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Pharmaceutical emissions on the example of the Baltic Sea catchment: comparing measurements with multi-tier predictive models

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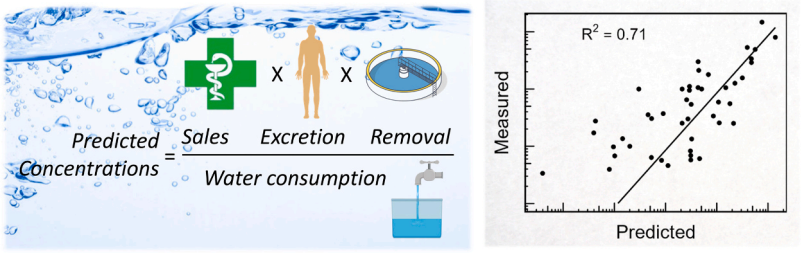
HIGHLIGHTS

- 35 pharmaceuticals were measured in 82 WWTPs across 8 countries.
- Predicted concentrations were refined with human excretion and WWTP removal rates.
- Measured concentrations were compared with predicted concentrations.
- A scalable method for estimating predicted pharmaceutical emissions is proposed.

GRAPHICAL ABSTRACT



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ABSTRACT

Currently, there is uncertainty about emissions of pharmaceuticals into larger closed ecosystems that are at risk such as the Baltic Sea. There is an increasing need for selecting the right strategies on advanced wastewater treatment. This study analysed 35 pharmaceuticals and iodinated X-ray contrast media in effluents from 82 Wastewater Treatment Plants (WWTPs) across Denmark, Estonia, Finland, Germany, Latvia, Lithuania, Poland and Sweden. Measured concentrations from Finland and Denmark were compared to predicted effluent concentrations using different levels of refinement. The concentrations predicted by the Total Residue Approach, as proposed by the European Medicines Agency, correlated with R^2 of 0.18 and 0.031 to measured ones for Denmark and Finland, respectively and the predicted data were significantly higher than the measured ones. These correlations improved substantially to R^2 of 0.72 and 0.74 after adjusting for estimated human excretion rates and further to $R^2 = 0.91$ and 0.78 with the inclusion of removal rates in WWTPs. Temporal analysis of compound variations in a closely monitored WWTP showed minimal fluctuation over days and weeks for most compounds but revealed weekly shifts in iodinated X-ray contrast media due to emergency-only operations at X-ray clinics during weekends and an abrupt seasonal change for gabapentin. The findings underscore the limitations of current predictive models and findings (...) demonstrate how these methodologies can be refined by incorporating human pharmaceutical excretion/metabolization as well as removal in wastewater treatment plants to more accurately forecast pharmaceutical levels in aquatic environments.

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1. Introduction

Pharmaceuticals are among the main environmental pollutants of emerging concern [1-5]. These compounds are primarily designed to be stable and to interact with living cells. The environmental impact of pharmaceuticals varies based on their type and concentration levels in aquatic environments. They may cause hormone disruption and behavioural changes, a few may accumulate in food chains, cause adverse effects in ecosystems, and antibiotic compounds can promote the emergence of antibiotic-resistant microorganisms [2,4,6-9].

Pharmaceutical emissions can significantly increase locally due to production sites, hospitals, agriculture and aquaculture; however, in the overall picture, their main pathway to the environment is via urban municipal wastewater, as the majority of the pharmaceuticals are administered at home [1,10-13]. Pharmaceutical concentrations in urban wastewater are influenced by local consumption patterns, regulatory measures and hydraulic conditions, including dilution with stormwater directed to Wastewater Treatment Plants (WWTPs) or accidental groundwater infiltration into sewer systems. Kookana et al., [14]. General physicochemical properties of pharmaceuticals like biodegradability, hydrophilicity and a high variety of molecular structures challenge a unified assessment of emissions from conventional WWTPs that trigger surface water pollution with pharmaceutical residues [15-20]. Many pharmaceuticals persist in the aquatic environment, which implies that water bodies with slow hydraulic turnover such as marine waters and lakes become their ultimate sinks [4,13,21,22]. This can be illustrated by the nearly landlocked Baltic Sea, which is one of the most polluted marine water bodies in the world [23,24].

Pharmaceutical residues were considered a major group of micropollutants in the proposal for an EU directive concerning urban wastewater treatment [25]. Furthermore, the European Commission proposed to include numerous pharmaceuticals on the water framework directive (2000/60/EC) list of priority pollutants [26]. Both the scientific community as well as administrative bodies like HELCOM and UNESCO agree there are essential knowledge gaps considering the emissions of pharmaceuticals [5].

We have conducted this study to contribute to filling these knowledge gaps on emissions and predictions of emissions by 1) carrying out a uniform sampling campaign and illustrating and comparing concentrations of a multitude of pharmaceuticals in the WWTP effluents from eight out of nine Baltic Sea states (Denmark, Estonia, Finland, Germany, Latvia, Lithuania, Poland and Sweden) and 2) correlating the measured environmental concentrations (MEC) with predicted environmental concentrations (PEC) in effluent wastewater derived in this study using basic methodologies with moderate success and more refined ones with a high correlation. We performed this by analysing 35 pharmaceuticals and X-ray contrast media in 82 WWTPs and comparing the findings to PECs derived from pharmaceutical sales, human excretion rates and measured WWTP removal efficiencies. The aggregated data provides an overview of both general trends and country-specific results and considerations.

2. Materials and methods

2.1. Measured environmental concentrations of pharmaceuticals (MEC)

2.1.1. Chemicals and reagents

The analytical standards of pharmaceuticals and the respective isotopically labelled internal standards were purchased from Sigma-Aldrich (Søborg, Denmark), Dr. Ehrenstorfer GmbH (Augsburg, Germany), Santa Cruz Biotechnology Inc, Toronto Research Chemicals, TLC Pharmaceutical Standards Ltd. (both Toronto, Ontario, Canada) and LGC standards (Teddington, UK) [27]. The respective stock solutions were prepared in methanol and stored at −20 °C until use. The methanol and water for chromatography and formic acid were LiChrosolv LC-MS grade from Merck (Darmstadt, Germany).

2.1.2. Analytical methods

All wastewater samples were centrifuged in 2 mL HPLC autosampler vials at 4000 g force for 7 min (Hermle Labortechnik GmbH Z 206 A) to settle particles. 900 µl of each supernatant were transferred into a new vial, mixed with 100 µl of solution of 12 isotopically labelled internal standards, representing all chemical classes analysed and analysed directly by injecting 100 µl of the mixtures in duplicates into a high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS). The HPLC autosampler, column compartment and an UltiMate 3000 dual-gradient mixing pump system (Dionex, Munich, Germany), were coupled to an API 4000 triple-quadrupole mass spectrometer (AB Sciex, Framingham, MA, USA), which was operated in positive electrospray ionization mode (capillary temperature 500 °C, voltage 5500 V). The chromatographic separation was conducted by a Synergi Polar-RP column with 150 mm length and 2 mm diameter with 4 µm particle size (Phenomenex, Torrance, CA, USA) that was thermostated at 30 °C. The eluent was formed by mixing water (eluent A) and methanol (eluent B) that both containing 0.2 % v/v formic acid, utilising the following multi-step linear gradient program: 0–1.5 min 0 % B, 1.5–3 min (0→40 % B), 3–9 min (40→60 % B), 9–12 min (60→80 % B), 12–12.5 min (80→100 % B), 12.5–18 min (100 % B), 18–19 min (100→0 % B), 19–22.5 min (0 % B); with the following flow program: 0–3 min 350 µl/min, 3–19 min (350→250 µl/min), 19–22.5 min (250→350 µl/min). Concentrations of each compound were determined by performing 9-point 0.01–30 µg/L standard calibration. The LC-MS/MS data was evaluated by using the software Analyst 1.6.2. The LC retention times, precursor- and product ions, internal standards applied, compound-specific optimised MS parameters and limits of quantification achieved are listed in [27].

2.1.3. Sample collection

Municipal WWTP operators from eight countries were invited to voluntarily participate in an anonymized study analysing pharmaceutical concentrations. Those who agreed (see Table 1) received a 500 mL pre-labelled LDPE bottle, styrofoam box and ice packs. They were instructed to collect a sample of the WWTP's effluent, ideally a 24-hour flow-proportional, during dry weather conditions. The samples were taken between June and July 2021. All samples were shipped cooled with an express delivery to the Berlin Centre of Competence for Water, Germany. At the day of delivery, an approx. 30 mL homogeneous aliquot was frozen and stored at −20 °C. After receiving all samples, the aliquots were shipped in cold conditions for pharmaceutical analysis to the Department of Environmental Science of Aarhus University (Roskilde, Denmark). The samples were analysed within 4 weeks after arrival at Aarhus University.

To supplement data with temporal pharmaceutical concentration dependencies, one middle-size WWTP (Hillerød, Denmark) has been sampled approximately every two weeks from February 2 to June 29, 2021 (n = 11) (Table S1 of the supplementary materials (SM)). These grab samples were collected in 2 L Duran wide mouth glass bottles (Schott, Mainz, Germany) equipped with teflonised silicone seals. The

Table 1
Population equivalents (PE) of WWTPs per country which provided the samples.

Country	Number of WWTPs by thousands of population equivalent					Total number of samples
	<10	10–50	50–100	100–250	>250	
Denmark	2	13	7	8	4	34
Estonia	0	3	1	1	1	6
Finland	0	0	0	8	3	11
Germany	0	0	2	1	2	5
Latvia	1	4	0	0	1	6
Lithuania	0	1	0	0	1	2
Poland	1	0	1	0	8	10
Sweden	0	0	0	6	2	8
Total	4	21	12	24	22	82

bottles were thoroughly washed and heated to 450 °C for 6 h before use for avoiding contamination. The samples were kept at -20 °C and analysed for pharmaceutical concentrations in batches every 1–2 months.

2.2. Predictions of pharmaceutical concentrations (PECs)

2.2.1. Acquisition of sales data

To calculate predicted environmental concentrations (PEC) in wastewater effluents, sales statistics for the analysed active pharmaceutical ingredients (APIs) were compiled. To provide a more robust correlation analysis of the predicted and measured concentrations, only the two countries with the most samples in the chemical analyses (see Table 1) were selected for concentration prediction, i.e., Denmark and Finland. This selection was also supported by data availability: the most comprehensive pharmaceutical sales data were found to be available for these two countries.

For Denmark, the data was acquired from the Register of Medicinal Products [28]. The dataset is based on mandatory reporting of pharmaceutical sales and covers all pharmaceuticals sold in Denmark. For Finland, the sales statistics were extracted from the wholesale data reported to the Finnish Medicines Agency. This dataset covers the pharmaceutical sales of the three largest wholesale companies operating in Finland.

In both datasets, the sales were commonly reported for the chemical form used in preparations. Often these are salts or esters of the active substance, containing a counter ion or are chemically bound to the respective alcohol (e.g., candesartan, which can be administered as pure API or as its ester, i.e., candesartan cilexetil). Whenever the preparation form was not the same as the active form, the sales data were converted to free molecule (e.g., candesartan) using Eq.(1). A more comprehensive description of the sales data compilation process is presented in the sales data compilation section of the SM.

$$m_{act} = \frac{n_{act} \times m_{prep} \times M_{act}}{M_{prep}} \quad (1)$$

where.

m_{act} = Mass of the active substance (kg/year),

n_{act} = Number of active moieties released from the preparation form (-),

m_{prep} = Mass of sold preparation form (kg/year),

M_{act} = Molar mass of the active form (g/mol),

M_{prep} = Molar mass of the preparation form (g/mol).

To enable predicting mass flows and concentrations on a catchment base, API sales per capita were calculated Eq. (2): The national total sales in active form were converted to per capita sales using information on population, using Eq. (2). In 2020, the Finnish and Danish populations were 5,822,763 and 5,533,793, respectively [28,29].

$$M_{pc} = \frac{m_{act} \times 10^6}{Pop \times D} \quad (2)$$

where.

M_{pc} = API sales per capita (mg/(d*person)),

m_{act} = Mass of the active substance (kg/year),

Pop = Population of the whole country,

D = Days in year (d).

Out of the 35 compounds analysed in the WWTPs, sales data for 30 were acquired from both Denmark and Finland. Sales statistics for the other countries, where WWTP sampling took place, were generally not found to be readily available. To give a few examples, the Estonian statistics on medicines [30] is only available in defined daily doses and only for some ATC codes. Pharmaceutical sales for Sweden are only readily available for prescription medicines [31]. On the other hand, while the numbers of sold packages of medicinal preparations in Lithuania are publicly available in a format resembling that in Denmark [32], there were only two WWTP samples from Lithuania included in our sampling campaign. Thus, taking into account, that the package sales would require translating into mass of sold pharmaceutical preparation and further to the active ingredient, where applicable, the Lithuanian pharmaceuticals sales dataset was excluded from further analysis.

2.2.2. Origin of excretion rate data

The excretion rates of APIs (i.e. the fraction of consumed API that is excreted unmetabolized) can vary significantly due to factors such as the chemical structure of the API, the medicine's formulation, the route of delivery (including injection, oral, topical, rectal and ophthalmological methods), disease states, drug interactions and individual variability. The pharmacokinetics sections of the approved Summaries of Product Characteristics (SmPCs) provided by the Finnish Medicines Agency [33] and Sweetman [34] were reviewed to find excretion rates for the analysed APIs. When the excretion rates varied from different sources, or a range of excretion was given, the average value was used.

2.2.3. Determination of removal of pharmaceuticals in WWTPs

Removal (R) in % was calculated using Eq. (3).

$$R = \frac{C_{\text{inf}} - C_{eff}}{C_{\text{inf}}} * 100 \quad (3)$$

where.

C_{inf} = inflow concentration.

C_{eff} =effluent concentration.

Removal of pharmaceuticals in WWTPs was determined by using the data from the 265,000 PE Avedøre WWTP (Copenhagen, Denmark) which was monitored by 24 h flow proportional composite sampling of influent and effluent on three consecutive days, starting on August 29th, 2019. Only when the data was not available in that dataset, data from WWTP Hillerød were used, as multiple influent and effluent samples from this plant were available. Grab samples of influent of Hillerød WWTP were taken once on April 14th, followed by daily sampling from April 19th to May 2nd (2021). For each influent sampling, three effluent samples were taken the same day. In both cases, the pharmaceutical removal was determined as a ratio between the average effluent concentrations and influent concentrations of the corresponding day. The standard deviation of the removal reflects the day-to-day variation. When effluent concentrations exceeded the limit of detection (LOD) but remained under the limit of quantification (LOQ), they were replaced with the LOQ value, indicating removal rates as equal to or greater than (≥) the estimated amount. If concentrations fell below the LOD, they were replaced with the LOD value, likewise reporting removal rates as equal to or greater than (≥) calculated values. When the calculated removal rate was close to zero and the range of its standard deviation covered the zero value, the rate was reported as zero (= no impact by the WWTP treatment). There are other ways to tackle values below LOQ: like using 0 for all values blow LOQ or a number between LOQ and 0. All of these are accepted procedures. The procedure we chose results in relatively low numerical removals but the indication that the removal is larger than this numerical value.

2.3. PEC/MEC correlation analysis

The PECs were calculated applying three tiers, which covered different levels of pharmaceutical removal processes. PEC_{TRA} represented the Total Residue Approach proposed by the European Medicines Agency [35] (see Eq. (4)). Here M_{pc}= sold amount of active ingredient/inhabitants in the respective country. More refined PECs were calculated adapting the approaches used by e.g. Verlicchi et al. [36-38]. These PECs were calculated by incorporating estimated excretion rates (PEC_{excr}, see Eq. (5)) and measured WWTP removal rates in combination with the excretion rates ($PEC_{excr\text{-}RR}$, see Eq. (6)) for each API.

$$PEC_{TRA} = \frac{M_{pc}}{V} \quad (4)$$

where.

M_{pc}= Per capita API sales (mg/(d*person)),

V = Volume of generated wastewater (L/(d*person)),

E = API-specific excretion rate (mg/(d*person)),

RR = API-specific removal rate at WWTPs (in ratios, 1 equalling 100 %)

$$PEC_{excr} = \frac{M_{pc} \times E}{V} \quad (5)$$

$$PEC_{excr-RR} = \frac{M_{pc} \times E \times (1 - RR)}{V} \quad (6)$$

A value of 200 L/(d*person) was used as the per capita volume of generated wastewater (V), as proposed by European Medicines Agency [35] and as feedback from WWTP operators. The three tiers of the PEC values for each API were compared with the mean effluent concentrations in both countries, separately for each country. To calculate the country- and API-specific MECs used in the comparison, the measured concentrations in the WWTP effluents were used. Whenever the MEC fell below the LOQ, the LOQ is used for the comparison.

To analyse the correlation between PEC and MEC, scatter plots were created for the dataset, categorized by both PEC type and country. Pearson correlations coefficients were then calculated and used to derive the R-squared values. APIs for which a $PEC_{excr\text{-}RR}$ could not be calculated due to missing information on WWTP removal were omitted from the correlation analysis. The Pearson correlations were adjusted to pass through the origin, a choice made to enhance data visualization. This assumption was considered reasonable, since, when PEC equals zero (i.e., sales equal zero), measured concentrations are expected to be zero as well.

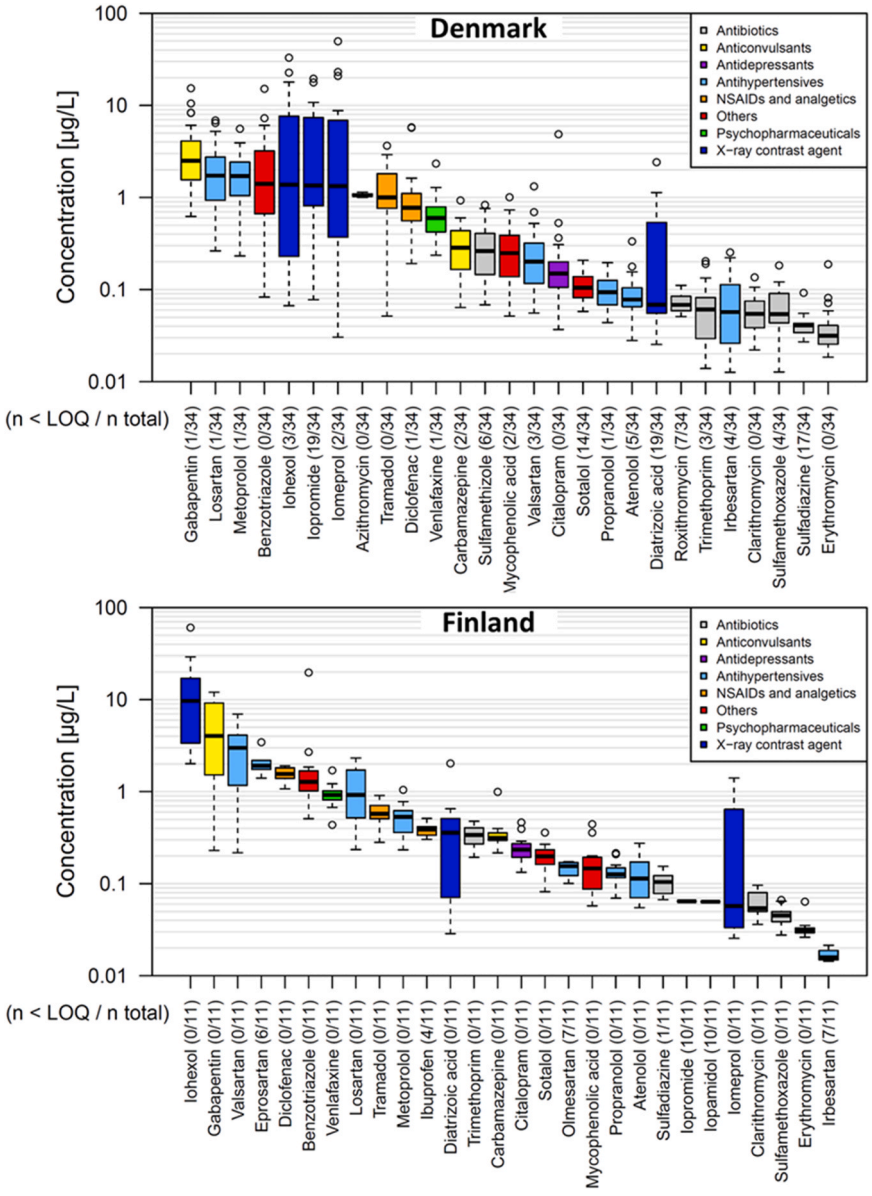

Fig. 1. Boxplot graphs with concentrations of pharmaceuticals, iodinated X-ray contrast media agents and benzotriazole in WWTP effluents measured in Denmark and Finland. Horizontal lines in the bars represent median values; the areas of the bars – the ranges between the first and third quartile; the error bars – minimum and maximum values within 1.5 interquartile range; the dots – outliers. The labels present the number of samples below the limits of detection in relation to the total number of samples - thus the indication 0/11 means no samples below LOQ.

3. Results and discussion

3.1. Measured pharmaceutical concentrations

Concentrations of pharmaceuticals, iodinated X-ray contrast media agents and benzotriazole in WWTP effluents in two countries (from which the highest number of samples have been obtained) are presented in Fig. 1. The graphs of the remaining countries are presented in Fig. S1, whereas numerical values in all countries are listed in Table S2 of the SM. Compounds that consistently occurred in concentrations exceeding 1 μg/L in all or nearly all countries were benzotriazole, at least one iodinated X-ray contrast media (diatrizoic acid, iohexol, iomeprol, iopamidol), at least one of the sartan blood pressure regulators (losartan, valsartan, eprosartan, olmesartan), as well as diclofenac, gabapentin and metoprolol. Their median concentrations are discussed below. The overall compound concentrations are relatively high and MEC/PNEC assessments show that the single compound risk factor usually exceeds 1 [27] while the cumulative risk factor exceeds 1 considerably [39], implying adverse environmental effects. However, the concentrations resemble those detected by [40] in a Europe wide monitoring.

X-ray contrast media dominated the concentrations of all measured compounds but were detected with different patterns among countries. In Sweden, the highest levels were measured for iohexol (median 16.7 μg/L) and iomeprol (median 3.6 μg/L) and in Finland for iohexol (median 9.7 μg/L). In Germany, the median concentrations of diatrizoic acid, iohexol and iomeprol exceeded 2.5 μg/L. In Denmark, the median concentrations for iohexol and iomeprol were very similar (1.4 μg/L and 1.3 g/L, respectively). However, variation in iomeprol concentrations was very high, with the highest measurement reaching over 100 μg/L. In Lithuania, iohexol and iopromide exceeded 1 μg/L in one of the two samples. The compound detected with the highest median concentrations in Estonia and Poland was iohexol (2.1 μg/L and 0.8 μg/L, respectively) and iopamidol in Latvia (2.4 μg/L).

The detection frequencies of individual compounds belonging to **Antihypertensives** and their respective concentrations varied by country. While sartan blood pressure regulators were a prominent group in our analyses, the β-blocker antihypertensive metoprolol was the compound detected in highest concentration in Germany and Sweden (median of 2.2 μg/L and 1.3 μg/L, respectively). The compound reached a median concentration of 0.5 μg/L in each country. In Denmark emissions were dominated by losartan and metoprolol (both occasionally reaching $>$ 5 μg/L levels, with medians of 1.7 μg/L), in Finland: by valsartan, eprosartan and losartan (medians exceeding ~1 μg/L). In Sweden, losartan was the sartan compound present in highest median concentration (1.0 μg/L), while valsartan dominated in Poland and Lithuania (median of 1.6 μg/L and 1.0 μg/L, respectively). Their substitute olmesartan dominated in Germany, Estonia and Latvia (~1 μg/L). On the other hand, candesartan concentrations fell below the LOQ in every sample.

Sulfonamide antibiotics were detected in all countries, sulfamethoxazole being the dominant compound in most countries, with median concentrations ranging from 0.05 μg/L in Finland to 0.25 μg/L in Germany. In Denmark, sulfamethizole was the compound detected in highest concentrations (median 0.26 μg/L), with individual samples reaching concentration levels of over 0.5 μg/L. In other countries, the compound fell below LOQ (0.1 μg/L). For comparison, Rodriguez-Mozaz et al. [41] found sulfamethizole concentrations to fall below 12 ng/L, in Finnish and German effluent samples. Sulfadiazine concentrations were always close to LOQ, being highest in Finland (median 0.1 μg/L). Previously, Rodriguez-Mozaz et al. [41] reported sulfadiazine to be below 14 ng/L in Finnish and German effluent samples. The sulfonamide booster **trimethoprim,** which is usually administered together with sulfonamide antibiotics, was consistently measured in all countries in median concentrations ranging from 0.025 μg/L in Lithuania to 0.34 μg/L in Finland. The trimethoprim concentrations are in line with concentrations reported previously by e.g. [41-43].

Macrolide antibiotics: erythromycin was detected in every country, with median concentrations ranging from 0.024 μg/L in Lithuania to 0.09 μg/L in Germany. Similarly, clarithromycin was detected in every sample, with median concentrations ranging from 0.053 μg/L in Latvia to 0.17 μg/L in Poland. As azithromycin had a higher LOQ (1 μg/L), it was not detected in German or Finnish effluent samples. In other countries the quantified concentrations remained in the vicinity of the LOQ, with the highest individual result reaching 2.0 μg/l in Poland. For roxithromycin, LOQ ranged from 0.05 μg/L to 1 μg/L. Previously, Grabic et al. [43] reported roxithromycin concentrations in Swedish effluent wastewaters to be below 0.05 μg/L. The compound was detected only in Denmark and Poland. In Denmark, where all samples were analysed with a LOQ of 0.05 μg/L, the median concentration was 0.068 μg/L.

The median concentrations of the **antiepileptic / antidepressant** carbamazepine ranged from 0.28 μg/L in Denmark to 1.91 μg/L in Poland. The concentrations measured from German samples (median 0.88 μg/L) are well in line with those reported previously by e.g. Brezina et al. [44]. Similarly, the **anticonvulsant** gabapentin concentrations ranged from 0.77 μg/L in Lithuania to 4.8 μg/L in Sweden. Venlafaxine was the antidepressant present in higher concentrations in each country, of the two compounds belonging to the group. It's median concentrations ranged from $\leq$0.11 μg/L in Lithuania to 0.95 μg/L in Germany. The concentrations for Finland (median 0.92 μg/L) are in line with those reported previously by Vieno & Arjonen [45] and for Sweden (median 0.37 μg/L) with those reported by Grabic et al. [43]. Citalopram concentrations ranged from $\leq$0.03 μg/L in Lithuania to 0.23 μg/L in Finland.

3.2. Predicted pharmaceutical concentrations

3.2.1. Sales data

We found that pharmaceutical products on the Danish and Finnish markets contain 11 out of the 35 analysed APIs in chemical forms incorporating a counter ion or were esters of the API that released the API in the gut. These pharmaceuticals were candesartan, diatrizoic acid, diclofenac, losartan, metoprolol, mycophenolic acid, olmesartan, propranolol, sotalol, sulfadiazine and tramadol. The forms used in pharmaceutical preparations are presented in the SM. Annual sales for the year 2020 are presented in Table 2.

As shown in Table 2, identifying the conversion factors from the salt form (e.g., diclofenac sodium) to the free ion (e.g., diclofenac) was crucial to prevent errors in PEC calculation. For instance, candesartan sales as candesartan cilexetil are 38 % higher than as free candesartan. Thus, when utilizing sales data to calculate PECs, it is important to consider the chemical form the reported dose or strength refers to.

Determining drug consumption from sales data has some limitations. The sales data may not reflect the actual consumption or adherence of patients. Some of the medicines accounted for may be stockpiled or left unused and eventually be disposed of. Furthermore, sales data is commonly available only on a national level and a yearly basis. Thus, potential variation in sales across regions, demographic groups, or seasons, is lost.

3.2.2. Excretion data

Indicative excretion rates for the 35 analysed APIs were obtained from Summary of product characteristics (SmPC) and literature. Table 2 shows the excretion rates used for the further calculations. The information sources used to compile the excretion rates are mainly aimed for the medicines prescribers and thus they may lack some aspects that are important for assessing environmental excretion of medicines. Information on excretion mainly focus on the excretion of the active pharmaceutical ingredient that is absorbed by the human body. Therefore, any part of the medicine that is not absorbed, such as medicines that are only partly absorbed from the gastrointestinal tract or skin and are largely metabolised, may not be fully accounted for. An example of such a pharmaceutical is diclofenac. When administered orally or

Table 2
Sales statistics of pharmaceuticals in Denmark and Finland and their determined WWTP removal rates. NA stands for not available. The sales presented in parentheses refer to the chemical forms used in pharmaceutical products. The WWTP removal rates in bold were used in PEC calculation.

Pharmaceutical	Pharmaceutical sales in 2020				Excretion rate	WWTP removal (R)	
	Denmark (2020)		Finland				
		Per capita		Per capita		Avedøre[1]	Hillerød[2]
	[Kg]	[mg/(d*capita)]	[kg]	[mg/(d*capita)]	[%]	[%]	[%]
Atenolol	289	0.136	291	0.144	100	**55.0 ± 3.4**	57.5 ± 6.4
Azithromycin	282	0.133	131	0.0647	65	NA	**0**
Candesartan	97.7 (135)	0.0458	797 (1,105)	0.394	93	NA	NA
Carbamazepine	1,590	0.748	2,550	1.26	2	NA	**28.5 ± 14.2**
Ciprofloxacin	803	0.378	651	0.321	70	**61.6 ± 18.1**	≥ 66.8 ± 7.5
Citalopram	646	0.304	4,780	2.36	18	**0**	26.2 ± 14.8
Clarithromycin	389	0.183	63.0	0.0311	34	NA	**0**
Clindamycin	218	0.103	625	0.309	10	NA	NA
Diatrizoic acid	56.9 (75.0)	0.0267	0	0	100	NA	NA
Diclofenac	986 (1,180)	0.462	2,020 (2,408)	0.996	oral 1 topical 94	**0**	43.6 ± 9.5
Eprosartan	0	0	NA	NA	90	**NA**	NA
Erythromycin	84.1	0.0396	3.98	0.00196	5	**19.1 ± 16.8**	NA
Gabapentin	19,600	9.21	15,500	7.64	100	**89.7 ± 1.6**	86.9 ± 1.9
Ibuprofen	56,800	26.7	123,000	60.8	1	**98.5 ± 0.3**	≥ 95.4 ± 0.8
Iohexol	10,600	4.99	13,700	6.75	100	**77.4 ± 3.3**	93.0 ± 3.2
Iomeprol	15,200	7.13	1870	0.924	100	**60.9 ± 2.9**	86.0 ± 8.5
Iopamidol	0	0	NA	NA	80	NA	**86.7 ± 8.1**
Iopromide	6,460	3.04	0	0	99	NA	NA
Irbesartan	217	0.102	0	0	2	**0**	NA
Losartan	10,400 (11,300)	4.86	6,500 (7,090)	3.21	4	**54.3 ± 4.7**	91.3 ± 2.2
Metoprolol	5,840 (7,460)	2.74	2,560 (3,130)	1.26	5		0
Mycophenolic acid	1,690 (2,290)	0.792	1,480 (1,970)	0.732	1	**89.2 ± 2.2**	NA
Olmesartan	1.10 (1.37)	0.000515	54.3 (68)	0.0268	100	NA	NA
Oxazepam	0	0	NA	NA	21	**22.9 ± 25.5**	12.9 ± 18.2
Phenazone	0	0	NA	NA	4	NA	NA
Propranolol	440 (502)	0.207	632 (721)	0.312	1	NA	**7.2 ± 13.2**
Roxithromycin	264	0.124	24.3	0.0120	50	NA	**0**
Sotalol	31.7 (36.0)	0.0149	131 (148)	0.0644	100	NA	NA
Sulfadiazine	0	0	NA	NA	75	**45.2 ± 11.2**	50.9 ± 13.6
Sulfamethizole	948	0.446	0	0	95	**47.1 ± 7.5**	67.6 ± 9.4
Sulfamethoxazole	408	0.192	518	0.256	20	**56.4 ± 24.2**	74.0 ± 9.0
Tramadol	3,210 (3,650)	1.51	1,460 (1,661)	0.720	30	NA	**0**
Trimethoprim	456	0.215	806	0.398	80	**46.2 ± 13.9**	35.3 ± 11.9
Valsartan	255	0.12	5,470	2.70	96	**63.4 ± 9.6**	≥ 60.6 ± 16.4
Venlafaxine	2,190	1.03	2,370	1.17	5	**0**	0

[1] Determinedby 24-hour composite samples (n=3).
[2] Determinedby evenly distributed grab samples (N influent = 15, N effluent = 45).

intravenously, diclofenac is fully absorbed and only circa 1 % is excreted untransformed [46]. However, when diclofenac is administered topically (i.e., on the skin to treat bruises), only 6 % of the diclofenac is absorbed and metabolised [47,48]. The rest (94 %) is lost, most likely to wastewater through washing hands, body and clothes.

Previous studies have highlighted the significance of different administration routes in determining excretion rates (e.g., [49]). Based on sales statistics, a substantial proportion of diclofenac usage is attributed to topical applications in Denmark and Finland, accounting for 69 % and 67 %, respectively. Thus, diclofenac excretion rates were calculated using the approach proposed by Austin et al. [49]. Considering that 94 % of topically applied diclofenac is washed off, while 1 % of the remainder is excreted, the country-specific excretion rates are calculated to be 64.9 % for Denmark and 63.4 % Finland.

3.2.3. Removal data

Removal at the two Danish WWTPs used for the evaluation was obtained for 18 compounds. From Table 2, it can be seen that in Hillerød and Avedøre WWTPs the removal rates were often quite similar. However, for some compounds Hillerød WWTP frequently had slightly higher removal as usually experienced in activated sludge plants due to its extensive multi-tank design and high total hydraulic retention time. This can be further illustrated by a non-pharmaceutical micropollutant corrosion inhibitor, i.e., benzotriazole which was removed by 41 ± 21 % in the more conventional WWTP Avedøre while Hillerød WWTP removed 64 ± 7 %. As Avedøre WWTP is considered as more representative conventional activated sludge (CAS) WWTP its rates were primarily taken for further calculations when differing from Hillerød. For the compounds that were not detected in Avedøre WWTP, the rates of Hillerød WWTP were applied (the used values are in bold, Table 2).

Removal rates in CAS WWTPs are reported to vary considerably for pharmaceuticals, depending on the precise process the respective WWTP operates on [40,50-53]. Our estimated removal rates are mostly in line with those reported by Vieno & Arjonen [45] for 17 Finnish WWTPs ranging from 55,000 to 1,300,000 PE. The most striking discrepancies are propranolol (mean 52.7 % ± 17.5 %) and trimethoprim (mean −4.9 % ± 117.8 %). On the other hand, the removal rates presented in literature often vary drastically. For instance, Sörengård et al. [20] reported removal rates of − 66 % and − 7.7 % for propranolol and trimethoprim, respectively. Similarly, the removal rates Rosal et al. [53] and Kasprzyk-Hordern [54] reported for propranolol range from 1 % to 33 % and for trimethoprim from 5.1 % to over 60 %, respectively. Moreover, removal rates in CAS WWTPs rates are reported to vary greatly for diclofenac, dependent on the respective process (Falås *et al.*, 2017[15]). Rosal et al. [53] reported a removal rate of 5 %. Conversely, Vieno & Sillanpää [55] report that the average removal rate in CAS is 36 %, with instances showing removal rates as high as 80 %.

Considering the variation present in previously reported removal rates, the values calculated from the Avedøre and Hillerød datasets values were considered good estimates.

3.3. PEC/MEC correlations

Necessary input data to calculate all three PEC values were available for 24 APIs. Fig. 2 shows the predicted and measured concentrations of each API in Denmark and Finland. Table S3 shows the numerical values for MECs and PECs. In general, the PEC_{TRA} (without human metabolism) exceeded MEC values in effluents, resulting in the lowest correlations observed (Fig. 2). The correlation between PEC and MEC showed notable improvement if metabolism was included as an elimination process (PEC_{excr}) (Fig. 2). While the correlation further improved when including WWTP removal ($PEC_{excr-RR}$), this improvement was more pronounced for the Danish dataset.

When comparing the PEC to the experimentally derived MEC values of the 24 APIs with complete datasets by country, PEC_{TRA} overestimated the MEC values on average 64- and 44-fold in Denmark and Finland, respectively. These values were affected heavily by ibuprofen, as this compound is well metabolised both in the human body and in WWTPs, thus a large fraction of the ibuprofen in the wastewater is rapidly oxidised to hydroxy and carboxy ibuprofen isomers in WWTPs [56]. For ibuprofen, PEC_{TRA} was 850 times higher than MEC in Finland. When excluding ibuprofen, PEC_{TRA} values for the remaining 23 APIs were on average 8.4 and 8.8 times higher than the MECs. When adjusting the PEC_{TRA} by including human metabolism after intake of the respective pharmaceutical, the resulting PEC_{excr} exceeded the MEC values on average only 3.8 and 2.6-fold in Denmark and Finland, respectively. The PECs matched MECs even better when WWTP removal was considered. Compared to MEC values, $PEC_{excr-RR}$ values were on average only 1.6- and 1.2-fold higher than measured for Denmark and Finland, respectively.

While the overall correlation between $PEC_{excr-RR}$ and MEC was good and the mean difference low, there was variation between compounds. The Relative Standard Deviation for the differences was 120 % and 150 % for Denmark and Finland, respectively.

$PEC_{excr-RR}$ matched the MEC well for gabapentin, iohexol and diclofenac. On the other hand, there were three APIs for which the MEC exceeded the PEC more than 10-fold. These were erythromycin, mycophenolic acid and propranolol. Mycophenolic acid exceeded this threshold in both countries. While erythromycin was overestimated in Finland, propranolol was overestimated in Denmark. These results indicate that the removal parameters used to describe the removal processes may be overestimates.

Moreover, some of the compounds that were not reported to be sold in Finland were still detected in the Finnish samples. Diatrizoic acid was detected in all of the samples, while irbesartan and iopromide were detected occasionally. This might be explained by uncertainties related to using sales data in PEC calculation, discussed in Section 2.2.1.

The results show that the total residue approach, proposed by European Medicines Agency [35], overestimates API concentrations in effluent wastewater, considerably. The strong correlation between $PEC_{excr-RR}$ and MEC demonstrates that incorporating removal processes, including metabolism and WWTP removal, can significantly enhance the accuracy of measured concentration predictions. However, care should be taken when selecting coefficients representing these removal processes, as discussed in Section 2.2.3.

3.4. Temporal trends

While most of the compounds did not show a temporal trend and were thus comparatively easy to model, several compounds followed distinctive patterns. Seasonal changes were detected for gabapentin, and cyclic weekly fluctuation of the X-ray contrast agents were detected in Hillerød WWTP. An abrupt drop in gabapentin concentration was recorded for the second half of March the year 2021 and successive low-level concentrations were observed (Fig. 3). During the same time, the concentrations between practically all other pharmaceuticals in the WWTP effluent remained consistent as demonstrated by the

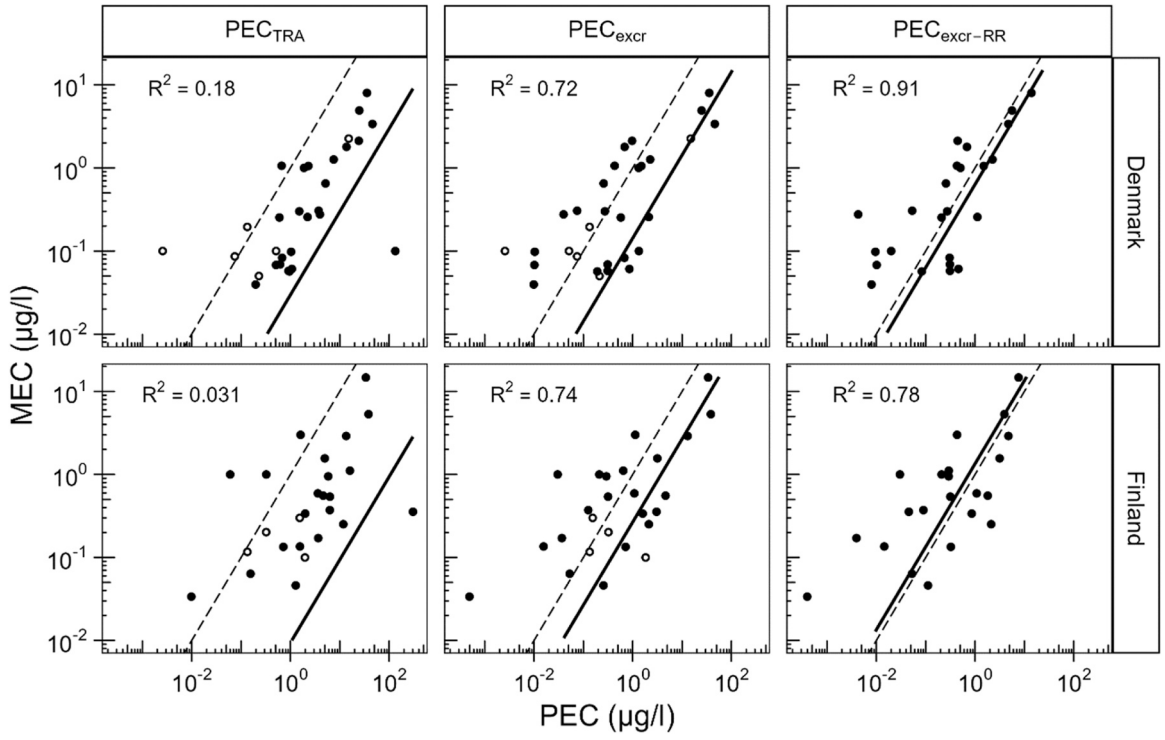

Fig. 2. Predicted concentrations (PEC) compared to measured concentrations (MEC). The dashed line presents a perfect fit, while the solid line presents the correlation line between PEC and MEC. • present the APIs for which all required input data was available and which were included into correlation estimation. ◦ represents compounds with data gaps.

concentrations of venlafaxine, diclofenac and tramadol pointing towards medical reasons and not reasons originating from the WWTP operation. Gabapentin is primarily prescribed for the treatment of epilepsy and neuropathic pain. The substance is also known to have abuse potential. It is not possible to conclude from the data the reason for the drop in gabapentin concentrations in the effluent water from Hillerød WWTP in the spring of 2021. In general, such a change could be related to changes in prescription habits due to, e.g., new safety or efficacy findings of a medicine, as well as a supply issue or seasonal variation of the diseases treated. Similar effects for antidepressants, antihistamines and antibiotics have been reported by Golovko et al. [57]. The drop in gabapentin concentrations also coincides with the removal of most quarantine restrictions due to COVID-19 pandemic in Denmark.

Fig. 4 demonstrates variations of the iodinated X-ray contrast media agent iohexol, in comparison to a steadily consumed blood pressure regulator metoprolol. It indicates the X-ray contrast agents leach to wastewater not steadily, and with slight decrease towards the weekend, possibly because examinations are being performed predominantly during the working days, and on weekends run only for emergencies. As expected, the X-ray contrast media agents did not follow any pattern of seasonal variation. Similar patterns of X-ray contrast media variations with lower weekend concentrations have been observed before [58].

4. Conclusions

This research offers insights into the levels of pharmaceuticals in WWTP effluents across eight countries in the Baltic Sea region and gives thus a basis for assessing inputs into receiving waters including the Baltic Sea. Generally speaking, the concentrations were similar in the different countries in the catchment, even though their socio-economic data differ considerably. However, it was noted in several cases, that in the different countries different compounds of the same group were prioritised.

This study has demonstrated a successful methodology for predicting pharmaceutical emissions, highlighting that the total residue approach, that only relies on sales data, drastically overestimates the measured concentrations. However, after incorporating human excretion rates, i.e., including the human metabolisation as well as WWTP removal, the correlation between predicted and measured values is good. Thus, the total residue approach should only be used to estimate worst case concentrations when no information on excretion rates or WWTP removal rates is available. However, it is important a) to calculate sales data in the same chemical form as the chemical analyses refers to and b) to recognise that this approach is relying on centrally accumulated sales data, that are not available in all countries. The proposed estimation approach as well as the vast dataset on measured concentrations can help administrators, water managers and scientists to provide first tier assessments as basis for initiating action plans and planning more detailed experiments.

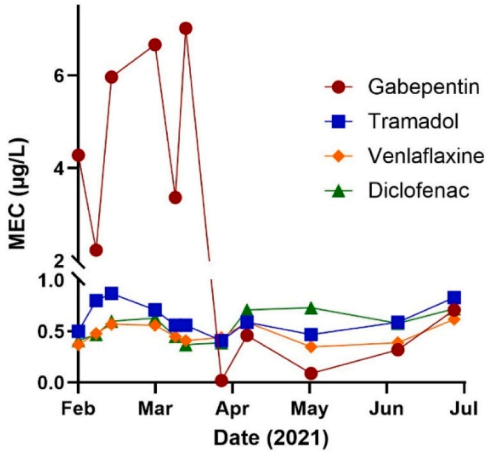

Fig. 3. Seasonal changes of gabapentin concentrations in effluent water from Hillerød WWTP in February – June 2021. (Analytical SD of gabapentin: 0.27 µg/L).

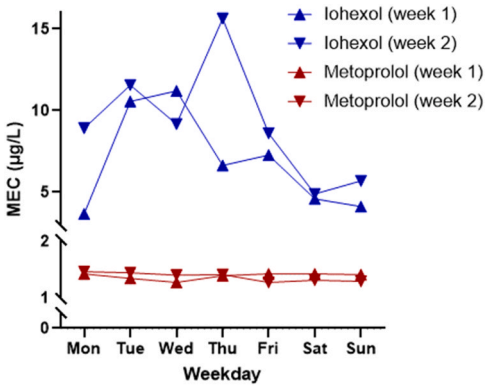

Fig. 4. Weekly variations in X-ray contrast agent iohexol, in comparison to a steadily consumed blood pressure regulator metoprolol. (Week 1: from 19 April, week 2: from 26 April 2021. Analytical SD of iohexol: 0.55 µg/L).

Furthermore, this study revealed possible seasonality for gabapentin concentrations and weekly cycles for X-ray contrast media, which made emissions predictions more difficult.

Environmental implication

This study focusses on emissions of pharmaceuticals by analyzing the effluents from 82 wastewater treatment plants (WWTPs) across eight countries. The data derived from this study illustrates that the real-world concentrations of pharmaceuticals contrasts with those predicted by conventional models based on pharmaceutical sales data, only. The findings underscore the limitations of current predictive models and findings demonstrate how these methodologies can be refined by incorporating human pharmaceutical excretion/metabolization as well as removal in wastewater treatment plants to more accurately forecast pharmaceutical levels in aquatic environments. Beyond the scientific advancement of the field, this study provides support for environmental regulators and policymakers in developing and prioritizing more effective regulations and treatments to mitigate the environmental impact of pharmaceutical residues by removing them from wastewater or other mitigation options.

CRediT authorship contribution statement

Vaidotas Kisielius: Writing – original draft, Investigation, Formal analysis, Data curation, Visualization. **Noora Perkola:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Kai Bester:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Veronika Zhiteneva:** Writing – review & editing, Formal analysis. **Suman Kharel:** Writing – review & editing, Formal analysis. **Michael Stapf:** Writing – review & editing, Formal analysis. **Lauri Äystö:** Writing – original draft, Data curation, Formal analysis, Investigation, Visualization. **Terhi Lehtinen:** Writing – review & editing, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2024.134998.

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