and analytical methods for API detection, including metabolites, hormones and antibiotics, prioritising those seldom analysed so far, should be further refined to enable more comprehensive quantification of API concentrations in the environment.

1. Introduction

Background

Following the release of the Helsinki Commission (HELCOM) and United Nations Educational, Scientific and Cultural Organization (UNESCO) report on pharmaceuticals in the Baltic Sea [1] as part of the Baltic Sea Action Plan (BSAP), numerous Interreg-funded research projects focusing on loading, treatment and reduction measures of active pharmaceutical ingredients (APIs) into the Baltic Sea have been conducted.

This report covers the results of the Clear Waters from Pharmaceuticals (CWPharma) project, which was funded by the Interreg Baltic Sea Region programme of the EU. CWPharma was a collaboration between project partners from Denmark, Estonia, Finland, Germany, Latvia, Poland, and Sweden, and other associated organizations. Over the span of 3 years, the project quantified the API loading into the Baltic Sea from six river basin districts. The concentrations of up to 80 APIs in surface water, soil, and sediment samples collected from coastal, rural, and agricultural locations within these river basin districts were analysed (Figure 1). The measured API concentrations in rivers were compared to predicted no effect concentrations (PNECs) to determine which APIs posed an environmental risk. API loads reaching the Baltic Sea from the different countries were estimated using a model developed within the project [2]. This model was then evaluated with modified input data to estimate the potential effect of different emission reduction scenarios on API loading. These emission reduction measures included both purification approaches, such as technical wastewater treatment plant upgrades (WWTPs) to reduce API emissions from WWTPs, as well as preventative approaches, including proper disposal of pharmaceutical waste from indirect dischargers, such as hospitals, households, pharmaceutical manufacturing plants, and animal farms.

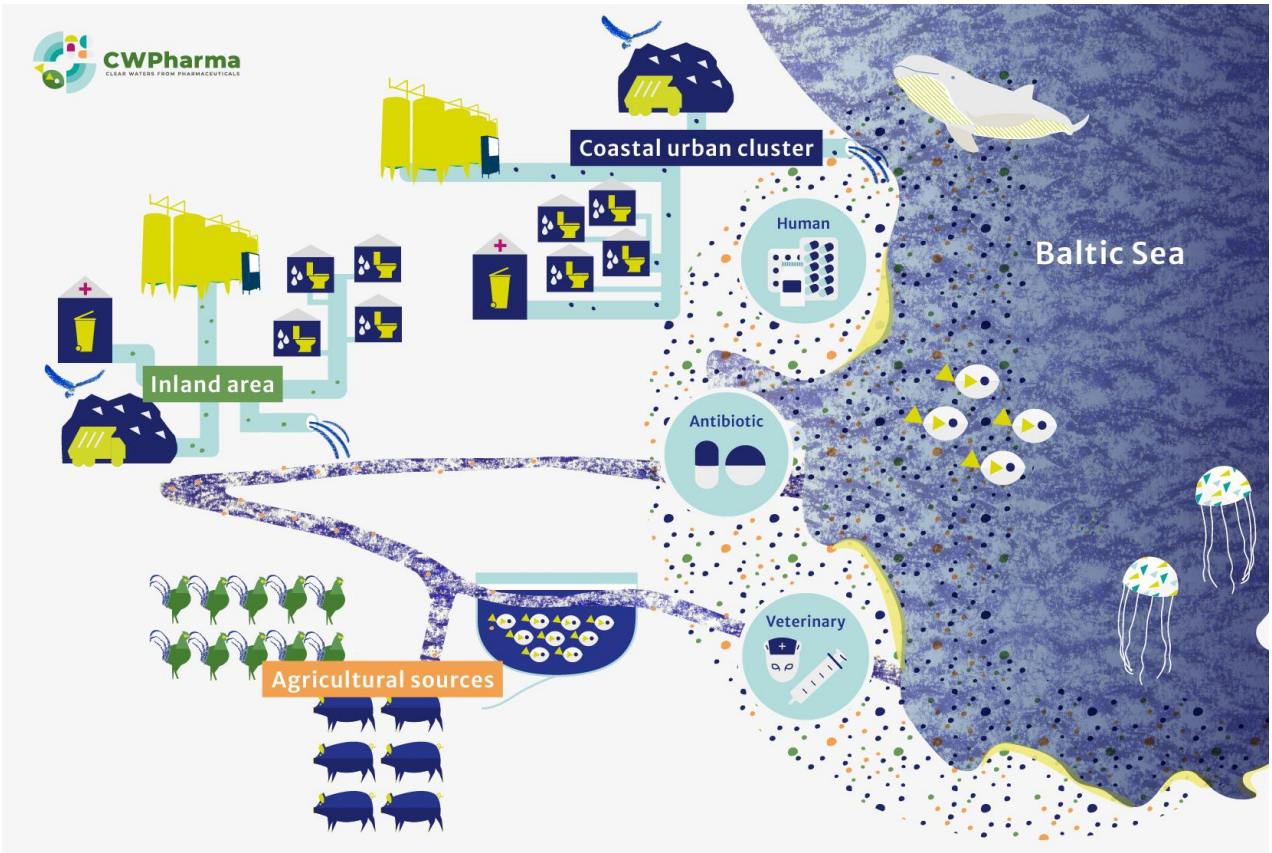


Figure 1: Sources of API contributions to the Baltic Sea.

Currently, except for Germany and Sweden, no CWPharma project partner countries have a national strategy for reducing API emissions. The Trace Substance Strategy of the German Federal Government was developed in 2017 through a multi-stakeholder dialogue, which included representatives from industry, environmental NGOs, municipal associations, drinking water suppliers, WWTP operators, federal government departments, public authorities and federal state representatives [3, 4]. In 2018, the German Environment Agency transferred this strategy into recommendations which outline mitigation strategies at the source, for the users, and for end-of-pipe measures [5].

The first National Pharmaceutical Strategy in Sweden was adopted by the Swedish Government and the Swedish Association of Local Authorities and Regions in 2011, and was revised in 2020 [6]. It supports reducing the environmental impact of medicines by minimizing medicine disposal and investigating the potential for voluntary environmental classification to ensure environmental aspects are considered when making decisions regarding benefits. The strategy also addresses responsible use of existing as well as newly introduced antibiotics. An action plan to supplement the strategy has been prepared and is revised once a year or as required. A knowledge centre for Pharmaceuticals in the Environment has also been set up at the Swedish Medical Products Agency, which provides a platform for dialogue and cooperation to increase the environmental awareness associated with APIs in both Sweden and the EU. The Swedish Environmental Protection Agency has also evaluated the needs, technology and consequences of advanced wastewater treatment [7]. As a result, Swedish municipal WWTPs can apply for financial support to implement advanced techniques for API removal.

CWPharma project partner countries without explicit API reduction strategies at the present time include Latvia, Lithuania, Finland, Denmark, Estonia and Poland. Many EU countries prefer to rather follow international agreements and EU directives and guidelines. However, more information on API emissions and occurrence is currently being generated in several projects within the Baltic Sea Region (BSR).

The objective of this report is to convert and consolidate CWPharma results into recommendations aimed at reducing API loading into the Baltic Sea. This report is structured as follows: first, several recommendations from CWPharma work packages 2-4 are summarized and discussed along with a suggested timeline for implementation, based on whether short-term (<1 year), intermediate (1-4 years), or long-term (4+ years) schedules are likely. Potential social, economic, technological and political barriers to the implementation of recommendations are then examined. Following this, lessons learned from CWPharma (including work package 5) are discussed together with outstanding research gaps to provide a clear path forward for reducing API emissions into the Baltic Sea.

2. Recommendations for reducing API loading

Recommendations for improving collection and disposal of unused pharmaceuticals and pharmaceutical waste

Recommendation #1: Residents should be able to return all unused human and veterinary household medicines anonymously and free of charge to dedicated collection points within all Baltic Sea countries. Although this was also explicitly recommended in the UNESCO HELCOM report [1], it is still especially applicable due to non-uniform take-back schemes in Germany, the lack of legislation defining parties responsible for take-back schemes in Latvia, and the lack of API collection information in Lithuania, Poland and Russia [8]. Permissible collection points could be pharmacies or hazardous waste collection sites. A sufficiently high density of collection points close to residents should be ensured. Information about the location of collection points and sorting instructions should be concise, understandable, and easily accessible for residents, for example through websites: portals which identify collection points already exist on a German[1] and European[2] level. Collection point operators are then responsible for transferring the collected waste to waste treatment facilities for proper disposal according to country regulations. For certain APIs which are extensively metabolized in the human body, such as ibuprofen and carbamazepine, improving disposal could notably reduce their loading into the Baltic Sea [9].
More detailed information can be found in the CWPharma Activity 4.1 [8] and 5.1 [9] reports.
Timeline for implementation: As establishing collection points likely requires accompanying legislation, implementation could take between 1-4 years or 4+ years

Recommendation #2: Increase the awareness of residents, medical doctors, pharmacists, veterinarians and farmers about the negative effects of pharmaceuticals in the environment through targeted information campaigns. This was also explicitly recommended in the UNESCO HELCOM report [1]. For residents and farmers, communicating information on proper disposal of unused medicines and highlighting the harmful environmental impacts of incorrectly disposed human and animal medicines should be arranged and suited to the target audience. Pharmacists or veterinarians should verbally instruct their customers (residents or farmers) about proper pharmaceutical usage, disposal, and collection points when providing the medication. Billboards or other print (brochures), television, and/or online media (smartphone applications, videos) could be used to disseminate reminders about proper disposal of pharmaceuticals (Figure 2).

The negative effects of API emissions and improper disposal of unused medicines and other waste containing pharmaceutical residues, as well as good practices for proper disposal, could be included into the medical education of doctors, veterinarians, medical staff, and pharmacists.
More detailed information can be found in the CWPharma Activity 4.1 [8] and 4.2 [10] reports.
Timeline for implementation: Although this is a continuous activity, if it requires accompanying legislation, implementation could take between 1-4 years, but if agencies can conduct campaigns themselves, it could take <1 year to implement

[1] https://arzneimittelentsorgung.de/home/

[2] http://medsdisposal.eu/

Figure 2: Examples of German and Swedish marketing campaigns explaining the negative effects of pharmaceuticals in the environment, which have also been conducted in Finland and Denmark. Left image: a German billboard imploring residents not to flush unused pharmaceuticals down the toilet, while the right image reminding customers in a Swedish pharmacy of diclofenac's negative effect on the environment encourages mindful use.

Recommendation #3: Hospitals and other healthcare institutions should collect their own pharmaceutical waste and send it directly to the country-specific appropriate waste treatment facilities. Other healthcare institutions include housing services, retirement homes, assisted-living facilities, private clinics or other operators providing domiciliary care. This recommendation concerns all personal patient medication. Such systems are already in place in hospitals in Estonia, Denmark, Finland, Germany, Latvia, Poland and Sweden, as well as other health care institutions at least in Finland, Poland and Sweden, but there is still room for improvement. It should be noted that information on the situation in Lithuania and Russia is lacking.
More detailed information can be found in the CWPharma Activity 4.1 report [8].
Timeline for implementation: Depending on the scale and amount of legislation required for hospitals to sign contracts with waste treatment facilities and/or pharmacies, this could take from <1 year up to 4 years

Recommendation #4: Farmers should be responsible for organizing the transport of their unused veterinary medicines. If the amount of unused medicines accumulated is unreasonable (relatively high amounts), farmers should be responsible for organizing the delivery of the medical waste to appropriate waste treatment facilities, just as pharmacies and hospitals are obliged to do (i.e. via a contracted and licenced waste treatment company, see Recs. #1 & #3). Reasonable amounts (i.e. relatively small amounts) of unused veterinary medicines should be returned to the pharmacies or hazardous waste collection sites, in same way as the unused household medicines (see Rec. #1), or to veterinarians making site visits to the farm. The terms "reasonable" and "unreasonable" should be more specifically defined by the local authority overseeing the collection program, or possibly at higher national level.
More detailed information can be found in the: CWPharma Activity 4.1 report [8].
Timeline to implementation: As this likely requires accompanying legislation, implementation could take between 1-4 years

Recommendation #5: For separately collected pharmaceutical waste, high temperature incineration (~ 1100 - 1300°C) is the recommended treatment method, unless a lower temperature is proven to irreversibly transform the active ingredients into non-hazardous

substances. Unused medicines collected with mixed household waste and incinerated at lower temperatures is the next best waste treatment option. High temperature incineration systems for all types of separately collected pharmaceutical waste are already in place in Denmark, Estonia, Finland and Poland, and for some waste types in Germany. This recommendation does not apply to wastes including only vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, vaccines, and herbal medicinal products generated by the pharmaceutical industry.
More detailed information can be found in the CWPharma Activity 4.1 report [8].
Timeline for implementation: As this likely requires accompanying legislation, implementation could take between 1-4 years

Recommendations for wastewater treatment

Recommendation #6: The emissions of environmentally risky APIs could be reduced by reducing indirect discharges of APIs. This applies to hospitals, landfill leachates, pharmaceutical manufacturing facilities, farms, and other indirect emitters of APIs. If their emissions are reduced, this reduces the load on municipal WWTPs and loads which end up in the Baltic Sea.

Recommendation #7: The emissions of environmentally risky APIs could be reduced by upgrading municipal WWTPs with advanced wastewater treatment (AWT). This was also mentioned in the UNESCO HELCOM report [1]. For countries such as Latvia, Lithuania, and Poland, which as of 2016 were still not compliant with the Urban Waste Water Treatment Directive (UWWTD) [11], the first step is to ensure country-wide WWTP coverage. For countries which are already compliant, the upgrading of individual WWTPs with AWT techniques, such as ozonation (O_3) or activated carbon (AC), can significantly reduce loading of persistent APIs such as diclofenac (Figure 3).
More detailed information can be found in the CWPharma Activity 3.1 [12] and 3.2 [13] reports.
Timeline for implementation: As this likely requires accompanying legislation, implementation could take 4+ years before even countries currently compliant with the UWWTD have installed AWT in their largest WWTPs

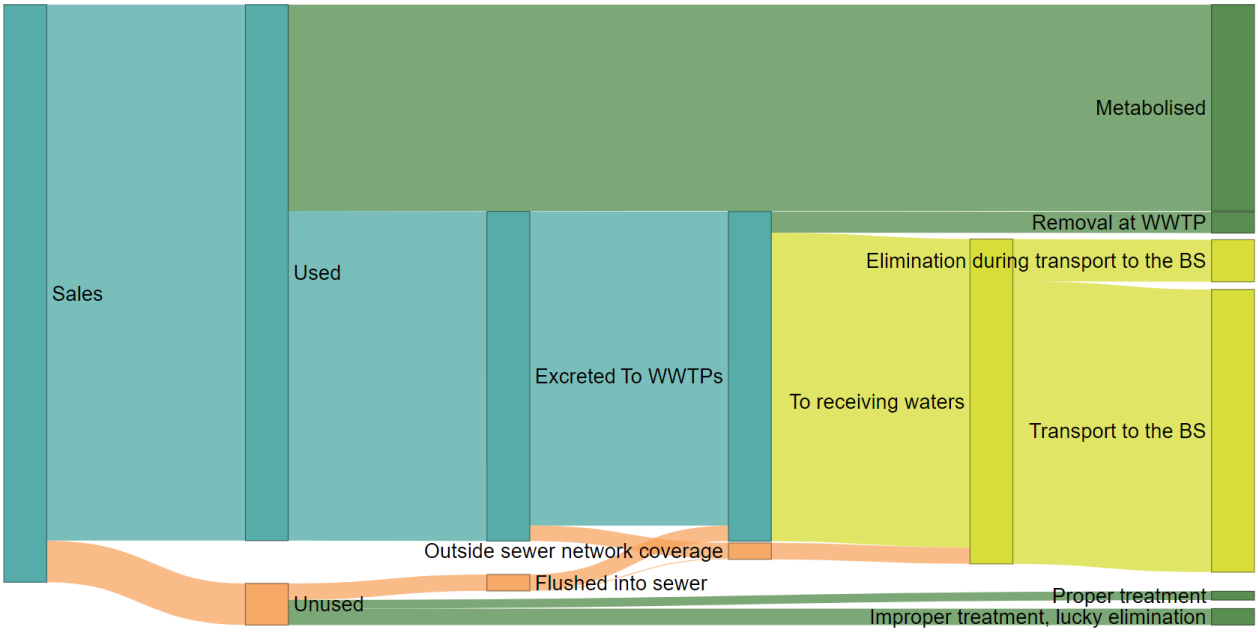


Figure 3: Sankey diagram showing that the majority of diclofenac reaching the WWTP is not removed by conventional WWTP processes, and therefore requires additional AWT prior to discharging to receiving waters to reduce the loading to the Baltic Sea (yellow path).

Recommendation #8: The suitability of AWT technologies should be determined on a site-specific basis by monitoring crucial water quality parameters and lab-scale testing. Water quality parameters relevant for the design of advanced wastewater treatment, such as dissolved organic carbon (DOC) (AC as well as O_3) as well as nitrite and bromide (O_3 only) can be monitored in the secondary WWTP effluent. In case elevated bromide levels are present in the wastewater, source tracking and mitigation strategies can be implemented so as to not exclude the possibility of ozonation. Conducting lab-scale experiments with the local water matrix can help determine other relevant design parameters (e.g. ozone depletion for O_3, type of AC, contact time, etc.) prior to the installation of a full-scale reactor.
More detailed information can be found in the CWPharma Activity 3.1 [12], 3.2 [13], and 3.4 [14] reports.
Timeline for implementation: Monitoring and lab-scale testing can be completed in ~1 year, depending on laboratory availability

Recommendation #9: The application of ozonation should be followed by a biological post-treatment step. Wastewater ozonation results in the formation of transformation products, which are often associated with toxicological risks. Thus, for safety, ozonation plants should always be combined with a biological post-treatment process.
More detailed information can be found in the CWPharma Activity 3.3 report [15].
Timeline for implementation: Depending upon the WWTP, the time to steady state removal in the biological post treatment step could take between <1 to 4 years

Recommendation #10: Implementing a national knowledge platform to share technical information on API removal will speed up WWTP upgrades and improve uptake of AWT technologies. Results from national studies are not often translated into other languages, and thus prevent local operators, advisors or utility companies from benefitting from their results. To circumvent this, implementing a knowledge platform or a competence centre for API removal in cooperation with national water associations would 1) compile national knowledge, 2) offer trainings, 3) facilitate inter-utility exchange and 4) translate relevant documents from other countries into the national language. It could also link to other national platforms, such as the Swiss VSA Micropoll platform[3], the German Kompetenzzentrum Spurenstoffe (KomS)[4], or the Swedish procurement group for API removal facilities[5]. This should be coordinated at the national level in cooperation with the Baltic Sea Pharma platform (BSR Pharma)[6].
Timeline for implementation: The implementation of a national platform could take 1-4 years

Recommendation #11: Depending on the target API, loading rates, and method of consumption, significant reduction in API emissions will require a combination of reduction measures. Improvements in waste management and sewer network coverage can decrease the emissions of APIs which are extensively metabolised in the human body as well as those efficiently removed in conventional WWTP (e.g. ibuprofen, carbamazepine, clarithromycin (Figure

[3] https://micropoll.ch/

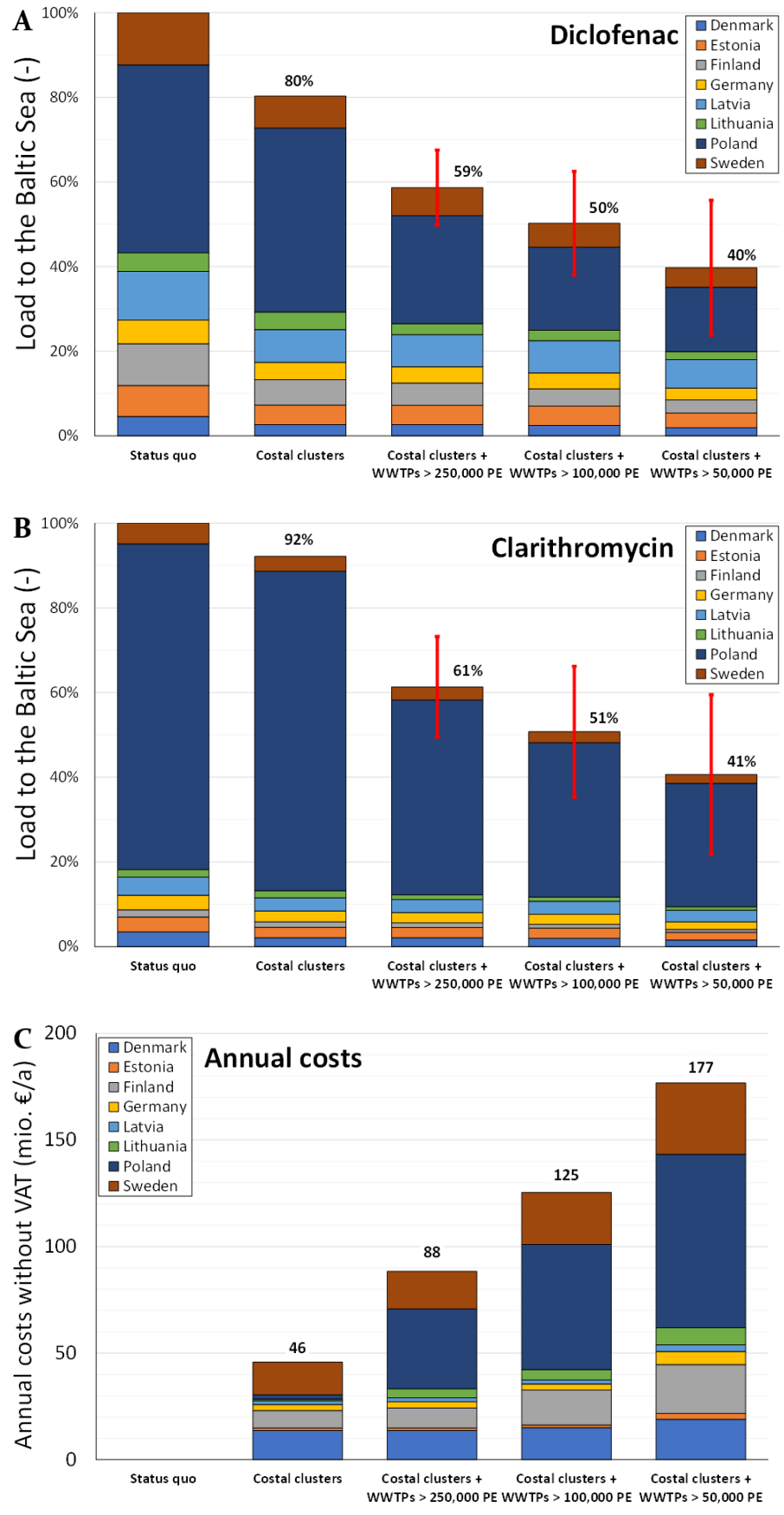
[4] https://koms-bw.de/en

[5] https://www.svensktvatten.se/vattentjanster/avlopp-och-miljo/reningsverk-och-reningsprocesser/bestallargrupp-lakemedelsrester-mikroplaster-och-andra-fororeningar/

[6] https://balticsea-region-strategy.eu/news-room/highlights-blog/item/40-baltic-pharma-platform

4B)), while AWT technologies eliminate APIs which are poorly removed in conventional WWTP (e.g. diclofenac) (Figure 4A). Emissions of APIs that are highly metabolized (e.g. diclofenac) could be reduced by decreasing their topical usage.

More detailed information can be found in the CWPharma Activity 5.1 report [9].



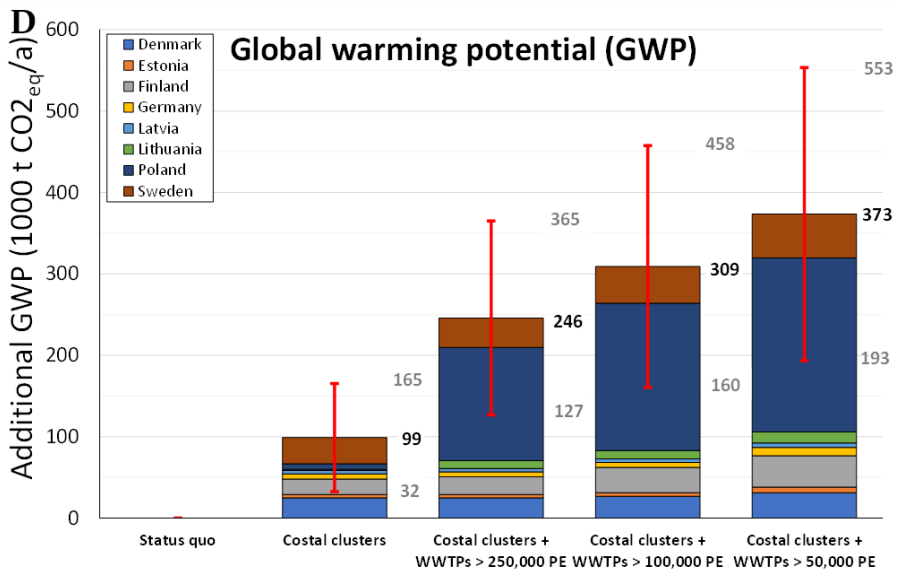


Figure 4: Modelling results for a) diclofenac loading into the Baltic Sea, b) clarithromycin loading into the Baltic Sea, c) annual costs of upgrading WWTPs, and d) global warming potential (GWP) for 4 technical best case scenarios. The results shown represent the evaluation of 8 countries (responsible for 90% of DCF load) and not for all countries (as was done in the CWPharma 5.1 report [9])

Recommendation #12: In terms of cost and technical efficiency, API elimination via AWT upgrading should be implemented first at larger WWTPs and then at smaller WWTPs. Upgrading WWTPs with AWT will increase the wastewater treatment costs (Figure 4C). To reduce the overall API load into the aquatic environment in the most cost-efficient way, initially implementing AWT at the biggest WWTPs (i.e. >250 000 PE) is recommended, as the specific costs per m^3 treated increase with decreasing WWTP size. AWT may make sense for smaller WWTPs in case the WWTP effluent contributes a notable percentage to surface water bodies, resulting in low dilution (e.g. Swiss API reduction guidelines[7]).
More detailed information can be found in the CWPharma Activity 5.1 report [9].

Recommendation #13: When evaluating AWT options, the carbon footprint of the different technologies should be considered individually for each country. Implementation and operation of AWT can have a significant impact on the carbon footprint of the associated WWTPs. The carbon footprint of an ozonation plant is highly sensitive to the national energy mix, whereas activated carbon is often purchased from the global market and thus less dependent on national boundary conditions. The specific carbon footprint ($gCO_{2,eq}$/PE) was evaluated for the different AWTs. Based on the national carbon footprint of energy production in 2017[8], to minimize global warming potential, ozonation should be preferred in Sweden, Finland, Denmark, Lithuania and Latvia, whereas GAC should be preferred in Poland and Estonia. The estimated overall impact is shown in Figure 3C. Nevertheless, the choice of the most suitable AWT technology should not be based on the carbon footprint alone but should also consider costs and other WWTP specific boundary conditions.
More detailed information can be found in the CWPharma Activity 5.1 report [9].

[7] https://www.bafu.admin.ch/bafu/en/home/topics/water/info-specialists/state-of-waterbodies/state-of-watercourses/water-quality-in-watercourses/micropollutants-in-watercourses.html

[8] https://www.eea.europa.eu/data-and-maps/data/co2-intensity-of-electricity-generation

Recommendations for improving knowledge on emissions, environmental concentrations and ecotoxicity of APIs

Recommendation #14: Environmental permits should require pharmaceutical plants to estimate their API emissions and impacts on WWTPs and surface waters. Legally enforceable emission limit values on API concentrations and biotesting in pharmaceutical industry wastewater should then be set if impacts on WWTPs or surface waters are estimated to occur. Emissions of pharmaceuticals processed in the plant can be estimated computationally, empirically, or using both approaches. Additionally, bioassays on nitrification inhibition in WWTP that indicate the impacts API emissions have on WWTP operation and function are recommended.

Pre-treatment of pharmaceutical wastewaters should be done in accordance with the Industrial Emissions Directive (2010/75/EU). All industrial level pharmaceutical production plants should uphold conditions set in relevant best available techniques (BAT) documents to minimize pharmaceutical emissions.
More detailed information can be found in the CWPharma Activity 4.3 report [16].
Timeline for implementation: As this is bound to legislation, the implementation will likely take 1-4 years

Recommendation #15: When necessary, environmental permit requirements for pharmaceutical plants should be further supplemented with industrial wastewater contract requirements. The pharmaceutical plant must first get initial approval from the authorities and water utilities to discharge industrial wastewater to the public sewer system. Although it is possible to draw up a contract with an industrial facility without an environmental permit, the permit itself ensures better control over the actions of the industrial facility and helps to enforce BAT on the premises and better API emission mitigation.
More detailed information can be found in the CWPharma Activity 4.3 report [16].
Timeline for implementation: As this requires legislative action, the implementation will likely take 1-4 years

Recommendation #16: The public availability of API consumption statistics should be improved. Current reporting formats impedes data analysis when attempting to identify trends in API consumption (e.g. due to demographic changes or changes in prescription practice) or to estimate loading. Data for all types of medicines, including combination products and topical formulations, should be made available in DDD format (defined daily dose) and in mass units (kg of API). Although increased data availability was already mentioned in the UNESCO HELCOM report [1], data on antibiotics usage should especially be made publicly available for research purposes.
More detailed information can be found in the CWPharma Activity 2.1 and 2.2 report [17].
Timeline for implementation: Bound to legislative and possibly data protection requirements, this could take 1-4 years to implement

Recommendation #17: Knowledge on the environmental risks of APIs must be improved. To assess the ecological risks, more ecotoxicological data on single APIs and their metabolites (previously highlighted in the UNESCO HELCOM report [1]) and on mixture toxicity is needed. Ecotoxicological studies should be performed on different trophic levels and on different matrices, e.g. in freshwater, coastal and marine waters, and on sediment and soil. Especially after ozonation but also after AC treatment and other AWT technologies, bioassays can be used to determine the

ecotoxicological risk of APIs and metabolites potentially remaining in the effluent. Most of the 17 ecotoxicological tests performed in the CWPharma project revealed no negative impact of ozonation, but rather a clearly positive impact for estrogenic effects [15]. Mutagenic effects detected at very high enrichment factors (1000-fold) were reduced by the post-treatment processes investigated.

Additionally, knowledge of chronic effects from long-term exposure to APIs should be improved. Further studies should be performed on the environmental levels and risks of antibiotics, including the spread of antibiotic resistance genes.
More detailed information can be found in the CWPharma Activity 2.1 and 2.2 [17] and 3.3 [15] reports.
Timeline for implementation: Likely requiring external funding, this would probably take 1-4 years

Recommendation #18: More studies on the use of veterinary medicines and their dispersal in the environment should be conducted. This was mentioned in the UNESCO HELCOM report [1]. Unnecessary usage of veterinary medicines should be restricted. The use of herd treatments and broad-spectrum antibiotics should be avoided, and the Baltic Sea member states should adhere to the EU One Health Action Plan against Antimicrobial Resistance (AMR)[9]. The CWPharma project results suggest that some livestock farms may be significant sources of APIs used for veterinary purposes, which requires further attention. In addition, antibiotics and other APIs were found in soils fertilized with manure. Hence, best practices for manure storage and application on agricultural fields should be implemented.
More detailed information can be found in the CWPharma Activity 2.1 and 2.2 report [17].
Timeline for implementation: Acquiring funding for more analytical studies will likely take 1-4 years, if not longer in certain circumstances

Recommendation #19: APIs should be included in regular environmental monitoring programmes managed by national or regional authorities. Broad screening campaigns of APIs should be performed regularly, preferably once every third year. API concentrations should be primarily studied in surface waters downstream of WWTPs and animal farms, and in sediments where API accumulation is expected, such as in lakes and Baltic Sea estuaries. Continuous environmental monitoring should focus on APIs and metabolites that pose environmental risks. The API list should be kept up-to-date with the newest information about environmental concentrations and risks and also reflect the latest Surface Water Watch List[10]. In case API concentrations in surface water bodies exceed PNEC values, operators of WWTP and pharmaceutical plants should be additionally required to monitor their emissions.
More detailed information can be found in the CWPharma Activity 2.1 and 2.2 report [17].
Timeline for implementation: If monitoring programs already exist, this could take <1 year, but is more likely to require 1-4 years, depending on availability of funding

Recommendation #20: Analytical methods for API detection, including metabolites and hormones, should be further refined to produce a representative overview of API concentrations in the environment. The analytical methods should be further developed to allow measurement of more APIs and metabolites to make comprehensive estimates of environmental levels and risks, which also mentioned in the UNESCO HELCOM report [1]. Comparing results from

[9] https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf

[10] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020D1161&from=EN

different instruments or data sets to ensure high quality data is generated from different analytical setups is important. The standardized method (ISO 21676:2018) should be revised to include all the environmentally risky APIs and metabolites at low concentrations. Standardized methods should also be developed/become available for soil, sediments and sludge.

More detailed information can be found in the CWPharma Activity 2.1 and 2.2 report [17].

Timeline for implementation: Due to the range of funding accessibility and technical capabilities within the Baltic Sea Region, this will likely take 1-4 years to implement in all countries

3. Barriers to implementation

Due to the varying social, economic, technological and political situations in each Baltic Sea Region country, implementing the aforementioned recommendations will require focused cooperation between numerous stakeholders. Potential barriers to implementation and suggestions for overcoming these barriers have therefore been assembled in an effort to provide solutions to foreseeable problems and increase the likelihood of implementation (Table 1).

Table 1: Potential barriers to implementation of recommendations.

Topic	Barrier	Recommendations for overcoming said barrier
Social	Lack of public/governmental awareness about environmental effects of APIs (Rec #2)	High transparency / communication with the local population can avoid misunderstandings, and also requires stakeholder meetings to communicate strategies to reduce API loads
	Low public awareness and/or acceptance of take-back programs (Rec #1)	Continuous and frequent information campaigns designed with input from all stakeholders to address all questions and concerns
Economic	Financial support is needed for developing and applying advanced treatment (Rec #7, 8, 9, 12, 13), or a knowledge-sharing platform (Rec #10)	Funding from local/regional/national funds can boost implementation
	Lack of defined financial responsibility for implementing take-back programs (Rec #1)	Requires transparent funding structure to ensure take-back programs are uniformly administered within a country
	Lack of defined financial responsibility for implementing information campaigns and education reforms (Rec #2)	Dialogue between several actors such as government (e.g. ministries on education, environment & agriculture), universities, and pharmacies to reform education for students and trainings for practicing professionals
	The polluter pays principle requires hospitals and farmers to pay for transport of unused pharmaceuticals to waste treatment facilities (Rec #3, 4)	Stakeholder discussions to explain why unused medicines need to be separately collected
	Lack of financing for monitoring programmes and analytical method development (Rec #17, 18, 19, 20)	Requires either mandating funding, or obtaining funding from EU or private sources for individual plants/operations

Technical/ Technological	High temperature (1100–1300 °C) waste incineration plants are not available in all Baltic Sea Region countries (Rec #5)	Requires building more high temperature incineration plants or transferring waste to existing plants in other countries. Must evaluate whether APIs are completely removed after non-high temperature incineration
	Differences in analytical results in different countries using different equipment (for API detection, ecotoxicity assessment, advanced wastewater treatment experiments) due to varying quality control (Rec #20)	Publication of standardized operating procedures and required instruments for analytical API detection and API risk assessments
	Lack of publicly available data on API consumption (Rec #16)	Publication of API consumption in DDD format (defined daily dose) and in mass units (kg of API), as well as a database for collecting, storing and presenting consumption data
Policy	Lack of oversight and enforcement for reducing API emissions (Rec #6, 7, 11, 14, 15)	Different models of enforcement (governance) must be setup depending on country specific governance structure (see CWPharma Activity 5.3 Action Plan report)
	Existing regulations in countries might hinder the uptake of takeback programs (Rec #1)	In some countries, unused pharmaceuticals are disposed of with mixed household waste, which is often incinerated, therefore implementing a take-back program would require revising national/regional policies
	Existing regulations in countries may hinder or encourage the uptake of advanced treatment at local WWTP level (Rec. #7, 8, 9)	In some countries, the cost for upgrades cannot be transferred to the customers, whereas in others customers are willing to cover the cost of advanced treatment – regulatory considerations are covered in more detail in the CWPharma Activity 5.3 Action Plan report

4. Research gaps

The European Union Strategic Approach to Pharmaceuticals in the Environment (PiE) recommends adding additional chemicals, such as cytotoxic pharmaceuticals and X-ray contrast media, to the review of the Surface Water Watch List of the Water Framework Directive [18]. It additionally supports the sharing of collected data, especially from hotspots, through the Information Platform for Chemical Monitoring, so that future projects and investigations can benefit from more current analytical information on the status quo of surface water quality [18]. The report also explicitly states that EU programs should be used to invest in technologies improving the efficiency of pharmaceutical removal and assess whether the existing urban wastewater treatment legislation sufficiently controls pharmaceutical emissions, and when not, investigate the feasibility of upgrading selected urban WWTPs to more advanced treatment technologies [18]. Upgrading WWTPs is subject to regional and/or local considerations, which vary greatly between member states. Therefore, a screening of EU-funded projects which investigated API emissions was done to evaluate how many addressed legislative considerations.

Overlap with research projects investigating APIs

The recommendations in this report echo numerous suggestions from the UNESCO HELCOM report [1] as well as mitigation options applicable at a variety of scales suggested by the SOLUTIONS project [19]. Additional concluded projects with partially similar focuses include BEST, PHARMAS, demEAUmed, IMI iPiE, MistraPharma, the German language projects ASKURIS, SAUBER+, RiskIdent, and SchussenAktivplus, and the Finnish language project EPIC, among others.

However, ongoing similar projects are continuing the push to further reduce API emissions, implement monitoring programmes, and investigate and develop more environmentally friendly API alternatives. The MEDWwater Interreg project in Latvia and Lithuania aims to draft water protection policies for removing APIs from WWTPs. Other projects focusing on API emissions in the BSR are concerned with mitigation of API emissions into the southern Baltic Sea (MORPHEUS), and evaluation of industrial wastewater emissions and treatment (BEST). The results of CWPharma and other projects will surely inform the update of the BSAP, which will be renewed by the end of 2021 and effective until 2030.

Although extensive research has been done on quantifying API pollution and emissions, as well as the impact on, for example, ecosystem toxicity, few of these projects have addressed the transfer of science to policy. Clearly, more emphasis on summarizing scientific results in language adapted to the political arena is needed. To fill this gap, CWPharma has written a separate political action plan of proposals for the EU, national, regional, and local levels taken from the scientific recommendations outlined in this report [20].

5. Conclusions

The recommendations outlined in this report were gathered from the results obtained in the field campaigns and scenarios modelled in CWPharma. The mitigation options presented encompass the different steps within the consumable lifetime of the API, including prescription, consumption, disposal, and treatment. The most important recommendations for improving collection and disposal of APIs and pharmaceutical waste, for improving WWTP API removal, and for improving knowledge of use, emissions, ecotoxicity and environmental concentrations have been outlined.

Based on the calculations outlined in the CWPharma Activity 5.1 report [9], it is apparent that a combination of mitigation measures will be necessary to minimize API loading into the Baltic Sea. This includes both technical measures, such as increasing API removal via AWT and increasing sewer network coverage, and other measures, such as minimizing API waste, improving API waste management, and rationalizing pharmaceutical consumption and prescriptions. The 5.1 report identified the best reduction measure combinations for eight of the most environmentally risky APIs, and determined that none of the measures evaluated alone resulted in notable removal of any of the eight APIs [9]. The following brief summary of the report's conclusions on the modelled compounds shows that upgrades and changes in pharmaceutical waste management are necessary for environmentally risky compounds. Modelled mitigation measures revealed that:

- For APIs extensively metabolised by humans, improved pharmaceutical waste management was most efficient at reducing loading (e.g. ibuprofen and carbamazepine);
- For APIs which are poorly removed during conventional wastewater treatment processes, improved wastewater treatment is necessary to reduce loading (e.g. diclofenac, clarithromycin, carbamazepine, tramadol, venlafaxine)
- For APIs which are efficiently removed during conventional wastewater treatment processes, increased sewer network coverage would decrease loading (e.g. ibuprofen, metformin, ofloxacin)

Presenting options for the aforementioned different target areas allows different stakeholders to take responsibility and prevent improper disposal of APIs to reduce API loading and improve the quality of the Baltic Sea. The Baltic Sea Action Plan update should consider the recommendations described in this report when re-evaluating the BSAP and its contributions to improving the water quality and environmental status of the Baltic Sea through 2030.

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