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Estimating environmental exposure to analgesic drugs: A cross-sectional study of drug utilization patterns in the area surrounding Sweden's largest drinking water source

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ABSTRACT

Use of pharmaceuticals is continuously increasing globally and their residues are recognized as a risk for the environment. The aim of this study was to investigate drug utilization patterns of analgesics in relation to environmental hazard in the region surrounding Sweden's largest drinking water source, Lake Mälaren. This was examined using sales data on pharmaceuticals from the Swedish E-health Agency. The total sales of analgesics (non-steroidal anti-inflammatory drugs, paracetamol, other non-opioid analgesics, and opioids) for both human and veterinary use in the region were analyzed for the years 2016 to 2020, in relation to the inherent environmental hazard for each active pharmaceutical ingredient (API). We found that a total of 454 tons of analgesics were sold in the region during these 5 years. Classifications of environmental hazard were available for 16 out of the 45 studied APIs, accounting for 98.8% of the total mass in kilograms. Paracetamol, ibuprofen, and acetylsalicylic acid, which are all classified as low-hazard compounds, were the most commonly sold APIs. Diclofenac, the only pharmaceutical classified as high-hazard, was the fifth most commonly sold API, with a total sold mass of 2321 kg. The majority of the total sold mass of analgesics originated from dispensed prescriptions for human use in urban areas. Visualization of drug sales for humans and animals in different settings can be used to identify the environmental burden of pharmaceuticals. Based on our study, we suggest that additional measures to reduce the impacts of pharmaceuticals on the environment should primarily be directed to prescribing physicians in urban areas and campaigns targeted at the high over-the-counter sales of diclofenac. Moreover, it is important to address the fact that many pharmaceuticals currently have limited data on environmental hazard.

1. Introduction

Pharmaceuticals play an important role in the prevention and treatment of disease in both humans and animals. However, the high and increasing use of pharmaceuticals, in combination with their persistence, bioaccumulative properties, and potential toxicity for aquatic organisms, has led to pharmaceutical residues becoming an increasing problem worldwide (Doerr-MacEwen and Haight, 2006; Daughton, 2016; Maack et al., 2022). Pharmaceuticals, including their residues and metabolites, are found in surface waters, groundwater, drinking water, manure, sediments, and soils globally, and these substances may further contaminate our food and water supply (Doerr-MacEwen and Haight, 2006; Boxall, 2004; aus der Beek et al., 2016; Wilkinson et al., 2022). In a recent study, concentrations of active pharmaceutical ingredients (API) were found at levels posing a threat to environmental and/or human health in more than 25% of the 1052 sampling sites that were monitored along 258 rivers in 104 countries (Wilkinson et al., 2022). At these contaminated sites, pharmaceutical

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concentrations were above levels that are potentially toxic to organisms, and in 72 countries antibiotics were detected at levels of concern in terms of selecting for antimicrobial resistance (Wilkinson et al., 2022).

Several pharmaceutical classes have a negative environmental impact. One of the most widely used groups of pharmaceuticals worldwide is analgesics, which have been detected in watercourses in many countries (Wilkinson et al., 2022; Marsik et al., 2017; Fick et al., 2015; Benotti et al., 2009). Analgesics include opioids, non-steroidal anti-inflammatory drugs (NSAID), paracetamol, and various other analgesics and antipyretics. Most of these analgesics are prescription pharmaceuticals but there are also substantial sales of paracetamol and NSAID over-the-counter at pharmacies (Wastesson et al., 2018; Kristensen et al., 2019; Conaghan, 2012). Analgesics also represent some of the most frequently administered pharmaceuticals in hospitals (Dix et al., 2004). In addition to human consumption, analgesics are commonly administered to livestock and domestic animals (Swedish Board of Agriculture, 2019). Diclofenac, a NSAID, has been detected in many freshwater ecosystems worldwide and is considered to be one of the pharmaceuticals with the highest environmental risk overall (Näslund et al., 2020). For example, in the 1990s, vulture populations in India and Pakistan were exposed to high concentrations of diclofenac, leading to acute toxic effects and severe population declines (Oaks et al., 2004). Due to its continuous accumulation in freshwater, diclofenac is considered a “pseudo-persistent” pollutant, and has been shown to have harmful effects on aquatic organisms(Acuña et al., 2015).

Sweden relatively early recognized the importance of reducing the environmental impacts of pharmaceuticals (Wennmalm and Gunnarsson, 2009; Wennmalm and Gunnarsson, 2005). In this regard, the MistraPharma research program, funded by The Swedish Foundation for Strategic Environmental Research (Mistra), resulted in increased awareness of the potential consequences caused by pharmaceutical residues in wastewater — e.g., showing that levonorgestrel can cause sterility of female frogs (MistraPharma Research, 2022; Kvarnryd et al., 2011). The Swedish regions also initiated activities to promote more environmentally friendly prescription practices (Gustafsson et al., 2011). Further, in 2001, a Swedish classification system for environmental hazard was initiated as a tool for policymakers and prescribers to prioritize activities to reduce the environmental impacts of pharmaceuticals (Ramström et al., 2020).

Drug utilization studies have been used to promote quality use of medicines in humans for more than five decades (Bergman, 2006). Although some attempts have been made to develop models to monitor pharmaceutical use in humans and animals in relation to environmental risk (Castensson et al., 2009; Committee for medicinal products for human use (CHMP) EMA, 2006), there is still a limited focus on the opportunity to use drug utilization data to assess the potential environmental impacts of pharmaceuticals. Consequently, the main aim of this study was to investigate drug utilization patterns of analgesics in relation to environmental hazard in the region surrounding Sweden’s largest drinking water source. We predict that this approach will be highly useful when seeking to identify possibilities to reduce the environmental burden of analgesics, both within Sweden and globally.

2. Materials and methods

2.1. Geographic study area

This study included the geographic area surrounding Lake Mälaren, Sweden’s third largest lake, which has been designated as an area of national interest for the drinking water supply (Eklund et al., 2018). The lake supplies more than 2 million people with drinking water, making it Sweden’s largest drinking water source (Eklund et al., 2018). The region surrounding the lake consists of five counties (Fig. 1), which are made up of forests, agricultural areas, and urban areas that are experiencing rapid population growth (Sonesten et al., 2013). Each county is responsible for organizing and financing healthcare to meet the needs of their citizens (Anell et al., 2012). Primary care centers and hospitals in these counties may be public or private, operating under contract with the public payer. Pharmacies and over-the-counter sales are privately organized, as is veterinary healthcare (Wisell et al., 2016). A total of 34 municipalities were included in our study, which, among other things, are responsible for environmental protection and wastewater treatment (SKR, 2023).

A report from the Swedish University of Agricultural Sciences (Malnes et al., 2021) shows that Lake Mälaren is a recipient of water from some of Sweden’s largest wastewater treatment plants (WWTP), which is polluted by organic micropollutants including persistent pharmaceutical residues. According to a risk analysis conducted by Mälaren’s water conservation association (MVVF), one of the greatest risks for Lake Mälaren as a raw water source and ecosystem is the emission of chemicals, including pharmaceuticals (WSP Environmental Sverige, 2021).

A catchment area is the area of land from which surface runoff, including water from rain and snow, drains into a river, basin, or reservoirs, such as Lake Mälaren. Emissions from human activities within the catchment area will influence the water quality. When deciding on necessary measures to safeguard the environment, including water quality, it is hence necessary to take the entire catchment area into account. The Lake Mälaren catchment area was therefore the basis for which municipalities were selected to be included in this study. The municipalities included in this study are shown in Fig. 1, and a list can be found in Supplementary Table 1.

2.2. Data collection and analysis

This study used aggregated sales data on pharmaceuticals from the Swedish E-health Agency — the authority responsible for collecting all data on pharmaceutical sales from pharmacies, retailers, and

Fig. 1. Lake Mälaren is surrounded by five counties (Stockholm, Södermanland, Uppsala, Västmanland, and Örebro). A total of 34 municipalities were included in this study.

wholesalers in Sweden. The total sales of analgesics (Anatomical Therapeutic Chemical (ATC)-groups (Q)M01A (NSAIDs), (Q)M02A (NSAIDs for topical use), (Q)N02A (opioids), and (Q)N02B (paracetamol and other non-opioid analgesics)) for both human and veterinary use in the region were collected.

Data used include information on all pharmaceuticals for human and veterinary use sold in the region — i.e., through prescriptions, over-the-counter, or to hospitals and other health facilities. Over-the-counter sales were further divided into pharmacy sales and sales outside pharmacies, including food stores, petrol stations, and other vendors. Veterinary use included dispensed prescriptions, over-the-counter, and outpatient supplies. The type of animal to which pharmaceuticals were administered was divided into the following three categories: food-producing animals, companion animals and other animals, according to the guidelines of the Swedish Board of Agriculture (Swedish Board of Agriculture, 2019). Pharmaceuticals sold from pharmacies to veterinarians for use in clinics and ambulatory activities usually belong to the category Pharmaceuticals for other animals. Extemporaneous preparations and products without market approval were excluded.

Information about Defined Daily Doses for each API was collected from the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC) (WHOCC - ATC/DDD Index, 2022). Prescription status and retail information was collected from a product register administered by the Swedish E-Health Agency (VARA) (The Swedish E-Health Agency, 2022).

Data were measured in terms of the number of kilograms of the APIs sold, and were analyzed in relation to the environmental hazard for each API for the years 2016 to 2020. Products containing fixed combinations were divided and calculated separately for each API. The total mass was divided by the population in the region (1.15 million inhabitants) and the total land area (24,523 km^2) to assess the intensity of environmental emission from a population and a geographical perspective, respectively. Furthermore, the utilization was presented in relation to the classification of environmental hazard, developed by region Stockholm, Sweden (Ramström et al., 2020; Committee for medicinal products for human use (CHMP) EMA, 2006). Due to confidentiality reasons, data for substances with only one manufacturer were not presented by API.

2.3. Environmental classification

Classification data on the environmental hazard of the APIs were collected from the database Pharmaceuticals and Environment at Janusinfo.se (Janusinfo, 2020). This classification system includes data on persistence, bioaccumulation, and ecotoxicity. Each property is assigned a value between 0–3, resulting in a total hazard score of 0–9. A high score indicates a higher environmental hazard (Ramström et al., 2020). In this study, we simplified the classification by making APIs with a hazard score of 0–3 green, 4–6 yellow, and 7–9 red to illustrate potential low, medium, and high hazard, respectively (Castensson et al., 2009). Hazard information for APIs only used for veterinary purposes was searched for in European Public Assessment Reports (EPAR) provided by the European Medicines Agency (EMA) (European Medicines Agency, 2022). APIs lacking hazard scores were presented as grey. All APIs included in this study, alongside their environmental classifications, are presented in Table 1.

Proportions of low, medium, and high hazard pharmaceuticals were calculated by dividing the number of kilograms of the API in each group by the total mass of the APIs in the study.

3. Results

A total of 454 tons of analgesics were sold in the region surrounding Lake Mälaren during 2016–2020. This corresponds to 396 kg/1000 inhabitants, or 18.5 kg/km^2. In total, 45 different substances and 26 million packages were sold in the region during the study period.

The three most commonly sold APIs were paracetamol, ibuprofen, and acetylsalicylic acid. These three APIs were all classified as low-hazard compounds and accounted for 95% of the total mass of analgesics sold. Naproxen was the fourth most commonly sold API and was classified with medium hazard. Diclofenac, the only high-hazard compound in this study, was the fifth most commonly sold API (Fig. 2). Tramadol (1802 kg) and codeine (1015 kg) dominated the sales of opioids. Most opioids lacked data on environmental hazard. Buprenorphine, fentanyl, and tapentadol were the only opioids with data on environmental hazard, and these accounted for a combined 152 kg.

An overview of how the sales were divided between human and veterinary use as well as by type of distribution is shown in Fig. 3. The most commonly sold APIs for human use (95% of the total mass) were classified as low-hazard, whereas the most of commonly sold APIs used in veterinary care (82%) lacked data on environmental hazard.

The total mass of analgesics sold by prescription dominated total sales (60%), followed by over-the-counter sales (36%). Hospital and outpatient sales together accounted for approximately 4%.

The geographical distribution of the total sales of analgesics is shown in Fig. 4 and the distribution of diclofenac in Fig. 5. The total sales ranged from 2232 kg to 76175 kg across the 34 municipalities. The relative distribution across the different APIs did not vary substantially between the municipalities. The largest total mass of analgesics, as well as the largest mass of diclofenac, were sold in urban areas. When displayed by 1000 inhabitants the differences between the municipalities became less pronounced.

For paracetamol, ibuprofen, and naproxen, tablets were the dominant formulation, accounting for approximately 99% of the total sales (Fig. 6). For acetylsalicylic acid, effervescent tablets were the dominant formulation, accounting for approximately 96% of the total sales. Of the five most commonly sold analgesics, ibuprofen and diclofenac were the only APIs that existed in topical formulations (i.e., gels). During the study period, a total of 118 kg of topical ibuprofen and 2321 kg of topical diclofenac were sold (87% *versus* 62% as over-the-counter sales for ibuprofen and diclofenac, respectively; 11% *versus* 34% as prescription sales; and 2% *versus* 4% as hospital care and outpatient supplies) (Fig. 6). Topical formulations accounted for approximately 50% of the total diclofenac sales, and a total of 1073 kg of topical diclofenac was sold over-the-counter, of which 182 kg was sold outside of pharmacies. Carprofen, phenylbutazone, and firocoxib were the three most commonly sold APIs for veterinary use and together accounted for 401 kg.

Sales data for analgesics used in veterinary care are presented in Table 2. A total of 1023 kg of analgesics were sold for veterinary use. Data on animal type were not always documented but, when they were, companion animals had the highest use of all analgesics in terms of veterinary use (58%), followed by food-producing animals (42%).

4. Discussion

This study explored and visualized analgesic drug utilization patterns surrounding Lake Mälaren, Sweden, in relation to environmental hazard. We found that more than 454 tons of analgesics were sold in the region over a 5-year period. Around 60% of these sales originated from dispensed prescriptions. Veterinary use was relatively small compared to human use, contributing a total of 1023 kg (0.2%). Paracetamol, ibuprofen, and acetylsalicylic acid accounted for the largest overall mass of sold pharmaceuticals. The most commonly used APIs were all classified as being low environmental hazard compounds, indicating that the choice of APIs was somewhat “environmentally friendly”. Still, there was some use of APIs with high environmental hazard, and some commonly used pharmaceuticals lacked environmental classification.

It is not possible from these figures to assess whether there is an overuse of analgesics. However, the large amounts of pharmaceuticals being released into nature, potentially posing a threat for wildlife and humans alike, calls for further analyses and strategies to optimize both the overall consumption of pharmaceuticals and the choice of analgesic

Table 1
Active pharmaceutical ingredients included in the study in relation to environmental hazard from the database Pharmaceuticals and Environment at Janusinfo.se (The Swedish E-health Agency, Janusinfo, 2020).

API	ATC code	Prescription status	Sold outside of pharmacies	Environmental hazard
NSAID				
Carprofen	QM01AE91	Rx	No	-
Celecoxib	M01AH01	Rx	No	-
Cimicoxib	QM01AH93	Rx	No	-
Dexibuprofen	M01AE14	Rx	No	5
Diclofenac	M01AB05, M01AB55, M02AA15	(Rx)	Yes	**
Dietylaminsalicylat*	M02ACÖÖ	OTC	Yes	1
Dimetylsulfoxid	QM01AXÖÖ	Rx	No	-
Etoricoxib	M01AH05	Rx	No	4
Firocoxib	QM01AH90	Rx	No	-
Flunixin	QM01AG90	Rx	No	-
Grapiprant	QM01AX92	Rx	No	-
Hydroxietylsalicylat	QM02AC99	Rx	No	-
Ibuprofen	M01AE01, M02AA13, N02AJ08, N02BE51	(Rx)	Yes	2
Ketoprofen	M01AE03, M02AA10, QM01AE03	Rx	No	5
Ketorolac	M01AB15	Rx	No	4
Mavacoxib	QM01AH92	Rx	No	-
Meloxicam	M01AC06, QM01AC06	Rx	No	4
Nabumeton	M01AX01	(Rx)	No	-
Naproxen	M01AE02, M01AE52	(Rx)	Yes	5
Parecoxib	M01AH04	Rx	No	-
Pentosan polysulfate sodium	QM01AX90	Rx	No	-
Phenylbutazone	QM01AA01	Rx	No	-
Piroxicam	M01AC01	Rx	No	-
Robenacoxib	QM01AH91	Rx	No	-
Tenoxicam	M01AC02	Rx	No	-
Vedaprofen	QM01AE90	Rx	No	-
Opioids				
Buprenorphine	N02AE01, QN02AE01	Rx	No	6
Butorphanol	QN02AF01	Rx	No	-
Codeine	N02AG01, N02AJ06, N02AJ08, N02AJ09	Rx	No	-
Fentanyl	N02AB03, QN02AB03	Rx	No	4
Hydromorphone	N02AA03	Rx	No	-
Ketobemidone	N02AB01, N02AG02	Rx	No	-
Methadone	QN02AC90, QN02AC52	Rx	No	-
Morphine	N02AA01, N02AG01, N02AA51	Rx	No	-
Oxycodone	N02AA05, N02AA55, N02AGÖÖ	Rx	No	-
Pethidin	N02AB02	Rx	No	-
Tapentadol	N02AX06	Rx	No	4
Tramadol	N02AX02, QN02AX02	Rx	No	-
Other analgesics and antipyretics				
Acetylsalicylic acid	N02BA01, N02AJ09, N02BA51	OTC	Yes	1
Bedinvetimab	QN02BG91	Rx	No	-
Cannabinoids (CBD and THC)	N02BG10	Rx	No	
Metamizole sodium	QN02BB02	Rx	No	-
Methoxyflurane	N02BG09	Rx	No	-
Paracetamol	N02BE01, N02AJ06, N02BE51	(Rx)	Yes	1
Phenazone	N02BB51	(Rx)	No	3

Rx: prescription only
(Rx): some preparations are sold over-the-counter
Q: veterinary pharmaceuticals have the letter Q in front of the ATC code
OTC: all preparations are available to sell over-the-counter without prescription
* Withdrawn from the market during the study period

** Diclofenac was classified as having a high hazard based on scientific literature. In a Swedish report published in 2020 (Svenskt vatten, 2020), diclofenac was measured at levels above the limit values for good water quality for lakes, watercourses, and coastal stretches at 18 sites around Sweden. In addition, the report concluded that there is a risk that limit values will be exceeded in a further 109 sites. As of 1 June 2020, diclofenac is a prescription-only pharmaceutical for oral formulations such as tablets and capsules. This decision was based on the increased risks of side-effects and not due to its environmental risks (Swedish Medical Products Agency 2020). The Swedish Agency for Marine and Water Management has classified diclofenac as a river basin-specific pollutant (RBSP) (Swedish Agency for Marine and Water Management).

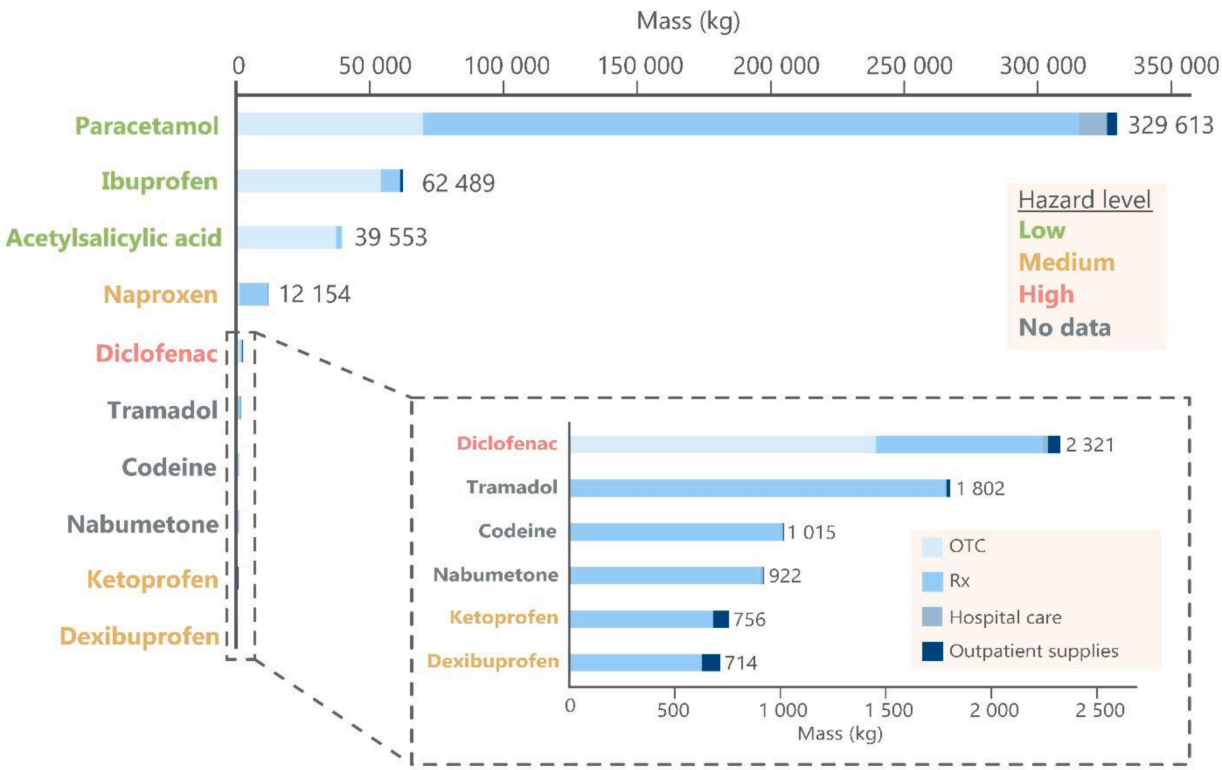

Fig. 2. Sales, in kilograms, of the 10 most-used analgesics and non-steroidal anti-inflammatory drugs for both human and veterinary use, from 2016–2020.

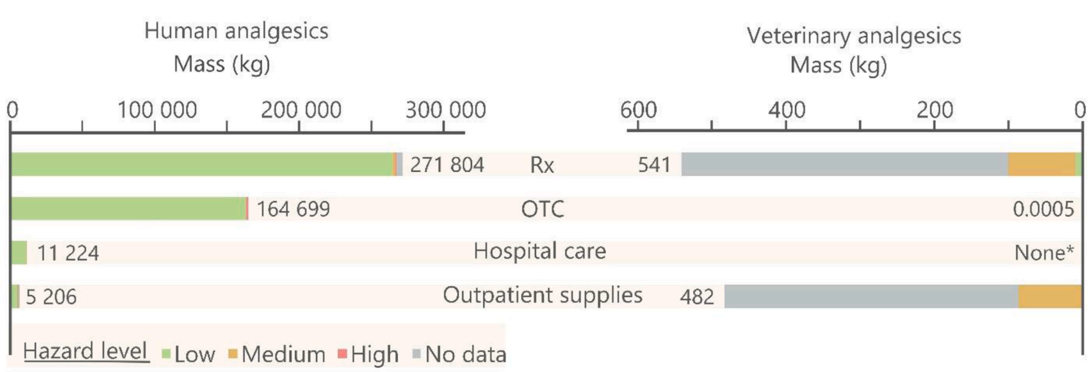

Fig. 3. Total sales of analgesics and non-steroidal anti-inflammatory drugs for both human and veterinary use, in kilograms, during 2016–2020. *Data for hospital care were not available for veterinary analgesics, sales to veterinary clinics were categorized as outpatient supplies. Outpatient facilities for human use include, for example, residential care and schools.

treatment. Previous studies have shown major problems relating to the inappropriate use of analgesics and that a reduction in prescribing could be beneficial both in terms of optimizing treatments, as well as reducing environmental damage (Moore et al., 2015; Vo et al., 2009; Degenhardt et al., 2019). To the best of our knowledge, no research to date has analyzed analgesics from a One Health perspective, focusing on the consequences, responses, and actions at the animal–human–ecosystem interface (Mackenzie and Jeggo, 2019). While the veterinarian community has adopted this systemic approach, the medical and pharmaceutical communities have been slower to engage (Rabinowitz et al., 2017). As such, few pharmaceutical classes other than antibiotics have been studied using a One Health approach (Schechner et al., 2013; Verloo et al., 2008; European Medicines Agency, 2011; Tiseo et al., 2020). We found that veterinary use was small compared to human use, although it may still contribute to stress on the environment, particularly as veterinary pharmaceuticals often find their way directly into soils and surface waters, unlike human pharmaceuticals which often first go through a wastewater treatment plant. We found that food-producing animals accounted for 42% of the total veterinary analgesic use. As previously mentioned, in intensive livestock

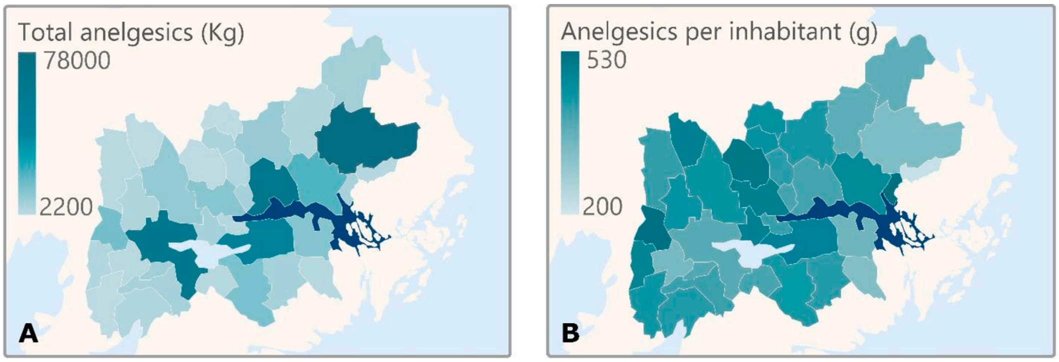

Fig. 4. A. Total sales of analgesics and non-steroidal anti-inflammatory drugs for both human and veterinary use, in kilograms, per municipality, from 2016–2020. B. Analgesic sales in grams per inhabitant, from 2016–2020.

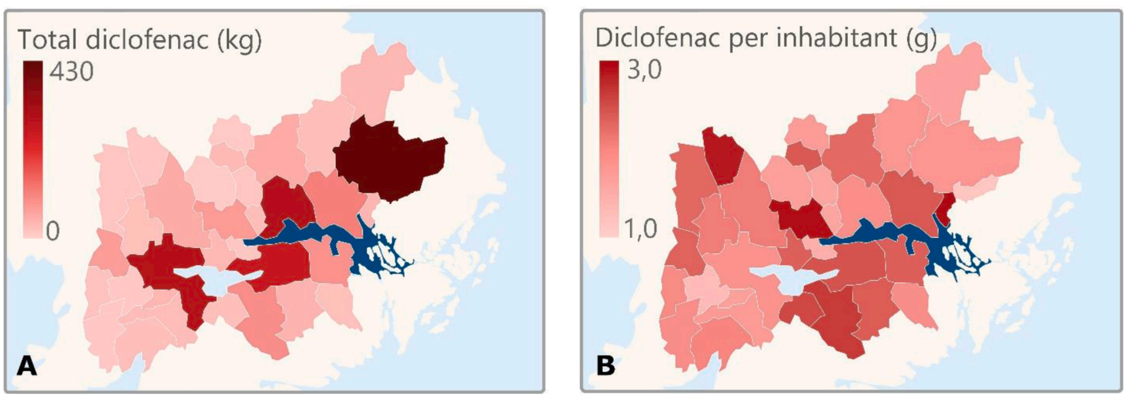

Fig. 5. A. Total sales of diclofenac in kilograms, per municipality, from 2016–2020. B. Diclofenac sales in grams per inhabitant, from 2016–2020.

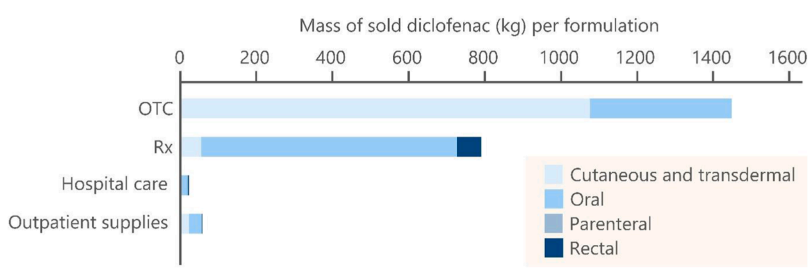

Fig. 6. Sales of diclofenac for human use, measured in kilograms, from 2016–2020.

Table 2
Veterinary analgesic sales by animal type, shown in kilograms.

	Food-producing animals	Companion animals	Other animals	No data	Total
Low hazard	4.5	5.6			10.1
Medium hazard	86.5	3.7	<0.1	85.3	175.5
High hazard	0.01	0.05			0.06
No data	138.8	301.9	<0.1	396.4	837.2
Total	**229.9**	**311.2**	**0.1**	**481.7**	**1022.9**

treatments, veterinary pharmaceuticals are likely to also enter the environment indirectly through the application of slurry and manure as fertilizers (aus der Beek et al., 2016).

The relatively high use of paracetamol, ibuprofen, and acetylsalicylic acid mirrors findings from other countries (Wastesson et al., 2018; Kristensen et al., 2019). All of these are considered to be low-hazard compounds. The high-hazard compound diclofenac was the fifth most-sold API. Various measures to limit the use of diclofenac in Sweden have been implemented to safeguard the aquatic environment, including the exclusion of diclofenac in treatment guidelines in some regions (Ramström et al., 2020), and adding information on shelves in Swedish pharmacies since 2018 about diclofenac's negative environmental impact (the Swedish Pharmacy Association, 2023). The continuously high use is thus concerning. We found that over-the-counter sales dominated the total sales of diclofenac, and that around 50% was sold in a topical formulation. Only 5–6% of the API in a topical formulation is absorbed into the skin (Svenskt vatten, 2020), which means that the rest — i.e., more than 90%—is rinsed off, and often runs down the drain. The pharmaceutical residues will then either end up directly in the sea, lakes, and adjacent water bodies, or in wastewater effluent (Svenskt vatten, 2020). The high use of the topical over-the-counter drug diclofenac suggest that more initiatives are needed to impact consumer behavior of environmentally harmful over-the-counter products.

The largest masses of analgesics consisted of prescription pharmaceuticals, which emphasizes the importance of involving prescribers in reducing emissions of pharmaceuticals into the environment. Such measures may include user-friendly guidelines, educational activities, and computerized decision-support systems, measures that have previously been shown to be powerful in influencing pharmaceutical prescription practices (Eriksen et al., 2018). An important component in these strategies is also feedback on prescribing patterns to encourage more prudent and “environmentally friendly” prescriptions.

Overall, over-the-counter sales accounted for one third of the total mass of analgesics sold in the region. Community pharmacists can play an important role in communicating with consumers about their choice of analgesics. Personnel at retail outlets other than pharmacies are not allowed to give advice about pharmaceuticals, and can thus not warn consumers about the harmful properties of the topical formulations of diclofenac. It should therefore be considered whether the benefit of easy access through providing these pharmaceuticals in non-pharmacy outlets outweighs the risk for misuse in humans and emissions to the environment (Gedeborg et al., 2017).

Analgesics used in hospitals were, in this study, found to contribute with only a few percent of the total sales (2%). Hospital use may be more important in other therapeutic areas such as oncology of infectious diseases where concentrations of pharmaceuticals found in hospital wastewater may be high (Verlicchi et al., 2012). Hospital use is, compared to household use, a well-controlled environment where healthcare professionals can monitor the use of pharmaceuticals. Introducing separate wastewater treatment in connection to hospitals could be one way to reduce the flow of pharmaceuticals to the environment.

Another important perspective generated by this study relates to which geographical areas that may be most beneficial to target in terms of introducing countermeasures. More specifically, analyses of spatial drug utilization patterns may help to identify hotspots where measures could be taken to reduce the release of pharmaceuticals into the environment. In this regard, the largest total mass of analgesics was sold in urban areas, something which is not surprising but nevertheless highlights that these areas should be prioritized. When displayed by 1000 inhabitants, the differences between the municipalities became less pronounced. Spatial comparisons of pharmaceutical use can be used for benchmarking and can provide an important indication of whether regional guidelines are being followed, and/or if further regional or local measures are needed.

Strengths of this study include a database with complete coverage for the studied ATC groups, including all sold pharmaceuticals, regardless of sales method or prescription status, and including both human and veterinary use. The sales data covered a 5-year period and were geographically granular. The ATC code and the Defined Daily Dose system is international, and this study could therefore be reproduced in other settings. The sales data also allowed for mass-based analyses, which enables comparisons of pharmaceutical use between geographical regions, sales methods, and environmental risk. Data may be broken down by geography and provider to plan for interventions targeting specific stakeholders.

However, we also acknowledge some important limitations of this study. First, while mass is an appropriate measure for studying environmental risk, it is not appropriate for clinical comparisons where Defined Daily Dose is the global standard when there are no patient-level data available (Bergman, 2006). Further, in this study, we used data on pharmaceutical sales, although sold pharmaceuticals are not always actually used. It has been estimated that approximately 5% of pharmaceuticals sold in Sweden are either returned to pharmacies for destruction, discarded in household waste, or flushed down the drain (the Swedish Medical Products Agency, 2012). Pharmaceuticals may also be consumed years later, and the place of consumption may differ from where the prescription was filled or where the product was purchased. Consequently, it is not necessarily straight-forward to link drug utilization patterns and subsequent residues in the environment. In addition, the municipalities included in this study were based on the Lake Mälaren catchment area and it is not certain that all WWTPs in these municipalities have Lake Mälaren as their main recipient.

There are also limitations related to the hazard score system used in this study. This system was developed for people not familiar with interpreting ecotoxicological data, and while this model enabled a pedagogical overview of these data, it also resulted in a scenario where an API with a higher score is not always of greater environmental concern. Due to the risk of misinterpretation, this hazard score is now in the process of being removed from the Janus database (Ramström et al., 2020). Although correct from a formal point of view, it illustrates the problem of using information from websites, where data may be changed or removed, making it difficult or impossible to reproduce or repeat studies. Despite an increased interest regarding pharmaceuticals in the environment (Daughton, 2016), publicly available and reliable producer-independent environmental data on pharmaceuticals are scarce. For instance, a recent study found that environmental toxicity data were lacking for 88% of the pharmaceuticals targeting human proteins (Gunnarsson et al., 2019). In this study, 29 out of the 45 APIs (64%) lacked data on environmental hazard, especially the opioids and veterinary APIs. For these APIs, it is important to address the limited data availability and stricter requirements should be placed on pharmaceutical companies to become transparent with data on their environmental risks.

Finally, it is important to acknowledge that we assessed the potential environmental burden of each API separately. It is also important to consider that pharmaceutical residues in the environment do not occur as single contaminants but rather as mixtures. This means that pharmaceuticals found at low concentrations can contribute to the total mixture effect. For instance, a study from 2004 (Cleuvers, 2004) observed mixture toxicity of diclofenac, ibuprofen, naproxen, and acetylsalicylic acid at concentrations considerably lower than toxic effects for the separate APIs. It is thus important to recognize mixture toxicity when assessing environmental risk.

Despite these limitations, we believe that the analyses and visualizations conducted in this study could be used as a valuable tool for promoting a more sustainable use of pharmaceuticals. The analyses could preferably be combined with wastewater-based epidemiology, including analyses of wastewater from different origins, such as households, hospitals, and agriculture, as well as indicating differences in consumed *versus* disposed pharmaceuticals. Further analyses may also include qualitative studies and surveys of different stakeholders to provide the comprehensive information needed for different decision-makers to reduce the environmental impact of pharmaceuticals (Boogaerts et al., 2021).

5. Conclusions

In this study focusing on sales of pharmaceuticals around Sweden's largest drinking water supply, the three most commonly sold APIs were all classified as low-environmental hazard compounds and accounted for 95% of the total mass of analgesics sold. The majority of the total mass of analgesics sold were prescribed, used in urban areas and for human use. One identified area of improvement is the use of diclofenac, which is still high despite many countermeasures taken by various stakeholders in Sweden. Based on our results combined with previous research, we suggest that additional measures may be needed to reduce the impacts of pharmaceuticals on the environment, especially in urban areas and targeting the high over-the-counter use of diclofenac.

CRediT authorship contribution statement

Johanna Villén: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Marmar Nekoro:** Conceptualization, Writing – review & editing. **Sofia Kälvemark Sporrong:** Conceptualization, Writing – review & editing. **Helle Håkonsen:** Conceptualization, Writing – review & editing. **Michael G. Bertram:** Writing – review & editing. **Björn Wettermark:** Conceptualization, Methodology, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.envadv.2023.100384.

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