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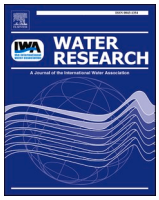
DOI: https://doi.org/10.1016/j.watres.2023.120017

Water Research 239 (2023) 120017

Contents lists available at ScienceDirect

Water Research

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



From market to environment – consumption-normalised pharmaceutical emissions in the Rhine catchment

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ARTICLE INFO

Keywords:
Micropollutants
Wastewater treatment plant
Surface water
Emission
Effluent
Large-scale fate modeling

ABSTRACT

Direct and indirect threats by organic micropollutants can only be reliably assessed and prevented if the exposure to these chemicals is known, which in turn requires a confident estimate of their emitted amounts into the environment. APIs (Active Pharmaceutical Ingredients) enter surface waters mostly through the sewer system and wastewater treatment plants (WWTPs). However, their effluent fluxes are highly variable and influenced by several different factors that challenge robust emission estimates. Here, we defined a dimensionless, theoretically consumption-independent 'escape factor' (k_{esc}) for estimating the amount of APIs (expected to be) present in WWTP effluents. The factor is determined as the proportion of marketed and actually emitted amounts of APIs. A large collection of German and Swiss monitoring datasets were analyzed to calculate stochastic k_{esc} values for 31 APIs, reflecting both the magnitude and uncertainty of consumption-normalised emissions. Escape factors provide an easy-to-use tool for the estimation of average API emissions and expected variability from numerous WWTPs given that consumption data are provided, thereby supporting simulation modeling of the fate of APIs in stream networks or exposure assessments.

1. Introduction

Thousands of synthetic organic chemicals are emitted into the environment, many of which are bioactive by design. Active pharmaceutical ingredients (API) undoubtedly belong to this category and therefore present a potential direct threat to exposed ecosystems (Brodin et al., 2014; Cunningham et al., 2006; Fent, 2008; Halling-Sørensen et al., 1998; Länge and Dietrich, 2002; Petrie et al., 2015) and indirectly to the humans relying on these ecosystems' services (e.g., Cunningham et al. 2010, Emmanuel et al. 2009, Peng et al. 2016). Such threats can only be reliably assessed and prevented if the exposure to these chemicals is known, which in turn requires a confident estimate of their emissions into the environment, namely into the most important receiving bodies: surface waters.

Emissions to surface waters can be traced back to two principal human activities, production and use of pharmaceuticals. Emissions may occur when a chemical is synthesised, i.e., from production facilities through accidental leaks or through routine wastewater disposal if the applied treatment technology is not capable of removing the compound completely (Anliker et al., 2022, 2020a, 2020b; Cardoso et al., 2014; Emara et al., 2019). The contribution of this pathway to total emissions is estimated to be in the range of a mere few percents, except for some developing countries with highly concentrated pharmaceutical industries (Caldwell, 2016). On the more important consumer side, there are two, partially intertwined, pathways incorporating a complex sequence of loss processes occurring from purchasing the chemical to actual emissions into surface waters (Delli Compagni et al., 2020). After purchase, the two consumer pathways get separated. The shorter „unintended usage" branch actually avoids human consumption and often involves direct disposal to sewage, while the „proper usage" branch follows the sequence of consumption, metabolism (where applicable), and excretion or other type of emission (Halling-Sørensen et al., 1998). The two pathways rejoin in the sewer system from where APIs travel to the communal wastewater treatment facilities and finally towards the point of emission of the treated sewage. Of these possible emission pathways for APIs, the "proper usage" pathway is usually the largest (Caldwell, 2016), corresponding to a mostly rational behavior from both producers and consumers.

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https://doi.org/10.1016/j.watres.2023.120017
Received 5 October 2022; Received in revised form 17 March 2023; Accepted 28 April 2023
Available online 29 April 2023

Pharmaceutical consumption may have long-term year-to-year variability that is influenced by the characteristics of the population, the actual epidemiological situation and the change in medical technology (van der Aa et al., 2011). Consumption may be steady or seasonal in a year, depending on the pathological feature targeted by the API. Drugs entering the human body undergo four main processes (absorption, distribution, metabolism, and excretion), which are affected by several factors such as characteristics of the API, dose of intake and health conditions (Caldwell et al., 1995; Hilmer et al., 2007).

After entering the sewer system, APIs may undergo various chemical and biological transformations in the sewer system, particularly in the receiving wastewater treatment plants (WWTPs). The latter may sometimes be circumvented and APIs may enter surface waters without treatment in case of active combined sewer overflows (Launay et al., 2016). To describe this series of processes in detail would require measurements after each phase. Yet, the majority of relevant studies concentrate on removal processes inside the WWTP (see e.g., Kasprzyk-Hordern et al. 2009, Oberoi et al. 2019, Patrolecco et al. 2015, Wang et al. 2020), whereas only few target sewer networks themselves (Gao et al., 2017; Jelic et al., 2015; McCall et al., 2016; O'Brien et al., 2017; Thai et al., 2014) due to the difficulty of sampling and the high variability of sources and pollutant transport (Ort et al., 2010a, 2010b). In the end, this series of linked processes produces high spatial and temporal variability in effluent and surface water concentrations (Baker et al., 2014; Burns et al., 2018; Daneshvar et al., 2010; Vieno et al., 2005).

Around the complex chain of transport and transformation processes between an API's synthesis and its entering the surface waters, the most robust, long-term data available are commercial sales information for APIs used in human medication. Such statistics have been collected regularly since many decades in regional and quarterly resolution at both product and API levels to monitor the effectiveness of pharmaceutical marketing. To use this data source for estimating emissions from effluents of several WWTPs, a mapping method has to be found that bridges sales/consumption to emissions to surface waters.

A related inverse method is routinely used in wastewater-based epidemiology. The so-called "correction factors" are used to back-calculate consumptions from measured loads of drugs (see e.g., Baker et al. 2014, Duan et al. 2022, Gracia-Lor et al. 2016, van Nuijs et al. 2011, Zuccato et al. 2005). Thai et al. (2016, 2019) reversed this definition and defined the "correction factor" as the ratio of daily consumption and daily load in wastewater that – beside estimating consumption or excretion rates – can also be used to calculate concentrations in the sewer network from consumption (Thai et al., 2016, 2019). Yet, these all exclude the WWTP itself, which is the major source of pharmaceuticals to surface waters (Daughton and Ternes, 1999). In this study, we apply a new, lumped treatment to the series of processes between sales of 31 APIs and the corresponding effluents of WWTPs based on national sales data and effluent concentration measurements. It was tested in the period of 2010–2019 at several WWTPs from Germany and Switzerland whether consumption statistics can be used to estimate API emissions regionally, i.e. for a multitude of WWTPs at once. We define a dimensionless „escape factor" (k_{esc}) as the proportion of the marketed APIs appearing in WWTP effluents, with the objective to deliver a less case-specific indicator of the transfer of marketed pharmaceuticals into surface waters, which can then be used to estimate emissions over multiple WWTPs. Some former studies used a somewhat similar approach to estimate WWTP effluent concentrations from annual national sales data (Alder et al., 2010; ter Laak et al., 2010). However, these studies were carried out on a narrower set of WWTPs and compounds and focused on the conceptual description of involved factors (such as metabolism and removal) instead of trying to gather a wider body of empirical evidence (Alder et al., 2010; ter Laak et al., 2010).

By its definition, k_{esc} integrates all of the above-mentioned processes in a single number that should theoretically be between 0 (marketed API is not emitted to surface waters at all) and 1 (the entire marketed amount in the catchment reaches the rivers), unless releases from production, formation in the sewer system or in the WWTP, or veterinary usage of an active ingredient are significant.

2. Materials and methods

2.1. The escape factor

The lumped escape factor is defined simply as the ratio between the marketed amount of the API and the amount showing up in WWTP effluent:

$$F_{eff} = k_{esc} f_{cons} N_{pop} \quad (1)$$

where F_{eff} is the flux in the effluent [ng d^{-1}], f_{cons} is the mean per capita marketed daily dosage of the API [ng d^{-1}], and N_{pop} [–] is the population connected to the WWTP. The escape factor as defined by Eq. (1) fully describes the relationship between marketed amount and emissions. For analytical purposes the escape factor can be decomposed into parts describing known transport and transformation mechanisms. If the oral administration pathway is assumed to be dominating, k_{esc} can be decomposed into the following form:

$$k_{esc} = \left(\left(1 - k_{flush}\right)k_{exc} + k_{flush}\right)\left(1 - k_{rem}\right) \quad (2)$$

where k_{exc} is the excreted fraction of the non-metabolized API from the body (dimensionless), k_{rem} is the removal efficiency in the wastewater infrastructure, i.e., the sewer network and the WWTP (dimensionless), and k_{flush} is the fraction of the marketed amount entering the sewer system without ingestion (dimensionless). The improperly disposed ("down-the-drain") fraction is more dependent on the targeted disease class and prescribed application method than the bio/chemical properties of the API (Caldwell, 2016). Its parameter, k_{flush} can be roughly estimated for APIs with known very low k_{exc} and k_{rem} from Eq. (2). One could further extend Eq. (2) by adding factors representing, e.g., separate transformation in the sewer system and in the WWTP, deconjugation (Delli Compagni et al., 2020), loads from topical application (Kannan et al., 2023), etc., yet in the absence of relevant data from the targeted spatial scale, this would not contribute to a better estmation of emissions for multiple WWTPs.

In practice, k_{esc} can be estimated from marketing and effluent data by rearranging Eq. (1):

$$k_{esc} = \frac{C_{eff}\ Q_{eff}}{f_{cons}\ N_{pop}} \quad (3)$$

where C_{eff} is the characteristic concentration of the API in the WWTP effluent (ng L^{-1}) depending on the time-scale of the study and Q_{eff} is the corresponding discharge measurement (L d^{-1}). The task is to find the relevant values of f_{cons} and N_{pop} that can be used in combination with existing measurements of C_{eff} and Q_{eff}.

2.2. APIs and their sales

We selected 31 widely used APIs that often show up in surface waters of Europe in significant quantities (Table 1 shows the relevant properties related to k_{esc} calculations: main fields and types of application, usage in veterinary medicine and significant seasonal variability in consumption) as the subjects of our analysis.

API sales data for the actual amount of active ingredients (kg per year or quarter) were obtained under license from country representatives of IQVIA (formerly IMS Health, www.iqvia.com) through the federal environmental agencies of the two countries (Umweltbundesamt for Germany, Bundesamt für Umwelt for Switzerland). Sales data covered all application types (oral, other types of internal usage [eye drops, ear drops, rectal suppositories, etc.], intravenous and topical). Annual API sales for Germany were available for the period of 2010–2018 (IQVIA

Table 1
APIs selected for this study (NSAID: nonsteroidal anti-inflammatory drug). Usage in veterinary medicine: ‚Rare' means negligible or low use, ‚Frequent' means frequent use (based on information provided by the University of Veterinary Medicine Budapest). Types of common application: ‚O' refers to oral,„OI' for other types of internal use (eye drops, ear drops, rectal suppositories, etc.), ‚IV' for Intravenous and ‚T' for topical (based on the database of DrugBank ONLINE (www.drugbank.com) and private consultations with pharmacists). Seasonal variability is flagged by ‚Yes' if at least one of the seasonal variability factors (see in Table SI1) is lower than 0.95 or higher than 1.05.

#	Compound	Abbre-viation	Function/class	CAS ID	Usage in veterinary medicine	Types of application	Seasonal variability
1	Aliskiren	ALI	renin inhibitor	173,334–57–1	Rare	O	No
2	Amisulpride	AMI	atypical antipsychotic	71,675–85–9	Rare	O	No
3	Atazanavir	ATA	protease inhibitor	198,904–31–3	Rare	O	No
4	Atenolol	ATE	beta blocker	29,122–68–7	Rare	O	No
5	Bezafibrate	BEZ	lipid regulator	41,859–67–0	Rare	O	No
6	Bicalutamide	BIC	antiandrogen	90,357–06–5	Rare	O	No
7	Carbamazepine	CAR	anticonvulsant	298–46–4	Rare	O, OI	No
8	Citalopram	CIT	selective serotonin reuptake inhibitor	59,729–33–8	Rare	O, IV	No
9	Clarithromycin	CLA	antibiotic	81,103–11–9	Rare	O, IV	Yes
10	Clopidogrel carboxylic acid	CLO	antiaggregant	90,055–55–3	Rare	O	No
11	Diclofenac	DIC	NSAID	15,307–86–5	Rare	O, IV, OI, T	No
12	Fexofenadine	FEX	antihistamine	83,799–24–0	Rare	O	Yes
13	Gabapentin	GAB	anticonvulsant	60,142–96–3	Rare	O	No
14	Hydrochlorothiazide	HYD	antihypertensive diuretic	58–93–5	Rare	O	No
15	Irbesartan	IRB	cardiovascular agent	138,402–11–6	Rare	O	No
16	Lamotrigine	LAM	anticonvulsant	84,057–84–1	Rare	O	No
17	Levetiracetam	LEV	racetam anticonvulsant	102,767–28–2	Rare	O, IV	No
18	Lidocaine	LID	amino amide local anesthetic	137–58–6	Frequent	O, IV, OI, T	No
19	Mefenamic acid	MEF	anthranilic acid derivative NSAID	61–68–7	Rare	O	No
20	Metoprolol	MTO	beta-blocker	51,384–51–1	Rare	O, IV	No
21	Moclobemide	MOC	reversible inhibitor of monoamine oxidase	71,320–77–9	Rare	O	No
22	Oxcarbazepine	OXC	anticonvulsant	28,721–07–5	Rare	O	No
23	Phenazone	PHE	analgesic, NSAID, antipyretic	60–80–0	Rare	OI	Yes
24	Pregabalin	PRE	anticonvulsant	148,553–50–8	Rare	O	No
25	Propranolol	PRO	beta blocker	525–66–6	Rare	O	No
26	Ranitidine	RAN	histamine H2 receptor antagonist	66,357–35–5	Rare	O, IV	No
27	Sitagliptin	SIT	anti-diabetic	486,460–32–6	Rare	O	No
28	Sulfamethoxazole	SUL	antibiotic	723–46–6	Frequent	O	Yes
29	Trimethoprim	TRI	antibiotic	738–70–5	Frequent	O	Yes
30	Valsartan	VAL	angiotensin II receptor antagonist	137,862–53–4	Rare	O	No
31	Venlafaxine	VEN	antidepressant (serotonin-norepinephrine reuptake inhibitor)	93,413–69–5	Rare	O	No

Table 2
Wastewater treatment plant (WWTP) effluent datasets.

Campaign (Data source)	Coverage	Period	Sampling	Remark
CH1 (Singer et al., 2016)	C_{eff} and Q_{eff} for 6 WWTPs from Switzerland (6 cantons)	March 2012 (Spring)	flow- or time-proportional 24-h composite samples collected and mixed flow-proportionally into 1-week composite samples	
CH2 (Otto et al., 2014)	C_{eff} and Q_{eff} for 9 WWTPs from Switzerland (7 cantons)	May-August 2013 (Mostly summer)	flow- or time-proportional 24-h composite samples collected and mixed flow-proportionally into 3-day composite samples	
CH3 (Schymanski et al., 2014)	C_{eff} for 10 WWTPs in Switzerland (9 cantons)	February 2010 (Winter)	flow-proportional 24-h composite samples	WWTP-specific long-term mean daily discharge values from https://map.geo.admin.ch were used for Q_{eff}
CH4 (DGE-DIREV, 2021)	C_{inf}, C_{eff}, Q_{inf}, Q_{eff} for 40 WWTPs in Canton of Vaud, Switzerland (1 canton)	2014–2019 (Spring, summer, autumn)	flow-proportional 24-h composite samples	
DE1 (LUBW Landesanstalt für Umwelt, 2014)	C_{eff} for 6 WWTPs in Germany from the Federal State of Baden-Württemberg (1 state)	June 2012-April 2013 (All seasons)	6 WWTPs with automatic samplers provided 24-h composite and qualified grab samples (Qualifizierte Stichprobe (§ 2 AbwVO), i.e., a 10-minute composite sample of 5 grab samples taken every two minutes)	mean daily Q_{eff} was calculated from annual effluent discharge
DE2 (LANUV Landesamt für Natur, 2018)	C_{eff} and Q_{eff} for 79 WWTPs in Germany from the Federal State of North Rhine-Westphalia. (1 state)	2010–2018 (All seasons)	qualified grab samples (a 10-minute composite sample of 5 grab samples taken every two minutes)	

MIDAS® Annual Sales Data 2010–2018), whereas for Switzerland between 2014 and 2016 (IQVIA National–Dataview Sales APO/SD/SPI with Market Segmentation data extracts 2014–2016). Beside these datasets, Singer et al. provided estimations for the German and the Swiss sales for 2009 (Singer et al., 2016) based on pharmaceutical sales data obtained from IMS Health (MIDAS® Annual Sales Data 2009).

For the years of 2017 and 2018, IQVIA also provided quarterly market data for Germany beside the annual statistics (IQVIA MIDAS® Quarterly Sales Data 2017–2018). All consumption data referred to human medical usage, thus excluding other, e.g., veterinary applications.

2.3. WWTP data

WWTP effluent data were obtained from four Swiss and two German monitoring campaigns from the Rhine and Rhône catchments (Table 2). Swiss data were provided by Eawag (Swiss Federal Institute of Aquatic Science and Technology) and VSA (Verband Schweizer Abwasser- und Gewässerschutzfachleute – Association of Swiss Experts on Wastewater and Water Protection), German data were provided by the LUBW (Landesanstalt für Umwelt Baden-Württemberg – State Environment Institute, Baden-Württemberg) and LANUV (Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen – State Office for Nature, Environment and Consumer Protection, North Rhine-Westphalia). Emitted fluxes were calculated as the product of sample concentrations with the corresponding discharge, which may have been directly measured or estimated long-term effluent discharge (see "Remark" column in Table 2). Additional information on the characteristics of measurement campaigns can be found in Tables SI4 and SI5 in Supporting Information (SI).

The number of inhabitants actually connected to the WWTP (N_{pop}) is relevant to calculate k_{esc} (see Eq (3)). Datasets of the two German (DE1 and DE2) and one of the Swiss campaigns (CH4) contained information on the served population for the WWTPs. For the other Swiss WWTPs, served population data were collected from two sources. Data from 2005 were gained from the database of Maps of Switzerland (Federal Office of Topography swisstopo, 2018) as values characteristic for the initial years. Data for 2017 were collected from the webpage of the Swiss Federal Agency for (BAFU Das Bundesamt für Umwelt (Swiss Federal Agency for Environment), 2018). Wherever it was possible, actual served population values from the year of the sampling campaign were used. In other cases, we determined them by interpolating from other years or – when data gaps were too frequent for interpolation – by taking values from the closest available year.

2.4. Pairing consumption with effluent concentrations

Consumption data contained significant year-to-year and seasonal changes for numerous compounds. Long-term trends reflect the dynamics of the market share of a specific API. However, consumption can also vary seasonally, which may be significant for APIs prescribed for seasonally appearing symptoms (e.g., for allergy and flu).

To get a precise estimate of k_{esc}, it was important to match f_{cons} to the period when effluent concentrations were measured as much as possible, otherwise consumption dynamics would seriously bias k_{esc}.

The f_{cons} is equal to the mean quarterly consumption (the annual marketed amount multiplied with a seasonality factor (f(Q), see in Table SI1)) divided by the population of the given year (both on country level).

The highest temporal resolution of consumption data was quarterly, but this was limited to Germany and only available for two years. Therefore, we applied a multiplicative interpolation model of consumption dynamics that was used to estimate quarterly consumption from the annual data:

$$C(Y,Q) = \left(C_Y + \frac{S_C Q}{4}(C_{Y+1} - C_Y)\right) f(Q) \quad (4)$$

where C(Y,Q) is consumption (kg/quarter) in the Q^{th} quarter of year Y, C_Y is the mean quarterly consumption of the given year Y (kg/quarter), C_{Y+1} is the mean quarterly consumption in the next year, and Q is the quarter index (1–4), S_C is the slope of the local subannual trend in year Y (kg/year), and f(Q) is the seasonal multiplicator (dimensionless with the mean of 1 over all quarters).

The consumption model in Eq. (4) was fitted for each compound four steps (Fig. 1):

1. First, long-term trends were fitted for Switzerland and Germany separately to estimate mean annual values (C_Y) for years with effluent concentration measurements but with no consumption data. In other cases, national sales data were used as C_Y. As the Swiss data for 2009 were given as semi-closed intervals for some compounds by Singer and coworkers (Singer et al., 2016), this year was included in the calculations in two alternative ways, depending on the type of estimation. Explicit values were directly used for the consumption in 2009. When ranges were provided (e.g., consumption was higher than or equal to a given limit value), the final value for 2009 was decided based on a linear trend analysis. The linear regression value for 2009 was accepted when it fell into the range specified by Singer et al. (2016), otherwise the closer limit value of the interval was used. Based on the position of data gaps, extrapolation or interpolation was used to fill in missing annual values between 2010 and 2019.
2. After estimating the long-term trends, local subannual trends were calculated. The mean annual consumptions (C_Y) for two adjacent years were taken as the consumption in the first quarters of the years. Between these two values a linear trend was set as the subannual change inside a year. The slope of this subannual trend is S_C, and the mean annual consumptions were calculated for the other three quarters (with always 3 months shifting).
3. As the next step, f(Q) seasonality factors were determined for each compound based on the quarterly consumption data for Germany (2017–2018). Seasonal variability was assumed to be country-independent, thus f(Q) determined from the German quarterly datasets was applied to all the other years both in the German and Swiss consumption time series. To determine seasonal variability of consumption within a year (that is assumed to be nearly constant from year-to-year), we eliminated the trend component from the

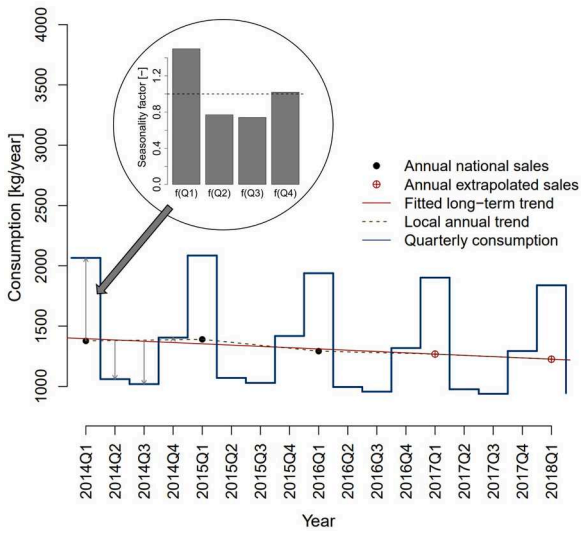

Fig. 1. Estimation example for quarterly consumption data.

quarterly consumption time series. Decomposition meant to separate the time series into trend and seasonality components. A multiplicative model was used in decomposition. Detection of trend requires smoothing the time series using the centered moving average method (Render et al., 2018). As quarterly summarized consumption data were available for 2 years, and there were 4 data points per year, moving average window of 4 was applied. Then, f(Q) could be determined from the ratio between the actual consumption and the trendline.

4. Quarterly consumptions were calculated for each year without quarterly sales data based on f(Q) values. Mean annual consumptions (C_Y) were multiplied by the seasonality factors.

To actually pair consumption with effluent concentrations, we used the following algorithm:

1. If quarterly consumption data was available for a compound, estimated consumption for the corresponding year and month of the effluent concentration measurements were used by applying Eq. (3).
2. If quarterly consumption data was not available but annual was, annual consumption from the corresponding year of the effluent concentration measurements was used.

3. Results

3.1. Market trends and seasonality

Seasonal multiplicators f(Q) were calculated for all compounds (see in Table SI1) from the quarterly datasets of Germany (2017–2018)).

CLA, FEX, and PHE showed significant seasonal variability, for all other APIs seasonal changes were negligible. CLA is an antibiotic to cure bacterial infections related mainly to the respiratory system with highly increasing consumption in the first quarter of the year (+50%), and lower consumption in warmer months. FEX is mostly used to treat allergy symptoms. Accordingly, it has a pronounced peak (+52%) in consumption in the second quarter of the year. PHE is a pain reliever and fever reducing drug. It shows a moderate 10% increase in consumption in the first quarter of the year, which can be explained by its use related to flu-like illnesses typical during the colder seasons.

3.2. Escape factors

Escape factors were calculated separately from all six datasets (see Table SI2), depending on data availability (not all compounds had been measured in all datasets). For all compounds, mean k_{esc} ($E[k_{esc}]$) values and standard deviations ($SD[k_{esc}]$) were estimated across the six datasets. Both country-based (‚DE studies' and ‚CH studies' columns in Table 3) and completely pooled (‚All studies' column in Table 3) statistics were produced by using weighted unique escape factors. Weights were determined based on the time interval represented by the samples, with weight of grab samples set to 1 [hour] and composite samples set to the actual sampling interval, again in hours (Table 3).

When it was possible to calculate escape factors for the same compound in both countries, the results could be compared. As it can be expected from its consumption-independent definition, escape factors of a given substance should be very similar in Switzerland and Germany given that wastewater treatment technologies are similar too. This assumption was better fulfilled in the first half of the period of analysis. The development of wastewater treatment plants equipped with the fourth treatment stage multiplied after the corresponding regulations were accepted in 2016 for Switzerland (Metz, 2017)and in 2018 for Germany (BMU/UBA, 2019). Thus, most of the effluent datasets used in this study are obtained from plants that have not yet been upgraded to the date of measurements). In most of the cases, national k_{esc} estimates were indeed similar (e.g., AMI, CAR, CLA, LAM, MTO, SUL, VEN). Still, in a few cases, major differences were detected in escape factors between the two countries (e.g., ATE, BEZ, GAB, HYD, TRI, VAL).

Table 3
Escape factors (E: arithmetic means, SD: standard deviations). a: only annual consumption data are used in k_{esc} calculation and no consumption (NC) in Germany from 2005.

	DE studies		CH studies		All studies	
Compound	$E[k_{esc}]$	$SD[k_{esc}]$	$E[k_{esc}]$	$SD[k_{esc}]$	$E[k_{esc}]$	$SD[k_{esc}]$
ALI	NA	NA	0.74	0.54	0.74	0.54
AMI	0.69	0.57	0.64	0.67	0.64	0.67
ATA	NA	NA	0.33	0.33	0.33	0.33
ATE	0.28	0.36	0.42	0.26	0.42	0.26
BEZ	0.20	0.14	0.55	0.55	0.53	0.54
BIC	NA	NA	0.35	0.32	0.35	0.32
CAR	0.11	0.06	0.11	0.08	0.11	0.08
CIT	NA	NA	0.37	0.23	0.37	0.23
CLA	0.14	0.09	0.17	0.17	0.17	0.16
CLO	NA	NA	0.11	0.05	0.11	0.05
DIC	0.14	0.07	0.39	0.19	0.37	0.20
FEX	NA	NA	0.81	0.47	0.81	0.47
GAB	0.44	0.25	0.66	0.47	0.65	0.46
HYD	0.49	0.21	0.38	0.15	0.38	0.15
IRB	NA	NA	0.26	0.14	0.26	0.14
LAM	0.43	0.23	0.47	0.34	0.45	0.31
LEV	NA	NA	0.16	0.22	0.16	0.22
LID	NA	NA	0.76	0.56	0.76	0.56
MEF[a]	NA	NA	0.03	0.03	0.03	0.03
MTO	0.09	0.04	0.11	0.07	0.11	0.07
MOC	NA	NA	0.12	0.06	0.12	0.06
OXC	NA	NA	0.15	0.10	0.15	0.10
PHE	0.40	0.62	NA	0.00	0.40	0.62
PRE	0.13	0.15	NA	0.00	0.13	0.15
PRO	0.00	0.02	0.11	0.06	0.11	0.06
RAN	NA	NA	0.13	0.09	0.13	0.09
SIT	NA	NA	0.33	0.23	0.33	0.23
SUL	0.11	0.11	0.10	0.09	0.10	0.09
TRI	0.14	0.20	0.27	0.19	0.27	0.19
VAL	0.14	0.18	0.33	0.36	0.32	0.36
VEN	0.13	0.07	0.09	0.05	0.09	0.05

Moreover, for certain compounds, calculated escapes rate values were higher than 1, which would mean negative removal rates or excretion over 100%. While such findings are to some extent related to uncertainty in sampling and analytical quantification, they might also stem from non-representative consumption data or formation of the API from conjugated metabolites in the WWTP. Formation of parent APIs in WWTP was identified for some of the target compounds, with occasional supporting literature evidence (see e.g., Verlicchi et al. (2012) for CAR and TRI; Sipma et al. (2010) for DIC, and SUL). Values greater than 3 were not included in the calculation of ($E[k_{esc}]$) and ($SD[k_{esc}]$) due to their high uncertainty.

For the CH4 dataset, $E[k_{esc}]$) and ($SD[k_{esc}]$) values were also calculated separately for all quarters of the year, yet there was no significant change compared to annual values (see Table SI3). Thus, it can be concluded that the effect of seasonally variable processes such as the removal rate of WWTPs are negligible compared to the overall variability of escape factors observed, for instance, at the cantonal or country-level.

3.3. Variability of emissions from WWTPs

The k_{esc} estimates showed large variability between the individual samples in the six involved studies (Fig. 2). For some compounds, the standard deviation of values was lower (e.g., PRO, VEN), but for other values varied broadly between the theoretical limits of 0 and 1 (and occasionally also above 1) (e.g., AMI, ATE, BEZ, GAB, LID). Based on the k_{esc} values calculated from all studies for both countries (Table 3, column: 'All studies'), compounds can be divided into three categories:

A APIs with high variability ($SD[k_{esc}]>0.25$): ALI, AMI, ATA, ATE, BEZ, BIC, FEX, GAB, LAM, LID, PHE, VAL;

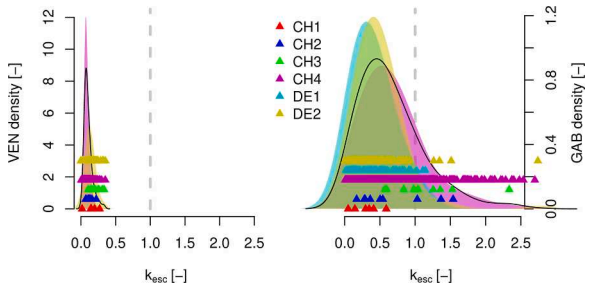

Fig. 2. Escape factor (k_{esc}) estimates in the six involved studies (CH1,CH2,CH3, CH4,DE1,DE2). Left figure: Venlafaxine (VEN), Right figure: Gabapentin (GAB). Black curve shows the density function plotted from all values weighted with sampling time length, symbols show individual estimates above the k_{esc} axis.

B APIs of medium variability (0.1<SD[k_{esc}]<0.25): CIT, CLA, DIC, HYD, IRB, LEV, OXC, PRE, TRI, SIT;
C APIs with low variability (SD[k_{esc}]<0.1): CAR, CLO, MEF, MTO, MOC, PRO, RAN, SUL, VEN.

Using relative standard deviation, an indicator of the relative uncertainty of emission estimates derived from k_{esc}, the following categories apply (setting category boundaries so that the category populations remain the same as above)

a APIs with high variability (CV[k_{esc}]>0.73): AMI, ATA, BEZ, BIC, CLA, LEV, LID, MEF, PHE, PRE, SUL, VAL;
b APIs of medium variability (0.62<SD[k_{esc}]<0.73): ALI, CAR, CIT, GAB, LAM, MTO, OXC, RAN, SIT, TRI;
c APIs with low variability (SD[k_{esc}]<0.62): ATE, CLO, DIC, FEX, HYD, IRB, MOC, PRO, VEN.

About half of the compounds (15 out of 31) fell into the same category based on both types of standard deviation, 12 shifted to a neighboring one category, while 4 jumped to the other end of the category list.

Variability could only be considered as randomness, as we found no significant deterministic relations between the individual k_{esc} estimates and potential influencing factors that were covered by data (e.g., the effect of seasons, WWTP size, or the relative contribution of industrial sewage). Randomness can of course originate from the variability of factors contributing to k_{esc}, but the final level of uncertainty is modulated by their expected values too (see section S4 in SI).

Removal rates of sewer systems and WWTPs are strongly dependent on the physico-chemical characteristics of the micropollutant, the composition of wastewater, the state of the system, the treatment technology, and they thus may vary in a wide range (Sewer-systems: Gao et al., 2017; Jelic et al., 2015; O'Brien et al., 2017; Thai et al., 2014; WWTPs: Cirja et al., 2008; Petrie et al., 2015; Sipma et al., 2010). For some of the compounds in the high variability category, highly variable WWTP removal rates are known too (BEZ, GAB (Petrie et al., 2015); ATE (Sipma et al., 2010); for the other compounds in the category we are not aware of relevant studies).

Specifically, there was no significant relation to WWTP size, although we initially expected the smaller plants to work somewhat less efficiently than the large ones. There appeared to be some weak connection between variability and the season of sampling in the Swiss campaigns, but the same did not show up in the German datasets and it turned out that the WWTP size classes in Swiss campaigns were not evenly distributed seasonally, i.e., the few large plants were sampled in the spring, while smaller plants were sampled both in the spring and late summer. Where known, the proportion of industrial sewage did not correlate with k_{esc}. Thus, the roles of k_{rem} and potential production-related emissions could not be properly resolved given the available data.

3.4. Estimation of k_{flush} values

If k_{esc} is decomposed along assumptions on the pathways between marketed amounts and emissions, hypotheses can be tested on its components. We use Eq. (2) to show such an application for estimating down-the-drain disposal of APIs, which can contribute to the emissions significantly (Kasprzyk-Hordern et al., 2021). In Eq. (2) the portion of marketed APIs that reach the sewer network without prior ingestion is accounted for as k_{flush}. The simplicity of Eq. (2) implies that compounds must fulfill several criteria that this decomposition remains meaningful: (i) they are unable to conjugate/deconjugate within the sewer system and WWTPs, (ii) human topical administration or veterinary usage is negligible, and (iii) they have insignificant input from production facilities (which may change with time (Anliker et al., 2020a)). Even under such strict conditions, there are still three factors contributing to k_{esc}, so one cannot identify them from k_{esc} alone. To overcome this, we selected compounds for which k_{exc} is known to be negligible. This condition eliminates the impact of the proper usage pathway from Eq. (2). Four compounds with very low excretion rates were investigated for which urine is the main clearance pathway and excretion efficiency is known, namely CAR with an excretion rate of unchanged parent compound in urine: kexc= 0.01 (Lienert et al., 2007), MEF with kexc= 0.02 (Naseer et al., 2007), MOC with k_{exc}= 0.01 (Jauch et al., 1990), and OXC with k_{exc}= 0.01 (FDA U.S. Food and Drug Administration, 2020). Among these, CAR is actually an outlier because it does not fulfill criterion (i), back-formation has been observed by several studies (e.g., Vieno et al. 2007). For the other compounds, k_{esc} is the direct conservative (minimal) estimate for k_{flush} (MEF: kesc,mean=0.03, MOC: $k_{esc,mean}$=0.12, OXC: $k_{esc,mean}$=0.15 using data from all studies), because assuming that $k_{esc} = k_{flush}$ neglects removal in the sewer system and the WWTP. For CAR the appropriateness of k_{esc} in estimating k_{flush} is uncertain. Further on, WWTP removal rates are known to be negligible for MOC and OXC, so for them k_{esc} is not only a minimal but a representative estimate for the proportion of improper usage pathway. In contrast, removal can be significant for MEF (Tauxe-Wuersch et al. (2005): 50%, Kasprzyk-Hordern et al. (2008): 70%), so k_{flush} is expected to be 2–3.3 times greater than k_{esc}.

4. Discussion

4.1. Scope of APIs

In this paper, a collection of relative emission estimations is presented for 31 widely-used APIs based on a broad monitoring dataset from several campaigns from two countries. According to our best knowledge, this is the so far largest analysis ever performed on estimating emissions from consumption data. Somewhat similar earlier studies concentrated on only a few compounds (Du et al., 2020; Gao et al., 2021; Thai et al., 2016, 2019).

The demand for more reliable data on emissions and environmental behavior of chemicals is increasing due to interest in PEC (Predicted Environmental Concentration) values, prioritization of compounds, and developing risk mitigation strategies (Tong et al., 2022). Emissions are the backbone of exposure and *in-situ* fate calculations. Marketed amounts of APIs are often considered as the most robust reference points when WWTP in- or effluent data are not available or not indicative, for example when a high number of WWTPs are involved in exposure assessment (see Oldenkamp et al. (2018) and references cited therein). Therefore, many regional exposure or fate models utilize parameters closely related to the here defined escape factor (e.g., Grill et al. 2016, Lindim et al. 2016, Oldenkamp et al. 2018). As shown by the case-specific escape factor values, the transfer efficiency between market and actual emissions is highly variable, therefore related parameters are optimal subjects for calibration. However, it is very difficult to identify emissions from in-stream concentration or flux profiles along rivers, as longitudinal flux profiles belonging to a wide range of

first-order degradation and emission rates look rather similar and almost any profile can be produced by pairing a wrong degradation rate to a wrong, but compensating emission (Honti et al., 2018). Thus, k_{esc} values and their uncertainty intervals may provide a useful reference point for regional exposure and fate modeling by constraining the market-independent transfer efficiency between the sold and emitted amounts of APIs (e.g., in form of parameter priors).

4.2. Strength of relation between marketed amounts and emissions

Effluent concentrations of APIs are highly variable for different WWTPs. Removal rates of the sewer systems and WWTPs are unique and strongly dependent on the state of the system (including the hydraulic residence time, and temperature, among others) and the applied treatment technology. The rate of removal fluctuates both annually, seasonally, and even diurnally. This intrinsic variability and the uncertainties related to the input data (see in Section 4.3) influence the uncertainty of k_{esc} estimates.

On the regional scale, escape factors calculated from several monitoring datasets are likely to provide more realistic links between marketed amounts and emissions than case-specific studies, as the wider data foundation provides a better overview on the real variability of emissions. This certainly only applies when the monitoring data are relevant for the study, e.g., the technological level of monitored WWTPs well represents the entire WWTP population of the catchment.

For the majority of compounds of this study, k_{esc} could be estimated with low to medium uncertainty (absolute variability categories B and C, 61% of APIs). These values suggest that the APIs in these categories indeed behave along the assumptions of the model used to back-calculate k_{esc}.

For the rest (variability category A) inherent variability and a presumably important role of neglected consumption patterns (i.e. illicit consumption, or seasonal or regional differences missing from nation-wide statistics) non-oral types of administration, and transport pathways (i.e. factory releases and accidental spills), or even measurement inaccuracies, precluded getting a clearly bound estimate for k_{esc}, despite the special attention paid to couple effluent measurements with representative consumption data.

As category A demonstrates, the uncertainty of k_{esc} estimates originates from both intrinsic variability and the uncertainty of measurements and consumption statistics used in the calculation. The mathematical sensitivity analysis of even the simplest decomposition of k_{esc} (section S4 in SI) highlights that even the low relative uncertainty of contributing factors does not guarantee that the relative uncertainty of k_{esc} will be correspondingly low too. This purely mathematical inflation and nonlinear propagation of uncertainty means that the high relative uncertainty of k_{esc} can be considered as its intrinsic property and in most cases it cannot be attributed to a single factor. More detailed decomposition, such as done by Alder et al. (2010) and ter Laak et al. (2010) is likely to aggravate this effect.

When emissions are calculated for a region possessing multiple WWTPs, the relative uncertainty of the total emission can be expected to shrink compared to the figures presented here (when the WWTPs involved in the calculation of k_{esc} are statistically representative for the case, the expected value will be the same as presented here). The non-intrinsic, e.g., measurement-bound uncertainty is definitely a confounding factor, yet it is inseparable due to lack of relevant evidence. For this reason, we recommend considering the full uncertainty of k_{esc} in large-scale fate modeling as it reflects existing factors that contribute to the variability of emissions. Normalised emission factors related to k_{esc} (such as excretion rate (Thai et al., 2016) and correction factors (Gracia-Lor et al., 2016; Thai et al., 2019) are seldom paired with adequately quantified uncertainty, mainly due to the limitations presented by the location-bound and time-consuming effluent measurements. Most studies emphasize the crucial influence of sample size, e.g., that calculations covering multiple WWTPs and larger catchments increase the robustness of estimates. The simplicity of the presented approach allowed comparing a wide set of WWTP effluent data to seasonally-corrected consumption statistics and thus overcoming this usual limitation.

4.3. Possible bias in k_{esc} related to input data

While k_{esc} obviously defines the empirical relationship between marketed amounts and observed emissions, its conceptual interpretation is difficult. Uncertainty of input data inevitably spoils k_{esc} beyond the scope of intrinsic variability. In this section we review the major uncertainty sources. Although k_{esc} does not depend on too many assumptions, one of these is that market statistics are appropriately reflecting the amount of consumed APIs. Sources obviously missing from the market statistics, like leakages from production facilities, illicitly acquired drugs (e.g., Venhuis et al. 2014) and veterinary applications are obviously biasing the estimates from a conceptual sense (k_{esc} will be overestimated due to the underestimated API basis). The ever-expanding illicit market covers almost all types of pharmaceutical drugs (World Health Organisation (WHO), 2012), however, it is impossible to quantify their exact amount (Hall et al., 2017). Veterinary applications are atypical for most of the investigated compounds, except for LID, TRI and SUL which are frequently prescribed for animals (see Table 1). Out of these, we only got $k_{esc}>1$ and high estimation uncertainty for LID (composite samples), so a significant veterinary usage of TRI and SUL could not be verified. It has to be noted, that the contribution from veterinary medication to WWTP effluents would be subject to a high uncertainty even when the usage was known, as the proportion of animal manure and urine emitted to the sewer system is strongly case-specific.

Inside the model domain there are uncertainty sources associated with each factor.

Estimates on the local use of APIs may not represent the reality well. National sales data on the marketed amount of active ingredients do not include all local consumption patterns. Health status, which is also closely linked to the consumption of APIs, has been shown to be associated with socioeconomic status of inhabitants such as education, income, occupation (inequalities in health for the European countries have been shown by several studies, e.g., Mackenbach et al. (2008), and this difference can also occur at regional level.

The lack of quarterly consumption data (which was the case for e.g., MEF) may increase uncertainty in escape factor calculations when the compound is subject to periodic fluctuations in consumption or strong uneven trends. Errors are also introduced with the interpolations or extrapolations for years lacking consumption data.

Different studies have not only shown seasonal variation in emitted concentrations of APIs (e.g., Pereira et al. 2015, Vatovec et al. 2016), but weekly (e.g., Moreno-González et al. 2014) and daily variations too (e.g., Plósz et al. 2010). Temporal variability of consumption due to e.g., travelling, commuting and demographic changes results in fluctuations in emissions of WWTPs (Been et al., 2014) (the actual number of persons discharging into the treatment plant does not fully correspond to the number of inhabitants, on which N_{pop} is based). Commuting may cause differences mainly on a subdaily and weekly scale, while travelling might be relevant during typical holiday seasons.

Sampling frequency and mode (grab or composite) of effluent concentrations at WWTPs play a crucial role in representativeness of measurements to a certain period of time and they have to be designed based on the characteristics of the compound and the WWTP (Ort et al., 2010a). Details on the sampling campaigns used for k_{esc} calculations can be found in Tables 2 and SI4–5. Measurement campaigns can be assessed for representativeness by considering the extent to which they cover temporal and spatial variability on catchment and national scale. In terms of temporal variability, composite samples may capture concentration peaks better than grab samples, which have the potential for information loss (such as in D2). Multi-day measurement campaigns

(such as in CH1 and CH2, data in CH3 are available for only two consecutive days) are preferable to capture weekly variation, while detection of seasonal variability can be ensured by sampling from different seasons (such as in CH4, DE1 and DE2). Possible regional variations were better represented by the Swiss datasets, as measurements were available for almost the whole country, while in Germany only for two states. In addition, it is true for the overall measurement campaigns in both countries that they cover all typical sizes of WWTPs. Beside, it has to be noted that the number of available measurements for each compound and campaign was highly variable, which in some cases may increase the degree of uncertainty (see in Table SI5).

4.4. Indirect supporting evidence for k_{esc} values: down-the-drain disposal of APIs

As compounds for this study were selected based on their presence in WWTP effluents, there was no compound where calibrated escape factors could not be distinguished from 0. Lowest k_{esc} distributions were typically centered around 0.05–0.1. However, for e.g., CAR, MEF, MOC and OXC, documented excretion rates of the unchanged parent compound are significantly lower than this range. As topical administration or veterinary application is atypical for these compounds, k_{esc} can be decomposed to estimate the proportion of API avoiding oral application. For MOC, and OXC the escape factor was most likely dominated by k_{flush}. MEF is degrading in WWTPs, so k_{esc} provided a minimal estimate for down-the-drain disposal. CAR is also used orally, but conjugation/deconjugation has been suspected in WWTPs, so the accuracy of estimating improper disposal is potentially low, although it obviously exists (Kasprzyk-Hordern et al., 2021). Caldwell (2016) reported k_{flush} estimates from industrial studies and found values spreading from 3 to 50%, depending on the API, time and location. For Germany, the mean disposal rate was 14% (BIO Intelligence Service, 2013). Improper disposal is triggered by over-prescription, patient incompatibility (experiencing side effects), or not completing the prescribed therapy (Caldwell, 2016). As these have different odds for different APIs and therapies, the typically flushed amount depends on the API with cardiovascular diseases, asthma, nervous system disorders, and gastro-intestinal tract problems being among the most affected targets (Caldwell, 2016). MEF, MOC and OXC fall into a frequently flushed category. MEF is known as a nonsteroidal anti-inflammatory drug (NSAID) that is used to treat mild to moderate pain. OXC is an anticonvulsant used to treat epilepsy and it is sold as a liquid on certain markets, which encourages disposal by flushing more than pills do. MOC is mainly prescribed to treat various forms of depression and requires a long follow-up treatment after the symptoms are gone. The calculated 6–15% as the minimum of down-the-drain disposal proportion of the marketed amount is thus in line with corresponding literature values. This supports the assumptions of the model used to decompose k_{esc} values.

5. Conclusions

On the large catchment scale, emissions of APIs can be highly variable due to heterogeneities in consumption, attitudes on disposal, and the characteristics of the wastewater collection and treatment infrastructure. The collective effect of this complex process chain can be summarised in an empirical escape factor (k_{esc}) that bridges the widely available consumption data to observed emissions to surface waters. When using large and high quality monitoring datasets for WWTP effluents, escape factors provide an easy and simple tool for estimating total inputs of APIs into surface waters and moreover support simulation modeling of API fate in stream networks or exposure assessments.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Data availability

The authors do not have permission to share data.

Acknowledgments

We thank the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety for funding (PIdent-2, FKZ 3717 65 409 0). We are grateful to Silvia Berkner and Janina Wöltjen from the German Environment Agency for contributing valuable comments on the text and the assistance in obtaining data.

We thank IQVIA for providing MIDAS® Annual Sales Data for the period of 2010-2018 for Germany, MIDAS® Quarterly Sales data for 2017-2018 for Germany, and 2014-2016 National–Dataview Sales APO/SD/SPI with Market Segmentation annual data extracts for Switzerland. Any analysis of the data featured in this study is independently arrived at by the authors on the basis of the Sales Data and other information, IQVIA is not responsible for any reliance by recipients of the data or any analysis thereof.

We thank Rebekka Gulde from VSA (Verband Schweizer Abwasser- und Gewässerschutzfachleute/Association of Swiss Wastewater and Water Protection Experts) for providing WWTP effluent measurements.

We thank the Landesanstalt für Umwelt, Messungen und Naturschutz Baden-Württemberg (LUBW), Division of Stream Ecology, Karlsruhe, and the Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen (LANUV) for kindly providing WWTP effluent measurements for Germany.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.watres.2023.120017.

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