Environment International 185 (2024) 108524

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Assessing city-wide pharmaceutical emissions to wastewater via modelling and passive sampling

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ABSTRACT

With increasing numbers of chemicals used in modern society, assessing human and environmental exposure to them is becoming increasingly difficult. Recent advances in wastewater-based epidemiology enable valuable insights into public exposure to data-poor compounds. However, measuring all >26,000 chemicals registered under REACH is not just technically unfeasible but would also be incredibly expensive. In this paper, we argue that estimating emissions of chemicals based on usage data could offer a more comprehensive, systematic and efficient approach than repeated monitoring. Emissions of 29 active pharmaceutical ingredients (APIs) to wastewater were estimated for a medium-sized city in the Netherlands. Usage data was collected both on national and local scale and included prescription data, usage in health-care institutions and over-the-counter sales. Different routes of administration were considered as well as the excretion and subsequent in-sewer back-transformation of conjugates into respective parent compounds. Results suggest model-based emission estimation on a city-level is feasible and in good agreement with wastewater measurements obtained via passive sampling. Results highlight the need to include excretion fractions in the conceptual framework of emission estimation but suggest that the choice of an appropriate excretion fraction has a substantial impact on the resulting model performance.

1. Introduction

Good water quality is essential to society and ecosystem health. A number of ecosystem services are directly linked to surface water quality, e.g., drinking water production and recreation. Currently, assessment of surface water quality relies heavily on empirical data. Within the European Water Framework Directive (WFD, European Commission (2000)), Member States monitor the chemical water quality of their surface water bodies for a number of reference compounds (European Commission, 2022). While this concerted effort offers the opportunity to compare the environmental status between different European river catchments over time, it is limited in scope as it provides retrospective information on a relatively small number of compounds. Pollution already occurred and conclusions on the overall risk of chemical exposure cannot be drawn as only a limited number of compounds are being measured.

With increasing numbers of chemicals used in modern society, assessing human and environmental exposure empirically is becoming increasingly challenging. In 2007, the European Union (EU) adopted a regulation to register, evaluate, authorize and restrict chemicals (REACH). Under REACH, the chemical industry and EU-importers have to register any chemicals that are used in quantities larger than one tonne per year via the European Chemicals Agency (ECHA). In 2023, the REACH database contains entries for >26,000 chemicals (ECHA, 2023). Those chemicals are prospectively evaluated regarding 'safe use' by evaluation of predicted environmental concentrations for a typical European water body and the predicted no-effect concentrations (PNECs). Despite technical advances, particularly in the field of non-target screening, quantifying all registered chemicals in environmental samples to ascertain 'safe use' is both technically and financially unfeasible.

Empirical monitoring comes with substantial limitations. Besides being time- and location-specific, quantification of environmental concentrations is limited to those compounds for which analytical detection techniques are available (target analyses). This is particularly problematic for compounds often occurring in environmental concentrations below the analytical detection limits such as natural and synthetic hormones (Gunnarsson et al., 2019; Ojoghoro et al., 2021) and for chemical structures for which no analytical standards are availabe (e.g.,

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https://doi.org/10.1016/j.envint.2024.108524
Received 4 December 2023; Received in revised form 31 January 2024; Accepted 20 February 2024
Available online 23 February 2024

human metabolites and environmental transformation products). While non-target screening can identify the presence of any chemical structures in environmental samples, including molecular structures of hypothetical tranformation products, quantification is only possible in combination with mass-spectrometry equipment. Therefore, analytical detection limits represent a major bottleneck in the holistic mapping of environmental pollution with chemicals of emerging concern (CECs).

Instead, databases with usage data, such as the REACH database, can in principle be used for prospective, model-based prediction of environmental quality provided that the pathways between the source and the target compartment are known. For example, van de Meent et al. (2020) estimated European-wide surface water concentrations of >5000 organic chemicals following such an approach within the SOLUTIONs project. Van Gils et al. (2020) refined this model by applying a more detailed hydrological model to derive spatiotemporal-explicit concentrations for a large number of contaminants of emerging concern (CECs). These examples demonstrate that model-based, prospective prediction of surface water quality is feasible and could offer an efficient alternative to measuring environment concentrations.

In this paper, we argue that for some compound groups estimating emissions to wastewater based on usage data can be a cheap and informative alternative for repeated monitoring. However, such systematic modelling approaches stand and fall with the quality of the input data. We hypothesize that due to the lack of sufficiently detailed information on emission sources and exposure routes, model-based prospective prediction of surface water quality is still running behind its full potential for the majority of CECs. Compared to other groups of chemicals, data on the usage of pharmaceuticals are relatively detailed and abundant. Particularly, data on prescription drugs used by the general public are in many countries accessible via public databases. Usage of pharmaceuticals in health care facilities such as hosptials and care homes are typically also registered in detail for financial (health insurance) reasons. Therefore, the data coverage on pharamceutical usage is relatively high for different geographical scales.

The aim of this study is to develop, validate and explore the potential of predicting mass loads of CECs to wastewater based on usage data for urban areas. Hereto, we collected monthly prescription and usage data of 29 active pharmaceutical ingredients (APIs) for a medium-sized city in the Netherlands. Local API data included the clinical use in a hospital and several long-term care facilities. City-wide emission estimates to wastewater were validated with field measurements obtained through passive sampling of the influent at the local wastewater treatment plant (WWTP). Our study bridges the gap between emission estimation efforts on the continental scale (Van de Meent et al., 2020, Van Gils et al., 2020) and studies describing highly granulated source-specific CEC emissions (e.g., Zillien et al., 2019), by aiming at refining land-use specific emission estimates on the regional scale. The methods presented in this paper can also be developed for other land uses and compound categories, for example, API emissions from livestock (Rakonjac et al., 2022), highlighting the potential of model-based emission estimation for other CECs provided that required data are accessible.

2. Materials and methods

2.1. Study area

The city of Nijmegen is located in the southeast of the Netherlands and counts approx. 180,000 inhabitants. The city population is comparably younger than the national average due to the presence of one university (ca. 24,000 students) and two other institutions for higher education counting together about 16,700 students in total (ROC, 2020). People aged 20–29 represent the largest group with 37,000 inhabitants (S1). The city has two hospitals (ca. 600 beds each) and 24 care homes for elderly and people requiring long-term care.

The city has one municipal WWTP with a capacity of 400,000 population equivalents (p.e.) that also treats wastewater from 11 neighboring villages which count in total ca. 100,000 inhabitants. Treatment steps include primary and secondary treatment using activated sludge. In this particular WWTP, wastewater is heated, resulting in relatively constant water temperatures around 15 °C in winter and 28 °C in summer. More details on the treatment steps and the typical wastewater composition can be found in S2. The sewer system is mainly composed of gravity sewers with a total length of 595 km, of which 352 km are combined sewers containing wastewater and surface run-off. Following the approach by Kapo et al. (2017), the estimated average sewer residence time within the city is approximately 2 h (maximum 4 h, S3).

2.2. Compound selection

In total, the emissions of 32 CECs to wastewater were estimated based on usage data (Table 1). All compounds were selected to cover a broad chemical spectrum within our analytical possibilities (for details see Section 2.4). Among the selected CECs, 29 APIs were chosen representing different treatment regimes, that is, to treat acute versus chronic illnesses, different routes of administration, different sources, that is, hospital-specific APIs, over the counter drugs (OTCs), prescription-only APIs and combinations thereof. We also included 3 human metabolites of selected APIs in the emission estimation and chemical analysis.

2.3. Prescriptions, usage and sales data of APIs

Efforts were made to create a comprehensive overview of the mass of APIs used, by combining data from different sources. For the Netherlands, annual prescription data to the general public on a national scale were collected for 2020 from the Dutch open-access databank on prescription data (www.gipdatabank.nl) for 29 APIs (Table 1). It was assumed that prescription data to the general public refers only to pharmaceuticals that can be self-administered thus orally or rectally. Data reported in GIPdatabank are based on declarations of 19 Dutch health insurance companies, covering together almost the entire Dutch population. Since data is based on declarations, only those pharmaceuticals are reported for which health insurances offer reimbursements. Furthermore, usage of pharmaceuticals in health care institutions such as hospitals or care homes is not registered in GIPdatabank (Zorginstituut Nederland, n.d.), neither are OTC sales. This means that data reported in GIPdatabank offer an incomplete overview of pharmaceutical usage in the Netherlands.

On a local scale, monthly prescription data of 2020 was purchased for 27 APIs for the city of Nijmegen and its surroundings from the Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK, www.sfk.nl). SFK collects data on pharmaceutical dispense from 97 % of all Dutch community pharmacies, covering 15.8 million inhabitants (Stichting Farmaceutische Kengetallen, n.d.). This dataset reports API usage expressed as total number of DDDs prescribed and sold in Nijmegen and the 11 surrounding villages that are connected to WWTP Nijmegen. The dataset allowed for further specification between routes of administration and age groups, and included OTC sales via pharmacies in the area. Usage of pharmaceuticals in health care institutions is not covered by SFK datasets and neither are OTC sales via retail.

To cover API usage by the health care institutions in Nijmegen, monthly usage data on all APIs were obtained from one of the two hospitals in Nijmegen as well as for 9 care homes in the city. Since no data could be obtained for the other hospital, we chose to neglect its contribution to the overall API emissions to wastewater. An earlier study demonstrated that individual hospitals contribute only very little (1–2 %) to the overall API load in wastewater in cities of similar size and that API usage can vary substantially between hospitals (Zillien et al., 2019). For these reasons, also contributions of the remaining care homes were neglected.

Table 1
Compound selection of this study. o = oral, p = parenteral, r = rectal, d = dermal. PRE = prescription drug, OTC = over-the-counter drug, HC = drug reserved for health care, CP = consumer product, n.a. = not applicable.

Group	API	Abbreviation	CAS-number	Route of administration	Type
Analgesic	Acetaminophen (Paracetamol)	PAR	103-90-2	o, r	PRE + OTC
Angiotensin II receptor blocker	Valsartan	VAL	137862-53-4	o	PRE
Antibiotic	Amoxicillin	AMO	26787-78-0	o, p	PRE
	Azithromycin	AZI	83905-01-5	o	PRE
	Cefuroxime	CEF	55268-75-2	o, p	HC (+PRE)
	Ciprofloxacin	CIP	85721-33-1	o, p	PRE
	Clarithromycin	CLA	81103-11-9	o	PRE
	Doxycycline	DOX	564-25-0	o, p	PRE
	Erythromycin	ERY	114-07-8	o	PRE
	Levofloxacin	LEV	100986-85-4	o, p	PRE
	Ofloxacin	OFL	82419-36-1	o	PRE
	Sulfamethoxazole	SUL	723-46-6	o, p	PRE
	Tetracycline	TET	60-54-8	o	PRE
	Trimethoprim	TRI	738-70-5	o, p	PRE
Anticonvulsant	Carbamazepine	CAR	298-46-4	o	PRE
Antidepressant	Fluoxetine (Prozac)	FLU	54910-89-3	o	PRE
Antilipemic	Gemfibrozil	GEM	25812-30-0	o	PRE
Beta-blocker	Atenolol	ATE	29122-68-7	o	PRE
	Metoprolol	MET	51384-51-1	o, p, r	PRE
	Sotalol	SOT	3930-20-9	o	PRE
Central nervous system stimulant	Methylphenidate (Ritalin)	RIT	113-45-1	o	PRE
Contrast agent	Iohexol	IOH	66108-95-0	p	HC
	Iomeprol	IOM	78649-41-9	p	HC
Diuretic	Hydrochlorothiazide	HYD	58-93-5	o	PRE
NSAID	Diclofenac	DIC	15307-86-5	o, p, r, d	PRE + OTC
	Ibuprofen	IBU	15687-27-1	o, p, r, d	PRE + OTC
	Naproxen	NAP	22204-53-1	o, r	PRE + OTC
Opioid	Codeine	COD	76-57-3	o	PRE + OTC
	Oxycodone	OXY	76-42-6	o, p	PRE
Human metabolite	4′-Hydroxydiclofenac	4OHD	64118-84-9	n.a.	MET
	5-Hydroxydiclofenac	5OHD	69002-84-2	n.a.	MET
	Ritalinic acid	RITAC	19395-41-6	n.a.	MET

The painkillers diclofenac, naproxen, acetaminophen and ibuprofen are also available as OTC drugs in most Dutch supermarkets, drugstores and pharmacies. To account for the OTC use of those APIs, a dataset covering the total volume of Dutch wholesales via supermarkets, drugstores and online retail in 2020 for diclofenac, naproxen, acetaminophen and ibuprofen was kindly provided by Nielsen (www.nielsen.com) at no cost. This dataset included also the sale of APIs via private labels.

For all APIs, it was assumed that prescription, usage and sale together equal consumption, hereafter referred to as 'consumption' or 'usage' interchangeably. Consequently, we did not account for unused left-over medicines or a delay between purchase and consumption.

2.4. Estimating API emissions to wastewater

To calculate national per capita consumption $C_{NL.per.capita}$ based on the total number of daily defined doses (DDDs) as reported in GIPdatabank, API-specific DDDs were collected for the matching ATC codes via the WHO ATC index (https://www.whocc.no/atc_ddd_index/). Subsequently, the annual per capita prescription (grams per person per year) was calculated for each API according to Eq. (1):

$$C_{NL.per.capita} = \frac{N_{DDD} \times DDD}{P_{NL.2020}} \quad (1)$$

where N_{DDD} refers to the total number of DDDs prescribed as reported in GIPdatabank.nl, DDD refers to the API-specific DDD as reported by the WHO (typically grams of milligrams per DDD) and $P_{NL.2020}$ refers to the total population of the Netherlands in 2020 as reported by the CBS (in our case 17,407,585 (2020); retrieved October 7th 2021). The same equation was used to calculate local per capita consumption using the population connected to the local WWTP instead of $P_{NL.2020}$.

To estimate API emissions to wastewater, predicted emissions loads (PEL) were estimated for each API (x) using Eq. (2):

$$PEL_x = \sum_i \left(M_{x,i} \times f_{exc,x,i} \right) \quad (2)$$

where $M_{x,i}$ is the total mass of API x prescribed (grams) for route of intake i, and $f_{exc,x,i}$ refers to the excretion fraction for API x and route of intake i.

Excretion fractions for all routes of intake were obtained via public databases such as Drugbank (drugbank.ca), the 'summary of product characteristics' (SmPc) available via the Dutch 'Medicine Information Bank' (www.geneesmiddelinformatiebank.nl) and scientific literature. Excretion of the two human metabolites of diclofenac and methylphenidate was estimated by using the excretion fractions referring to these two specific metabolites as reported in literature (S4).

Similarly, the excretion of conjugate metabolites was accounted for via excretion fractions reported specifically for those metabolites. Back-transformation of conjugate metabolites into the respective parent compound was considered by adding the excretion fractions reported for the conjugated parent compounds to the excretion fractions reported for the free parent compound as described earlier in (Delli Compagni et al., 2020). This was not in all cases unambiguous as reported excretion fractions sometimes seemed to refer to all kinds of conjugated metabolites but not necessarily exclusively to the conjugated parent compound (discussed further in Section 3.2). In the absence of empirical data on the kinetics of back-transformation from conjugate metabolites in wastewater, we assume complete back-transformation into the parent compound. An overview of the excretion fractions used in this study can be found in S4.

2.5. Field measurements

Wastewater at the WWTP influent was sampled using passive samplers to obtain weekly time-weighted average loads of APIs. Two sampling campaigns were conducted in May and September 2020. During each sampling campaign, one set of passive samplers (Speedisks©) containing DVB-HLB adsorption material was deployed for one week at the influent collection basin. To allow direct contact between sampler and wastewater, the outer rim of the Speedisk© was removed (S5). The samplers were attached to a metal rod to weigh them down and keep them submerged (S6). The exposure time was kept relatively short to ensure linear uptake of APIs to the sampler. The weather during both sampling campaigns was dry, so no dilution by surface run-off was expected. Upon retrieval, samplers were immediately transported in glass jars on ice to the laboratory and frozen at −18 °C until further analysis.

After addition of the internal standards, the extraction was performed following a 3-step-approach: during the first step, the passive samplers were extracted using 2 mL methanol. In a second step, samplers were extracted again using five times 5 mL dichloromethane. Both eluates were combined, dried with sodium sulphate over a glass frit and concentrated to 2–3 mL. In a third step, four times 5 mL of 1 % formic acid methanol was used to extract any remaining polar compounds. This eluate was then concentrated to 1–2 mL, subsequently completely dried under a stream of nitrogen to remove the formic acid and dissolved again in methanol. Per sampler, those three methanol fractions were combined and vortexed. The resulting extract was concentrated under a stream of nitrogen, then brought to a final sample volume of 1 mL and stored at −20 °C until the analysis.

Analysis was performed following the same protocol as described in Zillien et al. (2019). In short, samples and internal standards were analyzed using Agilent 1260 series high-performance liquid chromatography coupled with an Agilent 6460 triple quadrupole LC/MS with Jetstream Electron Spray Ionisation (ESI) and multiple reaction monitoring (MRM). The target compounds were determined with one precursor ion and two product ions. Calibration was done before measuring the samples with known amounts of the analytes in nine steps with concentrations ranging between 0 and 50 ng mL^{-1}. The limit of detection (LOD) and limit of quantification (LOQ) of the analytes were determined with signal-to-noise ratios of 1:3 and 1:10, respectively. Average analytical recoveries, calculated water concentrations and information on the LOD and LOQ are given in S7. The method resulted in LOQ values ranging between 0.5 and 1 ng mL^{-1} of extract. Given that the volume of the final extract was 1 mL, results were reported as load (ng) of APIs per set of samplers.

Measured loads of APIs per set of samplers were extrapolated to weekly emission loads *MEL* per API *x* according to Eq. (3) as described in Zillien et al. (2019):

$$MEL_x = \frac{L_x \times \overline{Q}_{WWTP}}{R_s \times T_{sampling}} \tag{3}$$

where L_x is the measured load (grams per week) of API *x* on the samplers per week at the WWTP influent; $\overline{Q}_{WWTP}$ is the total weekly discharge (liter per 7 days); R_s is the sampling rate per sampler (liter per day) and $T_{sampling}$ refers to the sampling duration (7 days). $\overline{Q}_{WWTP}$ was based on daily influent discharge measurements at the WWTP. To derive time-weighted average concentrations in WWTP influent, we assumed an average sampling rate of 50 mL per sampler per day (Smedes et al., 2013; Zillien et al., 2019).

2.6. Evaluation of model performance

Emission estimates were compared to field measurements obtained through passive sampling. To compare model performance when using different levels of detail in input data, two model performance indicators defined by Morley et al. (2018) were used: To assess the overall model spread (i.e., deviation from the 1:1 line), the Median Symmetric Accuracy was calculated. Applied to the context of our study, the Median Symmetric Accuracy (Xi) was calculated according to Equation (4):

$$Xi = 100\% \times \left(e^{\left(median\left(\left|ln\left(\frac{PEL_x}{MEL_x}\right)\right|\right)\right)} - 1\right) \tag{4}$$

where PEL_x is the predicted environmental load of API *x* in wastewater, and MEL_x is the measured environmental load of API *x* in wastewater. The Median Symmetric Accuracy can be interpreted as the unsigned percentage of error in which both under- and overestimations are penalized equally (Morley et al., 2018). The smaller X_i the better the predicted loads coincide with measured loads and therefore, X_i gives an indication of overall model spread. As indication, a factor of 10 deviation results in an X_i value of 900 %.

To assess whether the predicted loads are systematically over- or underestimating measured loads, the Symmetric Signed Percentage Bias (SSPB) was calculated based on Morley et al. (2018). SSPB in our context was calculated according to Eq. (5):

$$SSPB = 100\% \times signum\left(median\left(ln\left(\frac{PEL_x}{MEL_x}\right)\right)\right) \times \left(e^{\left(\left|median\left(ln\left(\frac{PEL_x}{MEL_x}\right)\right)\right|\right)} - 1\right) \tag{5}$$

A positive value for SSPB indicates a systematic overestimation, meaning that predicted loads are generally larger than measured loads whereas a negative value suggests predicted loads being smaller than measured loads and therefore indicate a systematic underestimation.

3. Results and discussion

In this section, we first present the comparison of modelled and measured API loads in wastewater using different input data (3.1), then showcase the utility of model-based emission estimation (3.2). Subsequently, we discuss in more detail the factors causing variability in emission estimates (3.3) and assess if accounting for in-sewer transformation via re-transformation of conjugated metabolites into their respective parent compounds improves emission estimates (3.4).

3.1. Estimating API emissions on city-scale: Proof of principle

Of the compounds selected for this study, mean annual emission estimates of 20 compounds were within a factor of 10 from mean wastewater measurements (Fig. 2). For 9 of the remaining 12

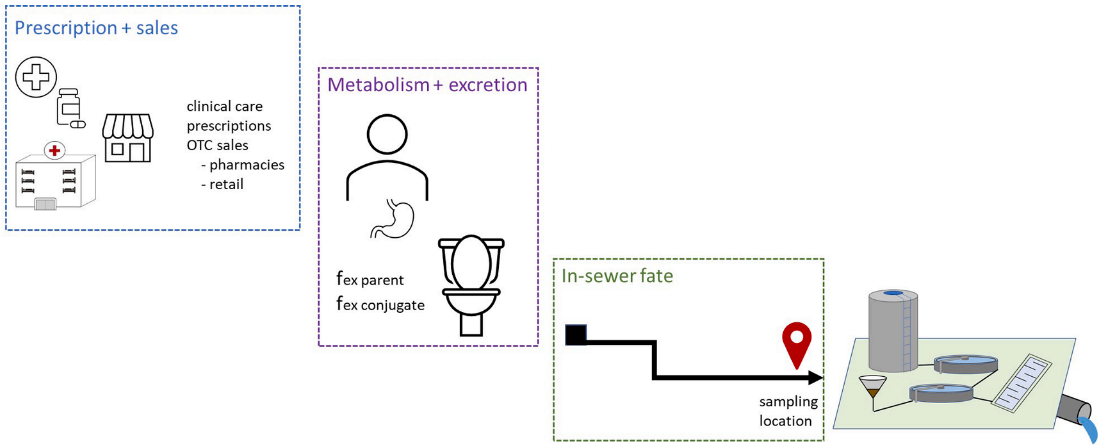

Fig. 1. Conceptual framework of this study.

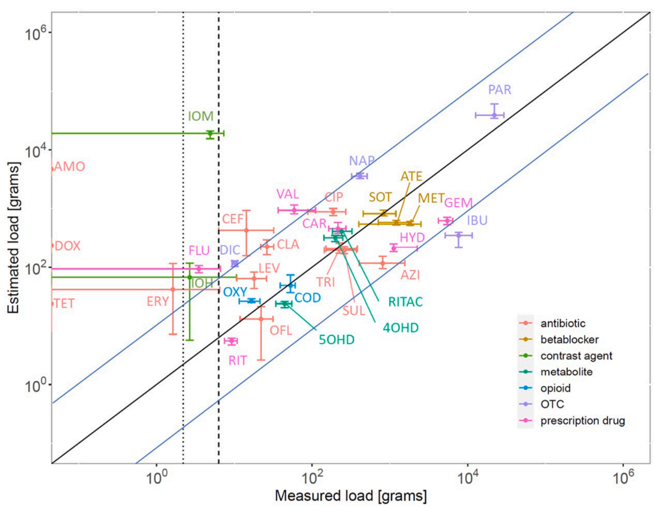

Fig. 2. Comparison of measured weekly load of 32 APIs at WWTP Nijmegen (influent) with estimated weekly loads. Measurements represent the average of 2 sampling campaigns, error-bars in measurements indicate min and max values. Estimates are based on local data and account for back-transformation of conjugate metabolites. Xi = 256 %, SSPB = 60 %. Vertical dotted line represents the limit of detection (LOD) and vertical dashed line represents the limit of quantification (LOQ). Black solid line represents ideal ratio of 1 (predicted emission equals measured emission), blue solid lines indicate a 10-fold deviation from it. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

compounds, deviation between estimates and measurements were larger than a factor of 10. For cefuroxime (29.7); diclofenac (11.6); erythromycin (25.7); fluoxetine (26.8); iohexol (25.1); iomeprol (3877.9) and valsartan (15.8) estimated emission loads were higher than wastewater measurements. Of those, 4 compounds (iomeprol, iohexol, fluoxetine, and erythromycin) were measured below the LOQ (Fig. 2). In contrast, for gemfibrozil (62.2) and ibuprofen (22.2) estimated loads were lower compared to measured loads. Emission estimates agreed particularly well with sewer measurements for compounds showing good average analytical recoveries (>60 %, i.e., trimethoprim, sulfamethoxazole, codeine, oxycodone, atenolol, methylphenidate).

While the parent compound diclofenac was overestimated, emission estimates for both its hydroxy metabolites 4OHD and 5OHD match well with wastewater measurements. This overestimation of DCF as parent compound suggests that either the excretion fractions used for the parent compound and diclofenac-glucuronide are higher than in reality; or less dermal DCF is used than is sold; or that the wash-off fraction of dermally applied DCF is estimated too high. On the contrary, the good match between prediction and measurements of 4OHD and 5OHD suggests that usage data seems rather accurate (further discussed in Sections 3.2 and 3.3). In comparison, methylphenidate (RIT), which is in the Netherlands only available upon prescription, and its metabolite ritalinic acid (RITAC) agree well with wastewater measurements. This observation highlights the utility of focusing not just on individual parent compounds but also on related human metabolites for model validation (Bakker-'t Hart et al., 2023).

Three of the remaining compounds were not detected (amoxicillin, doxycycline, tetracycline) despite being predicted above the LOQ. In the case of amoxicillin, this is surprising as it is by far (by mass) the most consumed antibiotic in this study and shows little variation in prescription over the year (S8). However, a laboratory study conducted by Hirte et al. (2016) demonstrated that amoxicillin undergoes abiotic hydrolysis via cleavage of the beta-lactam ring resulting in the formation of amoxicillin penicilloic acid. Additionally, subsequent condensation and decarboxylation result in two more transformation products (Hirte et al., 2016). When analyzing influent samples from different WWTPs, the authors detected the transformation products in all samples while amoxicillin was detected in only one of the five samples. Among the transformation products, amoxicillin penicilloic acid showed much higher peaks than the parent compound amoxicillin. The authors attribute this to accelerated hydrolysis due to microbial activity in wastewater (Hirte et al., 2016). Hence, formation of amoxicillin penicilloic acid due to hydrolysis within the sewer system could offer an explanation for not detecting amoxicillin in our study.

Tetracycline and doxycycline in their neutral forms are both lipophilic due to the benzene rings in their molecules. Furthermore, both compounds are zwitterions having an acidic group (OH) as well as a basic group (N). This means that both compounds can be charged either positively or negatively depending on the pH of wastewater. Given the pH of wastewater typically varies between 6.5 and 8 (Zillien et al., 2022), the basic groups of both compounds would mainly be present as deprotonated cation due to their pK_a values of 7.68 (tetracycline) and 8.33 (doxycycline). Consequently, both compounds could be electrostatically sorbed to negatively charged organic matter present in wastewater. This could explain why we were not able to detect both antibiotics in the water phase. Overall, this discussion highlights that compound properties like lipophilicity and the degree of ionization could affect the measured emission loads as, like most sampling methods, passive sampling only samples compounds present in the water phase. In contrast, predicted emission loads in this study refer to total emissions (i.e., dissolved and sorbed) and could therefore result in a mismatch between predicted and measured emission loads.

Emission estimation was performed using two different sources of input data: a national dataset and a local dataset (see Section 2.3 for details on data coverage). Model performance, assessed via SSPB and X_i, was generally better when the national dataset was used compared to the local dataset (Table 2). Furthermore, we assessed model performance for three different excretion scenarios (Table 2): Following the EMA-guideline for environmental risk assessment, a default excretion fraction of 1 was applied, meaning that the entire consumed dose is excreted as parent compound. This scenario led to the worst model performance as estimations deviated on average a factor of 5 to 6 from measurements (X_i) and resulted in a substantial overestimation (SSPB). Model performance consistently improved if excretion fractions for parent compounds were taken into account. For both datasets, model spread reduced to an average factor of 2.5–3.5 (X_i) while overall predictions were underestimating field measurements (negative SSPB). When in addition to excretion of the parent compounds also the excretion of conjugate metabolites was taken into account, the model spread remained unchanged, but resulted again in a slight overestimation compared to measurements (positive SSPB). This underlines the importance of considering excretion of parent compounds and conjugated parent compounds within prospective emission modelling.

3.2. Showcasing the utility of emission modelling

In this section, we illustrate the added practical value and flexibility of a model-based approach by showcasing the results of two simple analyses that can follow an emission estimation as presented in this study.

First, a reliable and comprehensive dataset on API usage and emission sources offers the possibility to assess the origin of APIs that cumulatively result in the predicted load at the WWTP influent. This 'source-tracking' enables the identification of the largest contributors, which represents valuable information regarding possible emission reduction targets. Fig. 3 displays the origin of the predicted influent load of WWTP Nijmegen in 2020. It becomes clear that at-home consumption of prescribed APIs accounts for the largest share of estimated loads to WWTP influent (42 %), followed by APIs originating from OTC sales via pharmacies and wholesales (together 29 %). The hospital included in this study contributed 27 % of the total influent load, while care homes contributed the least (2 %).

When taking a closer look at the contribution of the hospital to the predicted load, the two contrast agents iomeprol and iohexol stand out since together accounting for 75 % of the total hospital contribution. This can be explained by high excretion fractions in combination with the comparatively high molecular mass of contrast agents (IOM: 777.1 g/mol; IOH: 821.1 g/mol) and high usage volumes. When excluding contrast agents from the analysis, the hospital contribution decreases to 8 % to the overall PEL. This is still higher than reported in our previous study (Zillien et al., 2019) when measured loads in hospital wastewater were compared to measured WWTP influent loads. While it is difficult to pinpoint the exact reason for this, several factors could play a role, including differences in compound selection between both studies or analytical constraints regarding limits of detection and quantification in the previous study.

Second, besides general source-tracking as described above, a modelling approach to emission quantification can also shed light on temporal trends in consumption and hence excretion. Fig. 4 depicts the predicted load per capita to the WWTP, accounting for the different compound groups and emission sources on a monthly basis in 2020. It becomes clear that for most compound groups variation between months is relatively small. One exception here are substantially higher predicted loads of OTC drugs in March 2020, which are mainly attributed to higher OTC sales via pharmacies as well as higher prescriptions. An opposite trend can be observed for contrast agents that depict a declined use during March, April and May 2020 as compared to the rest of the year. Both observations are likely linked to the onset of the Covid-19 pandemic. For antibiotics, a substantially higher usage was observed during the first three months of 2020 as compared to the rest of the year. This is likely related to the lock-downs and social distancing measures that were in place to limit the Covid-19 outbreak (Zorginstituut Nederland, 2022) and is mainly attributed the usage pattern of amoxicillin (S8). Similarly, lower quantities of contrast agents were used during spring 2020 as clinical care focused mainly on Covid-19 patients at that time. Overall, the compounds selected in this study resulted in an estimated per capita excretion of 17.4 g per person in 2020. Of this, OTC drugs represent the major share (62.4 %) followed by contrast agents (20.3 %) and antibiotics (7.6 %). Although not the point of this study, caution is advised when generalizing the API-related results presented in this section as 2020 was anything but a 'normal year'. The purpose of this exercise was to showcase the utility of the modelling approach. The aim of this study was to develop a validated, generalizable modelling approach to quantify CEC emissions to wastewater.

While we only present the estimated mass loads for a selected number of APIs, we also highlight the utility of such simple analyses. The approach presented in this paper is easily transferrable to any API provided that a comprehensive and reliable consumption or usage dataset is available for a given study area. Combining the outcomes of such modelling exercises with ecotoxicity data enables prioritization of emission reduction measures on various spatial scales ranging from single hospitals (e.g., Zillien et al., 2019) to individual districts or cities to entire regions or countries. Furthermore, if comparable data were available for other groups of CECs, a similar conceptual framework could be developed to assess the emissions of other land uses. Similar approaches were followed to develop risk-based tools, for example, to assess emissions of veterinary pharmaceuticals via manure application (Rakonjac et al., 2022) or the environmental impact of pesticide use on a river catchments in Indonesia (Utami et al., 2020) and California (Parker and Keller, 2021). Furthermore, this type of analysis could help to assess trends in API usage if comparable datasets are available for several years and could help to forecast emissions, e.g. in relation to ageing societies. Additionally, source tracking of API emissions within urban areas could present a valuable tool to increase stakeholder interaction and could serve as basis to discuss and prioritize local emission reduction strategies (Moermond and de Rooy, 2022).

3.3. Variability in emission estimates

Variability and uncertainties are not unique to modelling emissions but also inherent to field measurements. While analytical variability can be assessed through stringent lab procedures (Section 2.5), quantifying uncertainties introduced during exposure of the samplers in the field is very difficult. Practical issues include the effect of toilet paper and other sanitary items wrapped around samplers or the impact of varying flow velocities on the uptake rate. These factors require more research in the future. Based on our results, substantial variation was observed in field

Table 2
Comparison of model performance for different scenarios assessed using either national or local dataset. Only those APIs were assessed that were present in both datasets (so acetaminophen, iohexol and iomeprol were excluded from local dataset).

Scenario	Dataset	Xi [%]	SSPB [%]	Remarks
Consumption				
f_{ex} = 1, ex metabolites	National	370	245	$n_{API} = 23$
	Local	555	497	$n_{API} = 23$
Excretion parent compounds				
f_{ex} = parent	National	157	−40	$n_{API} = 26$
	Local	245	−6	$n_{API} = 26$
Total excretion				
f_{ex} = parent + conjugate	National	157	15	$n_{API} = 26$
	Local	245	24	$n_{API} = 26$

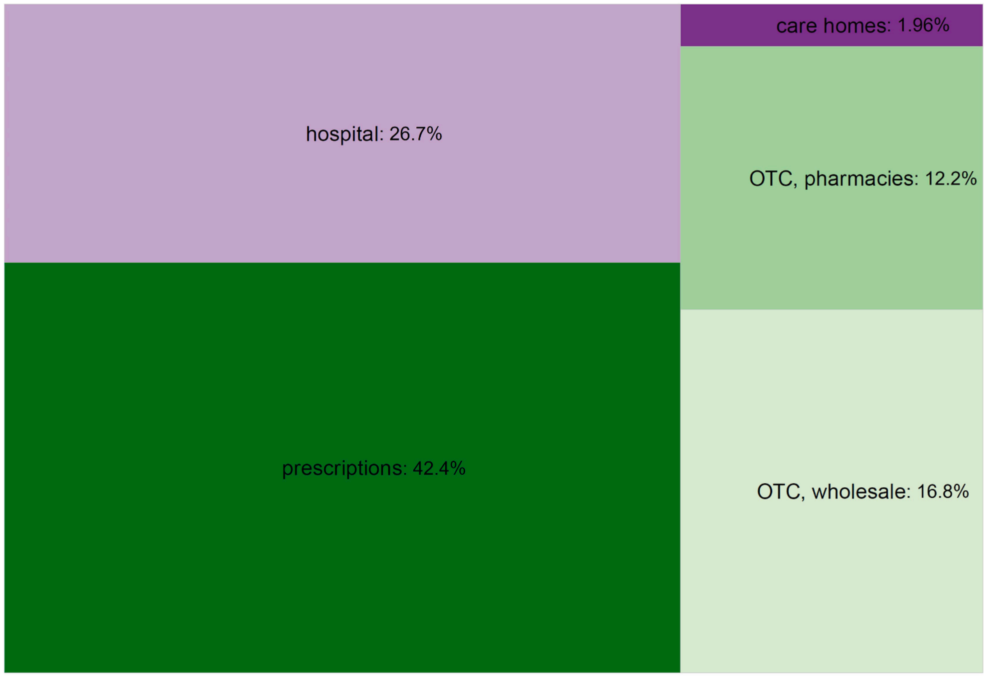

Fig. 3. Assessment of relative contribution per emission source to overall estimated API load at WWTP influent in Nijmegen for 2020. Color scheme: ColorBrewer.org.

data obtained via passive sampling. For many compounds, variation in measured loads was larger than the variation in estimated loads (Fig. 2). This could be partially due to different temporal data resolution since monthly usage data was compared to weekly time-weighted average measurements but suggests overall that also measured loads derived from passive sampling comes with limitations. In this section, we discuss the factors causing variability in emission estimates in more detail, particularly regarding uncertainties around usage and consumption data and excretion fractions.

3.3.1. Usage equals consumption?

Following the conceptual framework of emission estimation (Fig. 1), several factors can introduce uncertainty in the modelling steps and potentially cause over- or underestimation of predicted API emissions to wastewater. Starting with the prescription and sales data, it remains unclear if all medication prescribed or sold is actually being consumed. Furthermore, private import of pharmaceutical products from other countries could result in higher measured loads compared to estimated loads. For example, Vogler and de Rooij (2018) found that around 7 % of the medication found in municipal waste in Vienna was of foreign origin. Overall, several studies point to the fact that the general public accumulates substantial amounts of unused medication at home, which raises questions about what disposal routes people chose to dispose of the unused products and what types of medication the leftover consist of.

From a consumers' perspective, three main routes of disposal are available for unused medication: return to pharmacy or healthcare providers; disposal via household garbage; or disposal via toilets/sinks. Several studies investigated the behavior of the general public towards pharmaceutical waste (e.g., Coma et al., 2008; Fenech et al., 2013; Stone et al., 2022; Veiga et al., 2023; Vogler and de Rooij, 2018). For example, Veiga et al. (2023) assessed disposal routes of unused medication in Portugal via an online questionnaire and found that around 70 % of the 450 participants would return unused medicines to the pharmacy while 30 % would dispose them via the household garbage. In their study, mainly painkillers and antihistamines remained unused. Similarly, a study by Coma et al. (2008) analyzed pharmaceutical products returned to pharmacies in Barcelona (Spain) and found that returned products mainly belonged to ATC classes A (alimentary tract and metabolism) and N (nervous system) (18 % each), followed by class C (cardiovascular system, 11 %). Vogler and de Rooij (2018) studied pharmaceutical products in the municipal waste of Vienna (Austria) and found that 42 % of collected items were not identifiable and most identifiable products belonged to ATC classes A, N or R (respiratory system). In the Netherlands, initiatives to reduce pharmaceutical waste include trials to re-dispense unused medicines that have been returned to pharmacies (Bekker et al., 2019a; Bekker et al., 2019b). From a modelers' perspective, these factors can complicate the emission estimation unless detailed data is available.

To assess whether variability in consumption pattern could affect the model performance, we classified all APIs into two categories: APIs predominantly used against acute health issues (antibiotics, painkillers, contrast agents) and APIs that are mainly used to treat chronic diseases (beta-blockers, other prescription drugs). This distinction was made based on pharmacotherapeutic information available via www.farmacotherapeutischkompas.nl. Indeed, the model spread (Xi) was in both excretion scenarios smaller for the group of APIs used against chronic diseases than for the ones against acute health issues (Table 3). This seems logical as APIs used against chronic diseases are consumed on a regular basis over an extended period of time resulting in rather constant emissions to wastewater. The use of APIs against acute issues is likely incidental and therefore more variation can be expected. Noteworthy, however, the data used in this study is for 2020, which cannot be considered a 'normal' year due to the onset of the global Covid-19 pandemic. It has been demonstrated that measures to restrict the spread of Covid-19 reduced the prevalence of other infectious diseases affecting in turn the usage of APIs, especially antibiotics, used against acute health issues (Zorginstituut Nederland, 2022). This suggests that the differences in consumption between chronically and acutely used APIs will be larger in 'normal' years.

The assumption that prescription and sales equal consumption can introduce uncertainty in the modelling framework. While considering unused medication as being consumed and causes overestimation of API emissions to wastewater, unjust neglect of import of pharmaceuticals

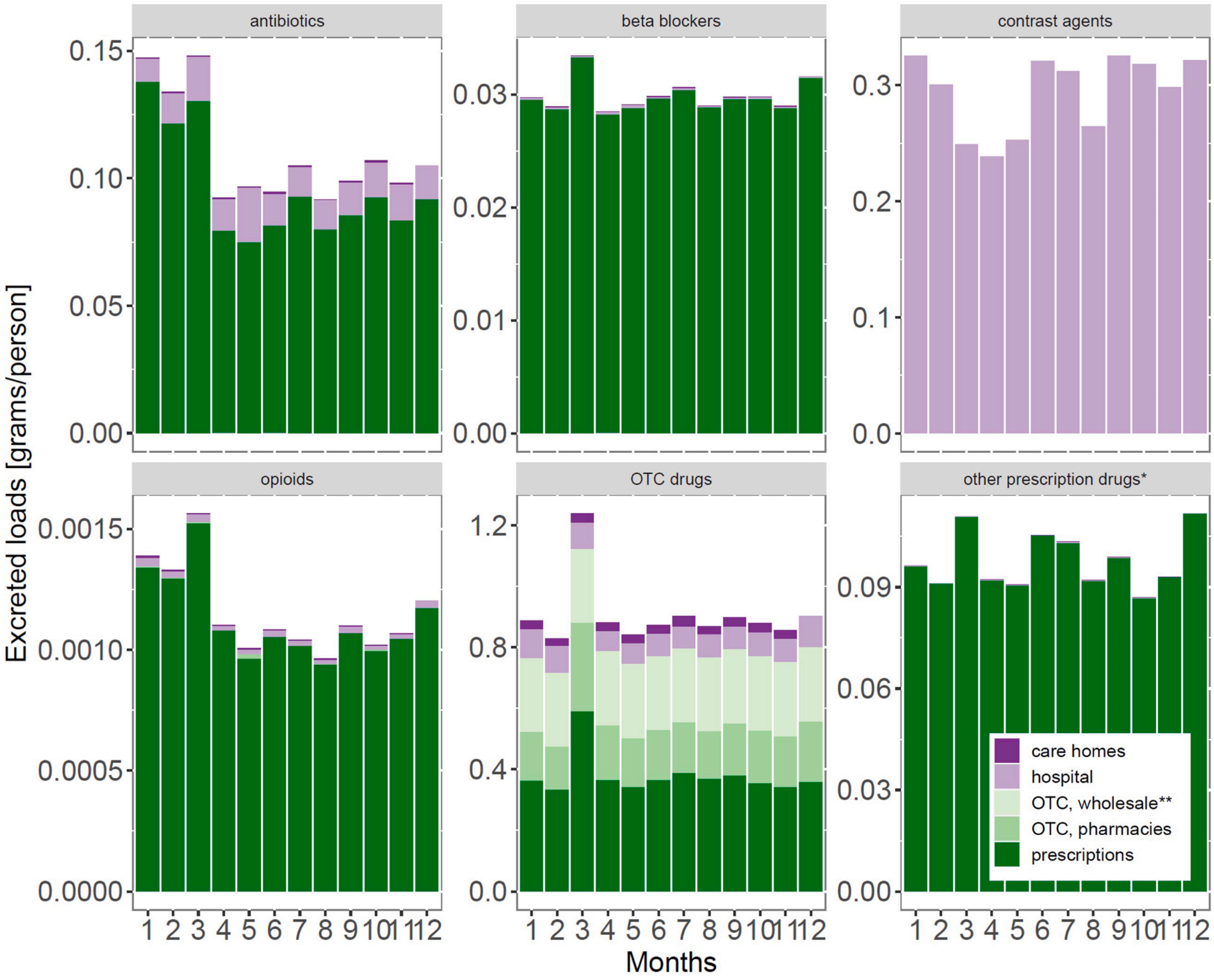

Fig. 4. Monthly contribution of compound groups per emission source to WWTP influent (predicted environmental concentration, PEC) in Nijmegen in 2020. *Other prescription drugs refer to carbamazepine, fluoxetine, gemfibrozil, hydrochlorothiazide, methylphenidate and valsartan. **OTC wholesales was provided on an annual scale and subsequently evenly distributed over the individual months for this graphic. Color scheme: ColorBrewer.org.

Table 3
Assessing model performance for APIs used against chronic vs acute health issues. For the classification of APIs according to group, see S9.

Scenario	Dataset	API group	Xi	SSPB	remarks
Total excretion					
$f_{ex} = parent + conjugate$	Local	Acute	471	151	$n_{API} = 18$
		Chronic	110	−2	$n_{API} = 11$
	National	Acute	228	25	$n_{API} = 15$
		Chronic	123	−51	$n_{API} = 11$

from abroad can result in underestimation. Similarly, disposal of unused medication via toilets and sinks can result in higher wastewater loads than expected based on emission estimation. Pinpointing the contribution of single factors to the overall uncertainty remains difficult as specific information is lacking. While consumer surveys provide insights into common practices of the general public, these surveys often sample only a small group of individuals that are not necessarily representative for the entire population. However, despite the variability around usage data, the associated uncertainty seems to have a smaller effect on the emission estimation compared to the choice of the excretion fraction.

3.3.2. Selecting ‘the right’ excretion fraction

The choice of the excretion fraction is a crucial step in estimating API emissions to wastewater. Generally, when working with pharmacokinetic data, it is important to keep in mind that reported excretion data are often based on a relatively small group of study subjects who do not necessarily reflect the general population. While especially older studies focused mainly on healthy males (Beery and Zucker, 2011) or ‘normal volunteers’ (e.g., Bodey and Nance, 1972), more recent research led to increasing evidence that factors like sex, age and ethnicity can cause substantial interindividual variability in toxicokinetic processes (Soldin and Mattison, 2009).

Physiological and hormonal differences between men and women have been shown to affect the activity of enzymes involved in drug metabolism and thus urinary excretion (Joseph et al., 2015; Scandlyn et al., 2008; Sinués et al., 2008; Tomicic et al., 2011). For example, the use of hormonal birth control medication and pregnancy increase metabolic activity in women affecting particularly glucuronidation of parent compounds (Scandlyn et al., 2008; Sinués et al., 2008; Tomicic and Vernez, 2014). Tomicic et al. (2011) observed that women not using hormonal contraceptives excreted significantly higher fractions for parent compounds than men or women who are using hormonal contraceptives after exposure to different solvents via inhalation. The use of hormonal contraceptives lead to a shift of 50 % in excretion ratio between parent compounds and metabolites (Tomicic et al., 2011). Other studies report that besides sex also age is an important factor to explain differences in the expression of human drug transporter genes affecting urinary excretion fractions (Joseph et al., 2015; Sinués et al., 2008). In comparison, the effect of ethnicity on the metabolism and excretion of drugs appears less pronounced (Darney et al., 2020; Kasteel et al., 2020). However, single studies did observe differences between ethnic groups. Critchley et al. (2005), for example, observed differences in the excretion of conjugate metabolites between Hong Kong Chinese and Caucasians after administration of a single oral dose of paracetamol. More research is required to accommodate socio-demographic diversity in toxicokinetics and to improve the mechanistic understanding of confounding factors. Altogether, those factors could explain the large ranges in excretion fractions reported for many APIs.

Due to the large ranges in excretion fractions, selecting appropriate excretion fractions for the emission modeling based on literature was in many cases challenging. For example, the American Food and Drug Administration (FDA) reports for orally administered gemfibrozil, marketed under the tradename 'LOPID': '*LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2 % excreted as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces*.' (Kimoto et al., 2015; US FDA, 2020). In contrast, Knauf et al. (1990) report: '*In healthy volunteers, only 0.02 to 0.15 % of the given dose was recovered in the urine as parent gemfibrozil [as the urine concentrations were close to the detection limit of the assay method, these values can be regarded only as rough estimates], while conjugates made up 7–14 %*'. Additionally, for conjugated metabolites, reported excretion fractions sometimes seemed to refer to all kinds of conjugated metabolites but not necessarily to the conjugated parent compound. Excretion fractions selected for this study are reported in S4.

The variation in reported excretion fractions can affect the estimation of API emissions to wastewater. Small deviations between assumed and actual excretion fractions have a substantially larger effect on small excretion fractions than on large ones. As for gemfibrozil, choosing an excretion fraction of 2 % or 0.02 % results in a factor of 100 difference in estimated emissions for the parent compound. Similarly, a 1 %-point deviation does not really affect the estimated emission if the excretion fraction of an API is above 90 % (e.g., f_{ex} clarithromycin: 0.95, f_{ex} atenolol: 0.93). However, it will result in double or nil estimations for the parent compounds of diclofenac of naproxen (both $f_{ex} = 0.01$). Selecting an appropriate excretion fraction is therefore the major challenge when estimating API emissions. For some APIs, it is recommended to also include excretion of conjugate metabolites as some conjugate metabolites can back-transform into their respective parent compounds via biological or abiotic fate processes.

3.4. In-sewer fate: Accounting for back-transformation of conjugate metabolites

Deconjugation of conjugated metabolites can lead to back-transformation into the respective parent compound. D'Ascenzo et al. (2003) suggested that deconjugation of glucuronide metabolites could be the result of enzymatic cleavage by β-glucuronidase secreted by *E.coli* bacteria present in wastewater. After cleavage, the unconjugated parent compound can be released into the water phase, which is also believed to offer an explanation for negative removal efficiencies observed for some pharmaceuticals, including diclofenac (Clara et al., 2005; Lee et al., 2012; Vieno and Sillanpää, 2014; Zorita et al., 2009). Since conjugation is an important phase II elimination process relevant to many orally consumed pharmaceuticals (Ge et al., 2016; Järvinen et al., 2022), this could also affect emission estimates of APIs to wastewater.

Based on the compound selection for this study, excretion of conjugated parent compounds is relevant for five APIs: diclofenac, naproxen, acetaminophen, codeine and gemfibrozil. Respective excretion fractions were collected from literature and subsequently added to the excretion fractions reported for the parent compounds (Delli Compagni et al., 2020). In the absence of empirical data on the kinetics of back-transformation in wastewater, we assumed complete and instant back-transformation into the respective parent compound.

For three of the five APIs (diclofenac, naproxen, acetaminophen), accounting for complete and instant back-transformation into the parent compound led to overestimations as compared to measured loads (Fig. 5, S10). However, precisely these APIs are available as OTC drugs for self-medication in the Netherlands. Hence, overestimation of those APIs could also suggest that some share of sold products remains unused. In contrast, gemfibrozil is only available upon prescription. While excretion of the parent compound of gemfibrozil resulted in a factor of 164 underestimation compared to measurements, including the excretion of the conjugated parent compound resulted in only a factor of 9 underestimation. In the case of codeine, accounting for deconjugation of codeine conjugates resulted in a factor of 1.8 underestimation. However, after completion of this research we found out that one codeine-containing cough syrup is available as OTC medication which we missed during data collection. Therefore, we cannot say with certainty whether the improved fit between emission estimates and sewer measurements is solely attributed to the effect of deconjugation or also partially to the missed OTC formulation. While only indicative due to the small sample size, our results suggest that back-transformation of conjugated parent compounds is likely a relevant fate process within the sewer system and therefore needs to be considered when estimating API emissions to WWTP influent.

4. Conclusions and recommendations

4.1. Conclusions from this study

Estimating API emissions to wastewater based on usage and consumption data is feasible on a city-scale. For most APIs, the estimated emissions based on usage data were within a factor of 10 from wastewater measurements obtained via passive sampling. Modelling based on sales and prescription data can provide additional insights into mass flows compared to field measurements.

Disentangling processes causing variability in API emission estimation remains difficult. Besides variability in usage data, the choice of excretion fraction has a major effect on the emission estimation. Model performance consistently improved if excretion of parent compounds and conjugated parent compounds were taken into account. Emission estimates for compounds excreted in low fractions are substantially more sensitive to small variations in assumed and actual excretion fractions than compounds excreted in large fractions.

Accounting for complete and instant back-transformation of conjugated parent compounds led to better emission estimates compared to wastewater measurements. This suggests that back-transformation is likely a relevant fate process within the sewer system, which therefore needs to be considered when estimating API emissions to WWTP influent.

Pharmacokinetic data reported in literature are often based on a relatively small group of study subjects who do not necessarily reflect the general population. More research is required to accommodate societal diversity in toxicokinetics and to improve the mechanistic understanding of confounding factors.

4.2. Recommendations and future research prospects

Based on the outcomes of this study, we suggest three main directions for future research. Firstly, we recommend evaluating if the method presented could be used and automated to estimate API emissions on a European scale. If country-specific usage data on APIs and a comprehensive overview of related excretion fractions were available, the approach we present in this study could be extrapolated e.g. via per capita emission loads to other locations. Given that our case study focused on a medium sized city, the applicability of the approach would need to be assessed for substantially larger cities as well as for lower

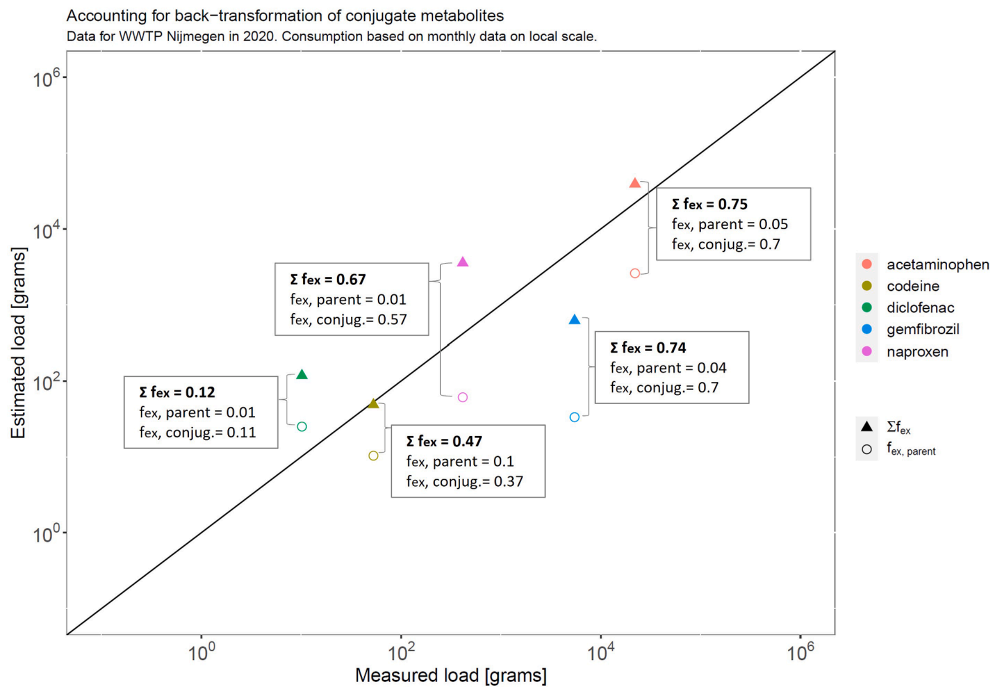

Fig. 5. Accounting for back-transformation of conjugated metabolites into their respective parent compounds. Usage data based on local dataset for 2020. Measured loads represent average of two sampling campaigns at WWTP Nijmegen in May and September 2020. $F_{ex,\ parent}$ refers to the excretion fraction for the parent compound; $f_{ex,\ conjug.}$ refers to the reported excretion fraction for the conjugated parent compounds; Σf_{ex} refers to the sum of both excretion fractions (parent + conjugated parent compound). More information on the selected excretion fractions can be found in S4.

populated areas. The contribution of health care facilities in terms of API emissions will need to be evaluated on a case-by-case basis, especially if hospitals have on-site wastewater treatment facilities in place. Depending on the temporal and spatial resolution of future studies, the implications of commuting and large-scale events would need to be studied.

Secondly, we recommend conducting more research into the impact of compound properties in relation to sampling techniques used in empirical monitoring campaigns of raw wastewater. Particularly lipophilicity or the degree of ionization could underestimate the measured emission loads if only the water phase is being sampled. Furthermore, more empirical research is necessary to assess the fate of conjugated parent compounds and metabolites in wastewater.

Thirdly, this study highlights that combining modelling with empirical monitoring offers substantial opportunities for a more efficient and more holistic approach to assessing emission loads of APIs to the environment. If the required data would become accessible, the presented approach could likely be expanded to other groups of chemicals of emerging concern besides APIs. Therefore, we recommend conducting more research into the identification and parametrization of emission sources and related emission pathways of other groups of chemicals to the environment.

Funding

This research was funded by the Dutch Research Council (NWO) domain applied technical research (TTW) under grant agreement number 15763 (SUSPECt).

CRediT authorship contribution statement

Caterina Zillien: Conceptualization, Data curation, Methodology, Formal analysis, Visualization, Writing – original draft. **Thijs Groenveld:** Data curation. **Odin Schut:** Data curation. **Henry Beeltje:** Methodology. **Daniel Blanco-Ania:** Supervision. **Leo Posthuma:** Conceptualization, Writing – review & editing, Supervision. **Erwin Roex:** Conceptualization, Writing – review & editing, Supervision. **Ad Ragas:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing, Supervision.

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

Research data that may be shared is publicly accessible via Zenodo under doi: 10.5281/zenodo.10722232. Note that part of the data cannot be shared because of confidentiality.

Acknowledgements

The authors thank Anouk Leenders, Bart van Holsteijn, Evelien Lutke Schipholt and Jos Henderik for helping with the data acquisition for this study; Andre Cinjee, Bart van Tintelen, Harm van Zuilen, Ivan Anton, Renske Hoondert and Tamara van Bergen are thanked for their help during the fieldwork. We thank Frank Heger, Sidney Stax and Sjoerd de Vreng for granting physical and digital access to the municipal sewer system. Furthermore, the authors thank Jeroen Lukaart for helpful discussions on local usage data, and the company Nielsen for providing the dataset on Dutch OTC sales in 2020 at no cost.

Appendix A. Supplementary material

SI1 contains additional information and supplementary figures. All related research data is deposited via Zenodo and publicly accessible under doi: 10.5281/zenodo.10722232. Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.10

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