Predicting Environmental Risks from Pharmaceuticals under Future Scenarios: A Norwegian Example

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"And all the science, I don't understand / It's just my job five days a week"

- Elton John

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Paper II: Predicting Environmental Risks of Pharmaceuticals from Wholesales Data: An Example from Norway

Welch, S.A., Moe, S.J., Nouri Sharikabad, M., Tollefsen, K.E., Olsen, K., Grung, M., 2022b. Predicting Environmental Risks of Pharmaceuticals from Wholesales Data: An Example from Norway. Environ. Toxicol. Chem. accepted.

Paper III: Bayesian Networks for the Assessment of Future Pharmaceutical Environmental Risk

Welch, S.A., Grung, M., Madsen, A.L., Moe, S.J., 2023. Probabilistic risk calculation for chemical mixtures: environmental risk of pharmaceuticals under future scenarios. OSF Preprints. https://doi.org/10.31219/osf.io/zbgp7

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Abbreviations

AF	Assessment Factor
API	Active Pharmaceutical Ingredient
BCF	Bioconcentration Factor
BN	Bayesian Network
CHMP	Committee on Human Medicinal Products
COP	Conference of Parties
CVMP	Committee on Veterinary Medicinal Products
DAG	Directed Acyclic Graph
DDD	Defined Daily Dose
DWSD	(Norwegian) Drug Wholesales Statistics Database
EC_x	Effective Concentration at which x% of organisms show an effect
EEA	European Economic Area
EEA ETC-HE	European Environment Agency European Topic Centre on Health and the Environment
EFTA	European Free Trade Association
EMA	European Medicines Agency (formerly EMEA)
EPAR	European Public Assessment Report
EQSD	Environmental Quality Standards Directive
ERA	Environmental Risk Assessment
EU	European Union
Fass	Swedish Pharmaceutical Specialities
Felleskatalogen	Norwegian Pharmaceutical Specialities
GCC	Global Climate Change
GDP	Gross Domestic Product
JRC	European Commission Joint Research Centre
K_{oc}	Normalised organic carbon to water partition coefficient
$logK_{ow}$	Log10 of n-octanol-water partition coefficient
MEC	Measured Environmental Concentration
NIPH	Norwegian Institute for Public Health
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Level
NORMAN	Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances
NorPD	Norwegian Prescriptions Database
OEC	Observatory of Economic Complexity
OECD	Organisation for Economic Cooperation and Development
OOBN	Object-oriented Bayesian Network
OPERA	Open (Quantitative) Structure-activity/property Relationship App
OTC	Over-The-Counter
PBT	Persistent, Bioaccumulative, and Toxic
PEC	Predicted Environmental Concentration
PiE	Pharmaceuticals in the Environment
PNEC	Predicted No Effect Concentration
QSAR	Qualitative Structure-Activity Relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RQ	Risk Quotient
SPC	Summary of Product Characteristics
SSB	Statistics Norway (Statistisk sentralbyrå)
TGD	Technical Guidance Document

UWWTD	Urban Wastewater Treatment Directive
VICH	Veterinary International Committee on Harmonization
vPvM	very Persistent and very Mobile
WFD	Water Framework Directive
WHO	World Health Organisation
WWT	Wastewater Treatment
WWTP	Wastewater Treatment Plant
ΣRQ	Sum of Risk Quotients

Summary

Pharmaceutical pollution has been recognised as an environmental issue since the 1990s. A wide range of APIs (Active Pharmaceutical Ingredients) are in use in pharmaceutical products and have been found in the environment. However, a smaller body of supporting literature exists for this group of substances than for many other pollutants. The environmental risk assessment of pharmaceuticals must often be conducted with less data, and more uncertainty, than other groups of chemicals. To prioritise pollutants and manage risk in line with national, European, and international environmental goals, it is vital that we can forecast how pharmaceutical environmental risk will evolve in the future, as the range of stressors facing humans and the environment changes. However, this act of forecasting itself introduces uncertainty, and strategies better able to transparently process and display this uncertainty will increase the quality of forecast environmental risk assessment.

In this PhD, emissions and risks of pharmaceuticals to the Norwegian environment are predicted. Using sales data from the Norwegian Institute for Public Health's Drug Wholesales Statistics Database, and information on the API weight content of different pharmaceutical products, a dataset covering more than 800 APIs was created with wholesale records over a four-year sales period. By comparing predictions to similar data sources, the accuracy of the work could be evaluated.

These predicted exposures were subsequently used, in combination with publicly available experimental and computation toxicity, persistence, mobility and bioaccumulation data to rank the risk of pharmaceuticals over four years. We compared our predicted values to measurements available for Norwegian wastewater treatment plants and found that predictions overestimated compared to measurements by a median of 20 times. While calculation of Risk Quotients (RQ) was only possible for a minority of APIs, more than 200 APIs could nevertheless be ranked by RQ, identifying sex hormones as some of the highest risk APIs in the Norwegian environment. Effects of veterinary and non-prescription pharmaceuticals were examined for both API environmental exposure and risk and found that 70% of exposure was attributable to only prescription medications, and 85% to only human medications. Little effect was seen on RQ prioritisation, though this was likely skewed by data availability. As pharmaceutical pollutant priority has been identified as a local (national) phenomenon, this work is important in improving the state of knowledge of pharmaceutical pollution in Norway.

Finally, to address the uncertainty in the predictions of risk, a novel Object-Oriented Bayesian Network was developed to forecast the risk of a subset of high-priority APIs in 2020 and 2050. Thirty-six plausible future scenarios were developed, covering variation in population growth, wastewater treatment removal efficiency, and three example Norwegian counties across the spectrum of urbanisation. For each scenario and API, the distribution of possible RQ values was predicted. A sum of RQs was subsequently calculated, as well as joint probability that any RQ would exceed a given threshold, across all APIs in each scenario. The highest overall risk was found in rural regions, especially under larger population growth scenarios. Improved wastewater treatment efficiency could mitigate risk.

Sammendrag

Forurensing av legemidler i miljøet har vært anerkjent som et potensielt problem siden 1990-tallet. Legemidler inneholder en rekke *Active Pharmaceutical Ingredients* (Aktive Farmasøytiske Ingredienser, API-er), og mange gjenfinnes i miljøet. Til tross for et økt fokus er det fremdeles mindre kunnskap om forurensning fra legemidler enn andre typer kjemisk forurensning. Miljørisikovurderinger må derfor ofte gjennomføres med begrenset datatilgang, og derved større usikkerhet, enn for andre grupper av kjemikalier.

For å forvalte risiko på linje med nasjonale, europeiske og internasjonale miljømål, må vi forstå hvordan legemidlers miljørisiko kunne kommer til å utvikles i framtiden, etter hvert som omfanget av stressfaktorer for mennesket og miljøet endrer seg. Effektiv forvaltning kreves dermed prioritering av nåtids og framtidens miljørisikoer av legemidler. Prediksjoner av framtidsscenarier medfører i seg selv økt usikkerhet, og strategier som kan forbedre prosessen med risikovurdering og øke transparensen av usikkerheten vil gi oss en forbedret miljørisikovurdering.

Fokus for denne doktorgraden er modeller for å forutsi utslipp og risiko av legemidler i norsk miljø. Vi har etablert et datasett som inkluderer flere enn 800 API-er ved å bruke salgsdata fra fire år fra Folkehelseinstituttets grossistbaserte statistikk over legemiddelforbruk og informasjon om den relative andelen API-er i ulike farmasøytiske produkter. Ved å sammenligne prediksjonene med lignende datakilder, har vi kunnet evaluere hvor presise estimatene er.

Predikerte legemiddelkonsentrasjoner sammen med publiserte eksperimentelle og data-baserte data for giftighet, nedbrytning i miljøet, bioakkumulering og mobilitet ble brukt til å rangere miljørisiko for legemidler over disse fire årene. Vi sammenlignet våre predikterte estimater med målinger fra norske renseanlegg og fant at våre prediksjoner overestimerte medianverdien relativt til målte verdier med en faktor 20. Selv om beregning av *Risk Quotients* (risikokvotientene, RQ-er) var mulig bare for en mindre andel av API-er, kunne vi allikevel rangere flere enn 200 API-er med tanke på RQ. Kjønnshormoner ble identifisert som API-er med den høyeste miljørisikoen. Den grossistbaserte statistikken over legemiddelforbruk inkluderer oversikt over bruk av veterinærlegemidler og reseptfrie legemidler, noe som mange land ikke har offentlig statistikk over. Resultatene viste at 70 % av total eksponering kunne tilskrives reseptpliktige legemidler og 85 % ble bruk av mennesker. Veterinærmedisin og reseptfrie legemidler hadde liten påvirkning på RQ-basert prioritering, men dette var trolig påvirket av fordelingen av data. Legemidler i miljøet har blitt identifisert som et miljøproblem, og dette arbeidet er derfor viktig som kunnskapsgrunnlag om legemiddelforurensing i Norge.

For å vurdere usikkerheten i forventet risiko, ble et nytt objektorientert bayesisk nettverk utviklet for å predikere nåværende og fremtidig risiko for legemidler med høy miljørisiko i 2020 og 2050. Trettiseks plausible framtidsscenarier ble utviklet. De inkluderte variasjon i befolkningsvekst og effektivitet av avløpsrensing, og viste risiko i tre norske kommuner med ulike nivåer av urbanisering. For hvert scenario og API, ble fordelingen av mulig RQ-verdier predikert. Til slutt ble en sum av RQ-er beregnet, og i tillegg en samlet sannsynlighet for at noen RQ-er var høyere enn en gitt grenseverdi. Den høyeste totale risiko ble funnet i distriktene, spesielt under en forventning om høyere befolkningsvekst. Forbedret avløpsbehandling ble vist å redusere miljørisiko.

1. Introduction

1.1 Background

Earth and humans today face a complex, dynamic landscape of interlinked environmental issues that represents a severe threat to health. In the World Economic Forum's 2023 survey, roughly 1200 academic, business, government, international and civil groups, and experts were asked to rank the top ten global risks facing humanity. Six of the top ten global risks selected were environmental: failure to mitigate climate change, failure of climate-change adaptation, natural disasters and extreme weather events, biodiversity loss and ecosystem collapse, natural resource crises, and large-scale environmental damage incidents (World Economic Forum, 2023). Likewise, the World Health Organisation (WHO) has identified climate change as the top risk to human health (WHO, 2021), while the *Lancet*'s Pollution and Health commission has found that pollution is the world's single largest environmental risk factor for disease and premature death (Fuller et al., 2022)

In her list of priorities for 2019-24, the President of the European Commission, Ursula von der Leyen placed in number one position (of six) the agreement of a European Green Deal, under which Europe will, by 2050, "*become climate-neutral*", "*move towards a zero-pollution ambition*", and "*present a Biodiversity Strategy for 2030*" (von der Leyen, 2019). Likewise, on an international scale, the increasing importance of environmental agreement is illustrated by the growing pace of climate change and biodiversity agreements, such as the UN Environment Programme's COP 15 and the United Nations Framework Convention on Climate Change COP 27 conferences, both in 2022.

To support its ambitious environmental goals, the European Union (EU) funds research through Horizon Europe. As part of its last programme, Horizon 2020 provided €80 billion of funding to address societal challenges including health and environmental issues. One such funded project was the Innovative Training Network ECORISK 2050, designed to train early career researchers to address critical questions surrounding how pollutant risk will evolve by the year 2050 (Welch et al., 2022a).

ECORISK 2050 encompassed four primary work packages – Scenarios, Exposure, Effects, and Risks & Mitigation, and aimed to assess global change's impact on the scenarios of chemical emission and consumption, the environments exposure to chemicals, changes in the effects of chemicals, and the overall risk landscape. The EU and European Free Trade Area (EFTA) are by environmental convention divided into three regions, North (from Denmark to Finland), Central (from the UK to Romania), and South (France and below). This PhD project was planned with the original title "*Assessing the combined toxicity, cumulative hazard, and cumulative risk of PPCP in wastewaters in the future*", with a principal focus of pharmaceutical pollution in Norway.

1.2 Pollution, Risk, and Uncertainty

Society and industry's widespread recognition of the universal importance of environmental issues is a marked improvement from the 20th century (World Commission on Environment and Development, 1987). However, rapid development in environmental pressures has far outstripped our ability, as a society, to understand, assess, mitigate, and adapt to the changes we have, are, and will continue to create in the environment.

Environmental issues are complex, and dynamic, and do not conform easily to human-imposed distinctions between, for instance, economics and ecology. The term "wicked

problems" is often applied to environmental issues – they are difficult define neatly and precisely, and surrounded by a network of dynamic social, economic and environmental factors (Kreuter et al., 2004; Levin et al., 2012).

The aim of governments and legislative bodies is to address a variety of concerns, of which environmental issues are a subset. Balancing the environmental costs of pollution against the benefits provided by whatever industry produces said pollution is a complex and highly values-driven process. Management of pollution on a national and global scale can be attempted by a variety of formal and informal means. A key tool intended to systemically assess the likely risk of existing or new substances is Environmental Risk Assessment (ERA). In Europe – and around the world – environmental risk assessment is one of the principal regulatory tools used to assess risks posed by pollution.

The regulatory management and assessment of environmental risks has evolved since its inception in the late 20th century, but due to its political nature, requiring political consensus and subject to strong pressures from industry, regulatory techniques struggle to keep up to date with the latest science. Different groups, industry, NGOs, and academics have criticised various aspects of contemporary European environmental risk assessment and management of pollutants in general, and pharmaceuticals in particular (Ågerstrand et al., 2015; Backhaus and Slunge, 2021; Jager et al., 2001; Landis and Chapman, 2011; Ragas, 2011).

One particular criticised aspect in contemporary environmental risk assessment (ERA) is its ability to handle uncertainty (including a lack of knowledge) in a transparent and quantitative fashion. A more in-depth discussion of uncertainty is made later in this thesis, but in general, existing ERA guidelines make great use of rules-of-thumb and large safety or assessment factors to build in uncertainty in the assessment of risk. Different forms of uncertainty – variability and, especially, lack of effect data – have been repeatedly highlighted as issues in ERA, particularly among less studied, more diverse groups of pollutants, such as pharmaceuticals (Ågerstrand et al., 2015; Verdonck et al., 2007).

Against this backdrop of issues, the output of the ERA process has been criticised for not fully expressing and quantifying uncertainty (Maertens et al., 2022; Verdonck et al., 2007). To this end, a contingent of the ecotoxicology community has long recommended the greater exploitation of probabilistic techniques to enhance existing ERA (Jager et al., 2001; Maertens et al., 2022; Moe et al., 2022). However, more development of techniques, case studies and stakeholder buy-in (EUFRAM, 2006) appears needed before probabilistic approaches can move beyond their existing foothold (EFSA, 2012; Landis, 2021; Mitchell et al., 2021) in ERA.

As a part of addressing these issues, this thesis will predict and assess the recent environmental risks of APIs (Active Pharmaceutical Ingredients) in Norway, explore future risk under various plausible scenarios, and develop a Bayesian network model as a probabilistic approach to characterising this risk and associated components of uncertainty towards 2050.

1.3 Research Objectives

This thesis and its component papers address the scientific challenges and methodology of the risk assessment, both conventionally deterministic and probabilistic, of pharmaceuticals in

Norwegian surface water under current and future conditions. The goal of this PhD project was broken down into subtasks, which are treated in the included papers.

- To predict the recent exposure of pharmaceuticals pollutants in Norway from wholesales data (Paper I)
- To characterise the recent risk of these pollutants from toxicity and physicochemical properties (Paper II)
- To develop a probabilistic model for predicting combined risk of pharmaceutical mixtures, and forecast how future pharmaceutical risk may change under plausible population and wastewater treatment scenarios (Paper III)

2. State of the Art

2.1 Pharmaceuticals and the Environment

History of Pharmaceuticals and the Environment

Sola dosis facit venenum - "only the dose makes the poison" – is an oft-repeated maxim in ecotoxicology, taken from the works of the renaissance polymath Paracelsus (1493 – 1541). Paracelsus worked in his time primarily as an itinerant physician, prescribing tonics of herbs, oils, spirits, and opiates to patients ("Paracelsus," 2023). In this era, medicine was a rather *ad hoc* process, treatments being made up in apothecaries' shops.

Three hundred years after Paracelsus' death, as the second industrial revolution kicked off in the mid-19th century, modern industrial pharmacy was born, as the converging interests of apothecaries and chemical and dye companies drove the mass production and marketing of early pharmaceuticals (Daemmrich and Bowden, 2005).

Since the heady days of the early pioneers, the development, manufacture and consumption of conventional medicines has surged – although difficult to qualify, we can observe that the value of the pharmaceutical market has more than tripled between 2001 and 2019 alone (González Peña et al., 2021). Through sickness and health and war and peace, reliance on manufactured medicines has become a core paradigm of treatment in Western medicine. Since the beginning of the 20th century, child mortality has dropped from more than 30% to less than 4% (Roser et al., 2013b) life expectancy has more than doubled (Roser et al., 2013a), and the global population grown from 1.7 to 7.1 billion (Roser et al., 2013c).

When, in the wake of Rachel Carson's *Silent Spring* (1962), a wave of popular concern gathered over humans' pollution of the environment, pharmaceuticals were largely omitted (Daughton, 2016) from public, scientific or regulatory attention. As awareness and understanding grew, supplemented by concern over issues such as endocrine disruption and antimicrobial resistance, pharmaceutical pollution grew as an issue in the minds of scientists, governments, and the public, but is still often eclipsed by concern for other environmental issues such as climate change (Desai et al., 2022; Vatovec et al., 2017).

Although isolated cases of pharmaceuticals poisoning people in the literature record date back to the 1940s, Daughton (2016) noted that disparate strands of analysis gathered steam in the 1970s-80s and coalesced in the mid-1990s into a field of research often shortened to *PiE*, for *Pharmaceuticals in the Environment*.

Exposure, Effects, and Issues

Today, pharmaceuticals have been detected in the environment on every continent (Beek et al., 2016; González-Alonso et al., 2017; Kallenborn et al., 2008; Wilkinson et al., 2022). Particularly heavy contamination has been detected in less economically developed nations in Africa and Asia, driven by manufacturing sites, insufficient wastewater treatment infrastructure, and arid climates (Wilkinson et al., 2022). However, the vast majority of research to date on environmental emissions and exposure has occurred in the developed West (Wilkinson et al., 2022).

The discovery of widespread sexual disruption of fish downstream of Wastewater Treatment Plants (WWTPs) in the UK due to contamination with pharmaceuticals sex hormones was one of the earliest findings of significant environmental impact (Jobling et al., 1998; Mills and Chichester, 2005). Famously, the human and veterinary analgesic (painkiller) diclofenac has been responsible for local vulture population extinctions via contaminated cattle carcasses in India and Pakistan (Cuthbert et al., 2016; Oaks et al., 2004). Likewise, antimicrobial resistance – an issue big enough to get its own awareness week (WHO, 2023) – is driven in part by antibiotic contamination in wastewater from dwellings, hospitals (Rodriguez-Mozaz et al., 2015) and manufacturing (Larsson et al., 2007; Lübbert et al., 2017).

A broad range of pharmaceuticals across many therapeutic classes have been identified as adversely affecting the behaviour (Brodin et al., 2013), growth (Yan et al., 2016), reproduction (Han et al., 2010) and survival of different wildlife (Fong and Ford, 2014; Świacka et al., 2023; Yan et al., 2016). However, the existence and availability of toxicity data and ERAs of pharmaceuticals remains extremely inconsistent, especially where older APIs are concerned (Ågerstrand et al., 2015). Consequently, moving from the characterisation of individual pharmaceuticals in the environmental to an understanding of global risks now and in the future remains difficult (Sumpter et al., 2022).

In 2012, pharmaceutical pollution researchers identified 20 key questions about the effects and risks pharmaceuticals in the environment (Boxall et al., 2012). Despite a great deal of work and research in the intervening decade (Maack et al., 2022), a considerable uncertainty remains (Sumpter et al., 2022), and progress on protecting the environment from pharmaceutical pollution has proven slow (Souza et al., 2021).

2.2 Environmental Risk Assessment of Pharmaceuticals

Principles of ERA

The concept of Risk, as used and understood in contemporary environmental protection, owes a lot to boats. The words origins may (sources differ) be traced back to the Ancient Greek *ῥίζα* (*rhíza*, “cliff”) in reference to the dangers of steering ships across rocky shores. The modern science of risk assessment developed under similar conditions, in the coffeehouses and underwriters of 17th century London, as insurers sought to understand and quantify the uncertain outcomes of their policies (Bernstein, 1996). In the intervening centuries, formalised risk assessment has developed and expanded, being applied to practically all processes with uncertain and potentially negative outcomes.

In its simplest form, traditional, risk assessment is the assessment of hazards – bad outcomes – and their probabilities, multiplying one by the other to obtain a single value for each outcome that can be compared (Equation 1, Figure 1). This format is ideal for comparing and managing the risk of discrete, obvious events with quantifiable impacts (such as a ship full of

pre-assessed trade goods sinking), but faces challenges when adapted to fuzzier, less quantifiable outcomes.

$$Risk = Hazard\ Magnitude\ \times P(Hazard) \qquad (Eq.\ 1)$$

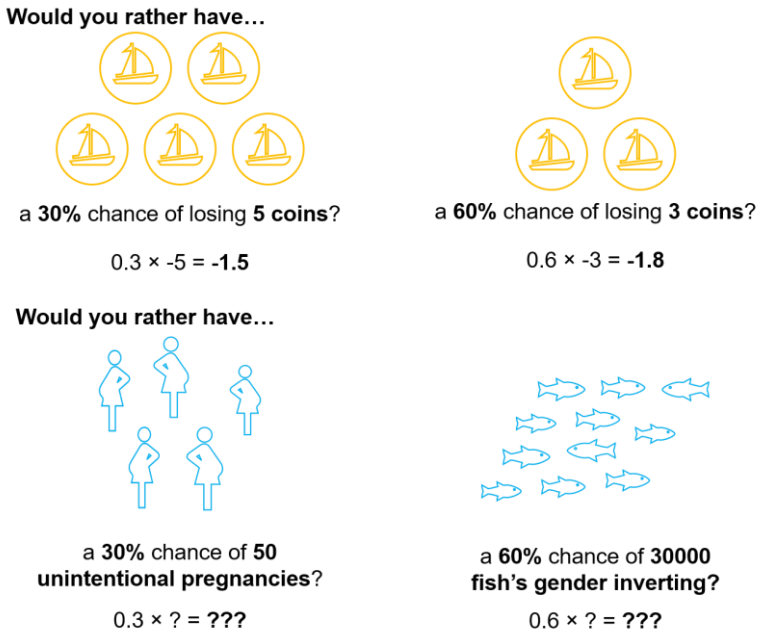

Figure 1: Comparing and ranking risks is trivial when adverse outcomes can be measured in directly comparable impacts. When endpoints are extremely different, ranking them is a more complicated and value-driven undertaking.

Environmental risk assessment itself grew from the field of occupational exposure, assessing toxicity from raw materials and pollutants in industrial workers (Ragas, 2011). Driven by the needs of resource extraction and manufacture, occupational hygiene committees set "threshold limits", concentrations of toxicants to which workers could be exposed daily and repeatedly without adverse effects (ACGIH, 2022). Over time, the concept percolated into public health, food sciences, and ecotoxicology, and thresholds were developed for a wide range of toxicants, media and protection endpoints (Ragas, 2011). The No Observed Adverse Effect Level (NOAEL) or No Observed Effect Concentration (NOEC), a dose or concentration below which adverse effects would not be expected to occur, became, and remains a central pillar of toxicological risk assessment.

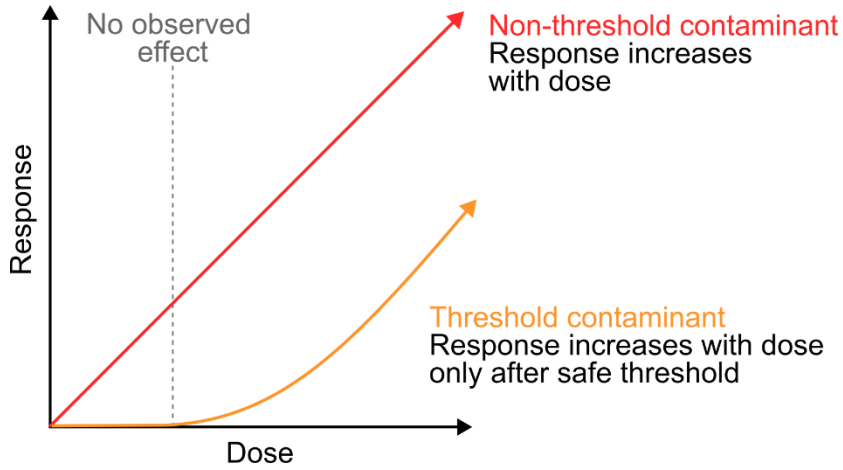

Figure 2: Diagram of dose-response relationships of theoretical non-threshold (red) and threshold (orange) contaminants. Below the no observed effect threshold contaminants produce no biological response. Adapted from Ragas (2011).

Simultaneously, it was recognised that not all stressors were subject to threshold effects (Figure 2). Certain stressors, such as genotoxins and ionising radiation, were hypothesised to have no safe threshold (Arora and Gardner, 1994), and parallel tracks of risk assessment were developed for these. The majority, however, were assessed under the dose threshold contaminant paradigm.

Extrapolating from limited, controlled lab toxicity tests – for instance, on rats – to derive a NOAEL protective of the broad and varied human population was not an easy task. Lehman and Fitzhugh (1954) proposed that a human dietary NOAEL should be set at 100 times the maximum safe dose in experimental animal studies. As the number's roundness implies, it was selected "not as an absolute yardstick", but to be "*high enough to reduce the hazard of food additives*", but "*low enough to allow the use of some chemicals which are necessary in food production*."

Regulatory environmental risk assessment (Figure 3) was first formalised and applied in the 1970s. This set of tools was developed by the newly-founded US Environmental Protection Agency (EPA), based on the concepts of human health risk assessment, to understand the impacts of proposed development and construction projects. In the 1980s, the EPA commissioned a set of ERA methods for synthetic fuels (Barnthouse et al., 1982) which were later generalised into a framework for use across the agency (Suter, 2008; US EPA, 1992).

In the European Union (EU) and European Economic Area (EEA), a framework for ERA was laid down in the Technical Guidance Document (TGD) on Risk Assessment (De Bruijn et al., 2002). The TGD lays out a process for assessing the exposure and potentially toxic effects of pollutants in a variety of environmental compartments, at a local and regional scale. The TGD was subsequently used to develop more specific risk assessment protocols for subsets of pollutants. In particular, the methods used in the TGD incorporate a safety factor or margin, known as an Assessment Factor (AF). Conceptually, AFs are variously also known as Safety Factor or Uncertainty Factors (Chapman et al., 1998), depending on geographical region and precise application.

According to the EU's technical guidance document on environmental risk assessment of biocidal products, AFs are intended to account for variation in and between laboratory toxicity studies, variation within and between species, extrapolation from short-term to long-

term studies and extrapolation from laboratories to impact in the field, possibly including interactive effects between pollutants (De Bruijn et al., 2002). Depending on the availability of data, especially long-term studies (i.e., NOEC vs Effective Concentration (EC_x)) and more sophisticated experimental ecosystems, lower assessment factors are used (Equation 2), increasing the Predicted No Effect Concentration (Table 1). Thus, in addition to accounting for uncertainty (including lack of knowledge), the AF provides a financial incentive for parties seeking authorisation to fund toxicity studies, as broader studies will reduce the AF and most likely the predicted risk.

$$PNEC = Lowest\ NOEC\ or\ EC50 \div AF \qquad \textit{(Eq. 2)}$$

PNEC: *Predicted No-Effect Concentration (g/L, prefixed as appropriate)*

NOEC: *No Observed (Adverse) Effect Concentration (g/L, prefixed as appropriate)*

EC50: *Effective Concentration 50% (g/L, prefixed as appropriate)*

AF: *Assessment Factor (unitless)*

Table 1: Summary of typical Assessment Factors used in the calculations of Predicted No Effect Concentrations (PNECs) for aquatic environments. Adapted from the EU Technical Guidance Document on Risk Assessment (De Bruijn et al., 2002)

Available Data	**AF**	**Comments**
At least one short-term LC50/EC50 for fish, *Daphnia*, and algae	1000	Can be lowered on a case-by-case basis, but not below 100
One long-term NOEC of fish or *Daphnia*	100	1000 if LC50/EC50 not *also* available from study
Two long term NOECs for two of fish/*Daphnia*/algae	50	Or LC50/EC50 ÷ 50, if lower than NOEC.
Three long term NOECs for fish, *Daphnia*, and algae	10	Normally fish, *Daphnia*, and algae, but if it can be demonstrated that the most sensitive species has been tested, its NOEC ÷ 50 can be used.
Species Sensitivity Distribution (SSD)	1 – 5 (Case-by-case)	Minimum 10 NOECs from 8 taxonomic groups.
Field Data, Mesocosms, or Model Ecosystems	Case-by-case	
Freshwater to Marine Extrapolation	(×10)	A separate set of AFs is used to calculate $PNEC_{marine}$ values, but a rule of thumb for extrapolation from only freshwater data is that the factor must be further multiplied by 10, to account for longer food chains and higher biodiversity in marine environments.

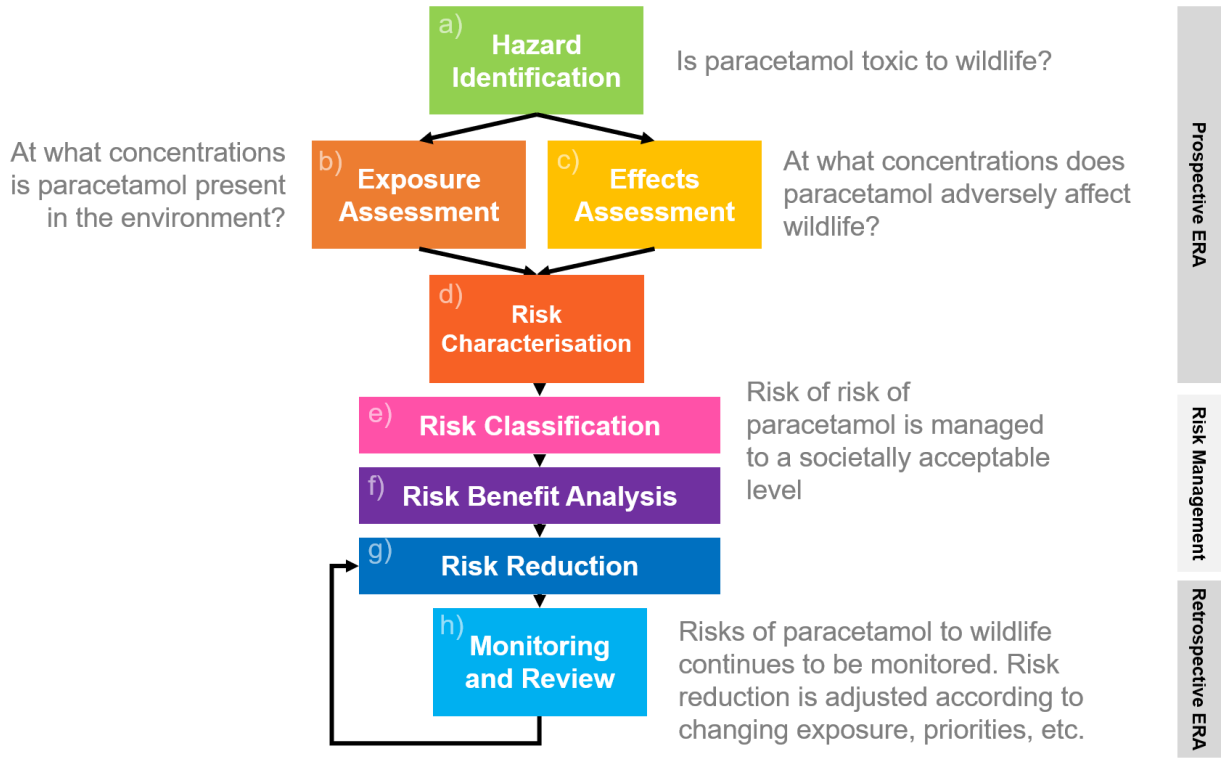

Figure 3: Environmental Risk Assessment's core paradigm, using paracetamol as an example. Prospective risk assessment (a-d) starts with an identified stressor (a), determines the levels wildlife are exposed to it (b) and the levels at which it has adverse effects (c), so that the risk can be characterised (d) and managed if beyond a societally acceptable level (e-g). Retrospective risk assessment (h) is typically carried out to aid risk management, by assessing risks to a given monitored ecosystem. Adapted from Leeuwen (2007).

Pharmaceutical ERA in the EU

Modern regulatory risk assessment runs along a continuum. Potentially toxic chemicals are typically first risk assessed *prospectively* to determine their impact on the environment (Figure 3a-g). They are then risk assessed *retrospectively* (Figure 3h) in specific ecosystems and/or media to determine if they pose an ongoing risk.

In the EU, prospective risk assessment of human pharmaceuticals is the responsibility of the European Medicines Agency (EMA) (and national equivalents) under the *Community code relating to medicinal products for human use* (European Parliament, 2001). Veterinary pharmaceutical prospective ERA guidelines are also regulated by the EMA under the Veterinary Medicines Product Regulation (European Parliament, 2019), in line with internationally harmonised procedures (VICH, 2004, 2000). In addition, the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) regulation requires any substance manufactured or imported into the EU annually in quantities greater than 1 tonne to undergo a separate risk assessment (European Parliament, 2006) (Figure 4).

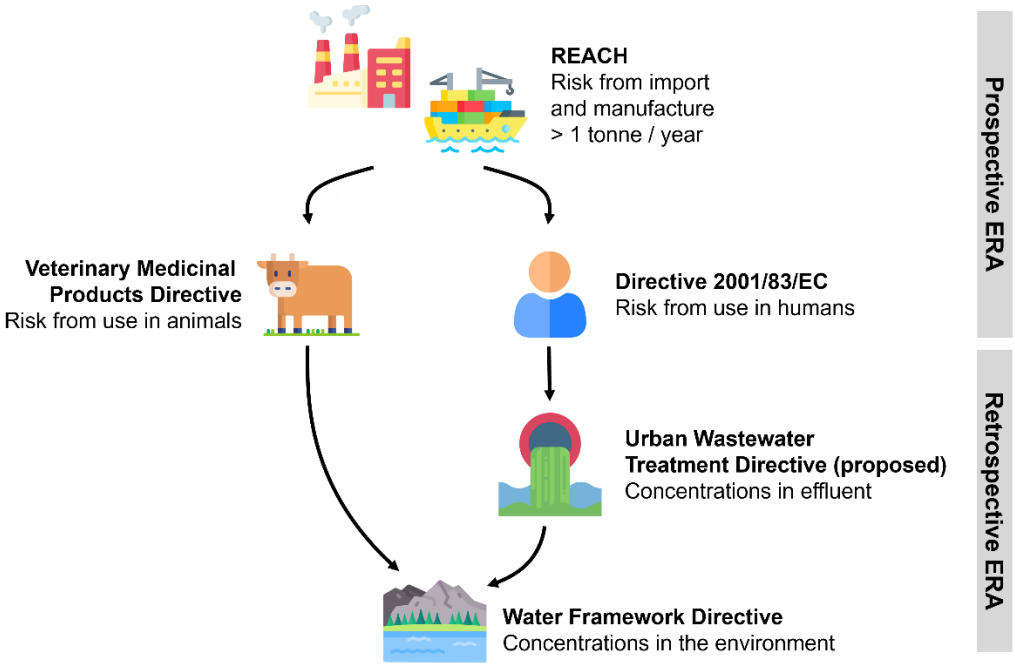

Figure 4: Points where a pharmaceutical may be prospectively or retrospectively environmentally risk assessed and relevant European Union literature. Icons courtesy of Freepik.

As a consequence of veterinary medicines' more recent legislation and the requirements of international harmonisation, its regulatory ERA requirements tend to be more up to date than human medicines'. Despite the EU's intention to revise human medicinal product legislation by 2022 (European Commission, 2021) and an accompanying draft proposal for the updating of ERA guidelines (EMA CHMP, 2018), this inequality remains at the time of writing. REACH, meanwhile, sets significantly more stringent requirements for the ERA of chemicals, and further bans import or manufacture of chemicals without a satisfactory ERA available – the so-called "no data, no market" requirement (ECHA, 2011).

Perhaps the most important difference between the two areas is the statement that "*Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions."*, found in the human medicine ERA guidelines (Ågerstrand et al., 2015; European Parliament, 2001). This means, in short that the outcome of human medicine ERA is largely advisory, and there is no requirement that retailer or regulator implement mitigation. By contrast, Fabrega and Carapeto (2020) identified in a recent study that under the previous veterinary medicinal regulations, 19 products triggered a referral for review due to a negative overall balance of risk to benefit, and two were even withdrawn from the market. Furthermore, veterinary antimicrobials are, as of the new legislation, required to consider environmental antimicrobial consequences in the overall risk-benefit analysis of a product (European Parliament, 2019).

Tiered ERA of Pharmaceuticals

European ERA of human and veterinary pharmaceuticals is built around a tiered system (called "*Phases*" in guideline documents) (Figure 5). Firstly, "exempt APIs" – those with APIs assumed to have no or negligible environmental impacts, such as vitamins, vaccines, and proteins, are excluded. Then, a prediction of exposure (Predicted Environmental Concentration, or PEC), is calculated from projected market share (using a default value of 1% of the population. This value is then compared to an exposure action limit of 0.01 µg/L.

Although nominally a conservative approach that assumes worst-case scenarios, if pharmaceuticals are used by more than 1% of the population, or if APIs have effects below 0.01 µg/L (Grung et al., 2008), this first step may be insufficiently protective (Gunnarsson et al., 2019).

APIs with no evidence of non-threshold effects that are below this limit are exempt from further assessment, while those above the limit are re-assessed with a less conservative model. Should an API (Active Pharmaceutical Ingredient, the ingredient of a drug responsible for its therapeutic effect) still show potentially high exposure, its effects and physico-chemical properties are quantified to determine its toxicity, persistence in the environment, and potential to bioaccumulate in biota.

Beyond toxicity, a substance's behaviour and fate in the environment, driven by its physico-chemical properties, may significantly affect its overall hazard profile. Persistent chemicals – those that are slowly degraded by biotic and abiotic processes – may pose chronic exposure risks to organisms. Bioaccumulative substances, which accumulate and/or biomagnify up the food web from producers to apex predators can also result in much higher organismal exposure to toxicants than might be expected simply by assessing concentrations in environmental compartments (Traas and Leeuwen, 2007). According to the TGD, substances that are persistent, bioaccumulative and toxic (PBT) cannot reliably have a safe concentration determined, and should be regulated accordingly (De Bruijn et al., 2002).

Within the human pharmaceutical ERA paradigm, substances are screened for potential Persistence, Bioaccumulation and Toxicity (PBT) by first determining the substance's hydrophilicity. A more hydrophobic substance – i.e., one with a greater affinity for lipids – is more likely to sorb to organic matter in the environment and accumulate in lipids, including living organisms. Should a substance have more than $10^{4.5}$ times more affinity for n-octanol than water (Log K_{ow} > 4.5), a PBT screening is triggered.

Substance persistence is generally determined as half-life (or halving time) in relevant media, under lab conditions. Persistence is a particularly worrying phenomena in pharmaceuticals, which are frequently designed to have therapeutic effects at low concentrations (Brodin et al., 2013), as this raises the possibility of chronic non-target exposure. Examples of persistent drugs include tetracycline antibiotics (Daghrir and Drogui, 2013) and endocrine disruptors such as ethinylestradiol (Miettinen and Khan, 2022; Porseryd et al., 2017). Substances that are rapidly broken down by biota and therefore not persistent are classed as "readily biodegradable", which typically corresponds to 60-70% breakdown of substance carbon within a 10-day window (OECD, 1992).

Bioaccumulation is assessed by the calculation of a Bioconcentration Factor (BCF), which can be predicted from Log K_{ow} values or determined experimentally using the ratio of pollutant in fish or mussel to water in an experimental study (De Bruijn et al., 2002). Bioaccumulation of a pharmaceutical in prey species can lead to exposure to high concentrations at high trophic levels ("biomagnification"), and where a BCF is sufficiently high (>500) exposure to predators via the food chain must be assessed (De Bruijn et al., 2002). In particular, veterinary product guidelines can also require an assessment of exposure to scavengers of treated livestock carcasses (EMA CVMP, 2018), and to dung-dwelling organisms via excretion (EMA CVMP, 2016a).

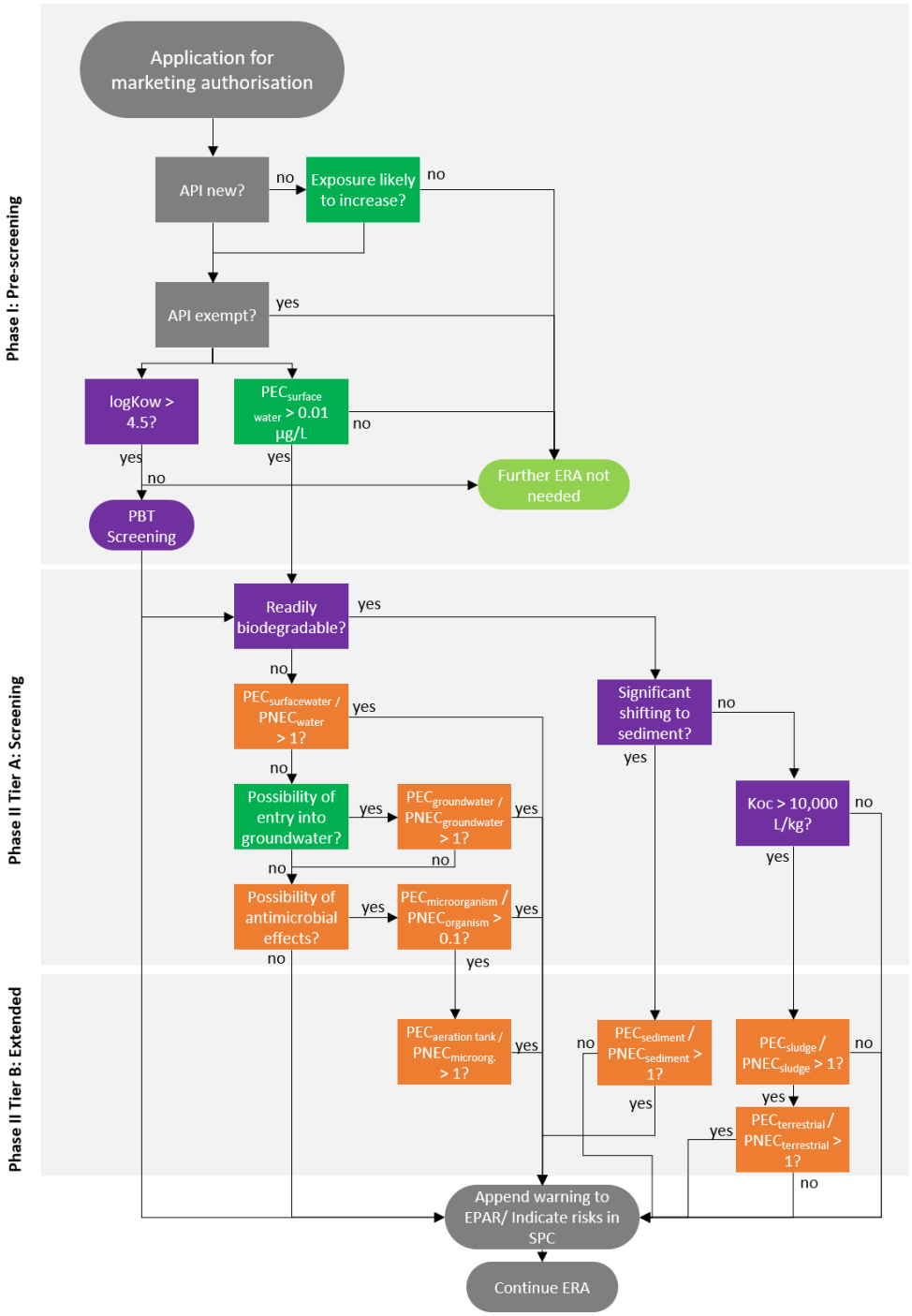

Figure 5: A diagram of the Environmental Risk Assessment Process from the EMA's guidelines on marketing authorisation for human pharmaceutical products. Modified from Welch et al. (2022b), originally after EMA CHMP (2006).

An assessment of the mobility of substances – their ability to move freely in the aquatic environment – is not yet part of any European ERA guidelines. However, the German Environment Agency (UBA) has identified that persistent, mobile and toxic substances (PMT) may not have their risk profile well assessed by only comparing exposure to effect thresholds (Berger et al., 2018). Based on this and earlier work, consideration of PMT and very persistent, very mobile (vPvM) properties has been announced for planned updates to both REACH and the Classification, Labelling and Packaging (CLP) regulation (Arp and

Hale, 2022). However, no requirement to assess mobility currently exists for either human or veterinary pharmaceutical products (EMA CHMP, 2006; EMA CVMP, 2016b).

PNECs are derived for a substance following the guidelines discussed earlier in this chapter. The earlier calculated PEC is then divided by this PNEC to give a unitless Risk Quotient (RQ) or Risk Characterisation Ratio (RCR) (Equation 3). RQs are designed, and often used, to rank the risk of substances driven by exposure/effect ratios, with the aim of, for instance, allowing the selection of less risky chemicals during risk management (Leeuwen, 2007). However, it is widely accepted that RQs provide no information on the actual magnitude or probability of risk occurring (Jager et al., 2001; Raimondo and Forbes, 2022).

$$RQ = \frac{MEC \text{ or } PEC}{PNEC} \qquad \textit{(Eq. 3)}$$

RQ:	*Risk Quotient (unitless)*	*MEC:*	*Measured Environmental Concentration (g/L, prefixed as appropriate)*
PEC:	*Predicted Environmental Concentration (g/L, prefixed as appropriate)*	*PNEC:*	*Predicted No-Effect Concentration (g/L, prefixed as appropriate)*

Retrospective risk assessment relevant to this thesis in the EU is instantiated by the Water Framework Directive (WFD), which regulates the chemical and environmental quality of surface and ground waters (European Parliament, 2014) and the Environmental Quality Standards Directive (EQSD) (European Parliament, 2008), which sets legal limits on certain substances under the WFD. A further potential future consideration is the proposed revision to the Urban Wastewater Treatment Directive (UWWTD), which would require an average removal rate of a panel of 12 easily treated or easily disposed of chemicals – including 10 pharmaceuticals – of 80% or higher in all plants treating the waste of 10,000 or more person-equivalents (European Commission, 2022a). However, the UWWTD update is currently in review, and it remains uncertain when and in what form it will come into force.

Under the WFD and EQSD, the European Commission is responsible for selecting a watchlist of pan-European priority substances, in addition to those selected for local monitoring by national authorities (European Commission, 2022b). This watchlist is subject to review at least every 4 years, and was last updated in 2022, where 25 new substances were added, including five pharmaceuticals (European Commission, 2022c). In addition, a list of high-priority pollutants was added via the daughter Directive on Priority Substances (European Commission, 2015), that requires states to act to progressively phase out the emission of said substances. The latest proposed update to the Priority Substances List includes nine pharmaceuticals, including the sex hormones estradiol, estrone and ethinylestradiol, the painkillers ibuprofen and diclofenac, an anti-convulsant, and a number of antibiotics (European Commission, 2022d).

Watchlist and Priority substances have Environmental Quality Standard (EQS) values compiled by groups of experts: AA-EQS, derived from chronic toxicity data, which sets an Annual Average threshold, and MAC-EQS, which sets a Maximum Allowable Concentration derived from acute toxicity data, based on the type of water body monitored (European Parliament, 2008). Where concentrations are found to be in excess of EQSs, there is a legal requirement that authorities consider actions to mitigate exposure of these substances to an

acceptable level, based on the type of water body monitored (European Commission, 2011; European Parliament, 2008).

Limitations of ERA

Under present conditions, the same chemical can be assessed multiple times by different groups depending on its manufacturing circumstances, application, and whether ERA is retrospective or prospective (Figure 4). This has been identified by scientists (Ågerstrand et al., 2015; van Dijk et al., 2021) and government as a key impediment to fair and effective ERA. The implementation of a "one substance, one assessment" system has been made a core research (Marx-Stoelting et al., 2023) and legislative priority in the EU (European Commission, 2020a). Recommendations have also been made that prediction of environmental effects be more informed by knowledge of clinical effects in humans, especially where targeted receptors are shared between humans and, for example, fish (Gunnarsson et al., 2019)

A further issue that regulatory ERA has yet to conclusively tackle is the interaction of multiple stressors, including chemicals. The recognition that stressors can interact to product unexpected effects is not a new one (Bliss, 1939; Loewe and Muischnek, 1926), but environmental study of the phenomena has exploded in the last few decades, along with the numbers of terms used to describe the phenomena, across the loose boundaries of ecology and ecotoxicology (Orr et al., 2020).

Though an in-depth discussion of multiple stressors and mixture toxicity is beyond the scope of this work, it has been demonstrated that safe concentration limits set by the EU do not protect against mixture effects (Backhaus et al., 2000; Carvalho et al., 2014). The introduction of the Plant Protection Products Regulation (European Parliament, 2009) and Biocidal Products Regulation (ECHA, 2017) include provisions for the assessment of cumulative and synergistic effects, and EU's Chemicals Strategy contains a commitment that the European Commission will introduce a mixture assessment factor to REACH and introduce combination effect provisions in "other relevant legislation" (European Commission, 2020b). However, no requirement to assess mixture toxicity has yet entered pharmaceutical ERA despite the considerable overlap in mode of action in many therapeutic classes (Backhaus, 2014).

Regulatory ERA's treatment of uncertainty, a crucial aspect due to limited data availability, has also attracted scientific criticism (European Commission, 2017; Raimondo and Forbes, 2022; Verdonck et al., 2007). As a tool for policy decisions, it is important that ERA is able to treat risk in as objective a manner as possible (Verdonck et al., 2007). Uncertainty, though an intrinsic part of risk assessment, is often treated in a less transparent fashion through the use of thresholds and assessment factors.

In the field of risk assessment, uncertainty is often broken down into two types: variability, or aleatory uncertainty and epistemic uncertainty, or incompleteness (Figure 6) (Sahlin et al., 2021). Uncertainty can also exist as indeterminacy between how factors relate, and ambiguity, where certainties contradict each other (European Commission, 2017).

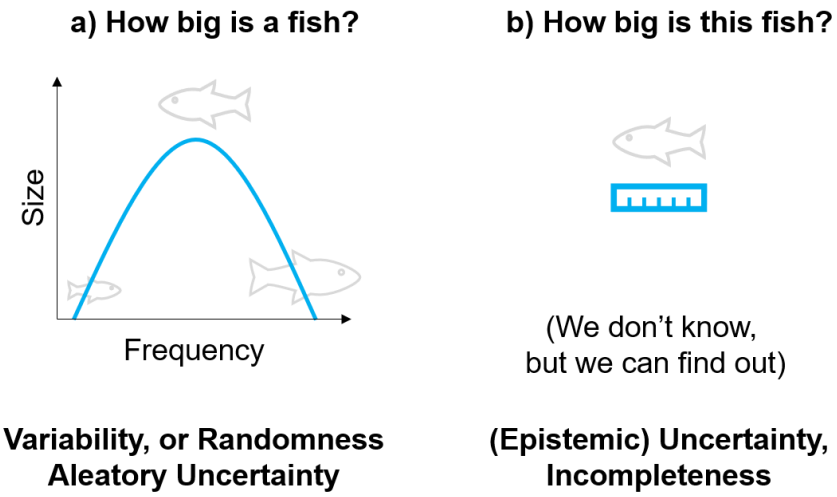

Figure 6: Uncertainty can be broadly divided into two types: a) things that we can only know to a probabilistic degree, and b) things we can directly measure, but haven't. Both types of uncertainty are important when assessing risks, but are at times combined in communication of risk.

Criticisms of how uncertainty in ERA relate principally to its lack of visibility, and its failure to consider "*all sources of uncertainty*" – covering known unknowns (variability) rather than unknown unknowns (epistemic uncertainty) (Verdonck et al., 2007). Many pollutant ERAs – and those of pharmaceuticals in particular – fail to transparently analyse the sources of uncertainty in their assessments (Verdonck et al., 2007).

Probabilistic approaches have long been recommended for the better consideration, analysis and reporting of uncertainty, but are yet to see widespread inclusion in ERA (Jager et al., 2001; Moe et al., 2022). Probabilistic approaches to ERA explicitly incorporate the probabilities of outcomes, rather than reducing uncertainty to thresholds, assessment factors and worst-case scenarios (Maertens et al., 2022). For instance, rather than assuming a worst case of pharmaceutical exposure and effects, probabilistic approaches would use the full distribution of these values to predict a probability distribution of possible risk (Mentzel et al., 2022a).

2.3 Norway: A Case Study of Pharmaceutical Pollution

Geography, Economy, and Legislation

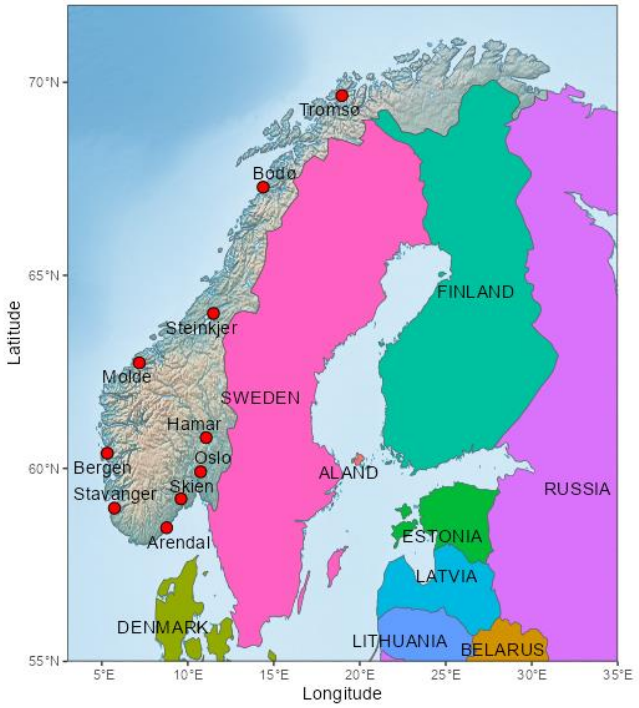

Figure 7: A map of mainland Norway and its county capitals. Data: Natural Earth and Simplemaps.com.

Sparsely populated, oil rich, highly developed, and cold, Norway encompasses the mountainous west coast of the Scandinavian peninsula, stretching 1770 km from Agder in the south to Finnmark in the far North-East of the country (Figure 7). Norway's population was estimated as 5.43 million at the start of 2022, roughly half of which live in Østlandet, the lower, South-Eastern region of the country. Norway's most populous city is Oslo, population 1.04 million. Norway's population density is comparatively low at 17 people per km^2, making it, next to Iceland and Finland, one of the least densely populated nations in Europe (Worldometer, 2023).

Norway is a prosperous country by global and Western standards, 13th in the world for real GDP per capita (CIA, 2020), with an economy based largely on services (65%) and industry (34%), of which 12% is oil exports. Norway's population have voted against joining the European Union in referenda in 1972 and 1994, but Norway is a member of the European Economic Area (EEA) and European Free Trade Association (EFTA), and a part of the European single market.

All major pharmaceutical companies are represented in Norway, but manufacturing facilities in-country are limited, and the export of pharmaceuticals represents a small part of the national economy (Weise et al., 2018). Norway is a net importer of pharmaceutical products – in 2020, it exported $1.08 billion and imported $2.13 billion's worth (OEC, 2020), although the nation's per capita spending on pharmaceuticals is below the European mean at $470

(OECD, 2021), driven in part by strong government control over the setting of prices (Norwegian Medicines Agency, 2022).

Norway's environmental policy is set by its government, but the terms of its membership of the EEA require regulatory harmonisation with the EU on non-agricultural and non-fishery environmental policies (EFTA, n.d.). Norway is consequently subject to a number of European directives regulating pollution and environmental quality, which are implemented into Norwegian law by national legislation (Table 2).

Table 2: Norwegian implementation of EU directives relevant to pharmaceuticals in the environment. (Lovdata, 2023)

European Directive	**Norwegian Legislation**	**Scope**
Water Framework Directive	**Vannforskriften (2007)** "Water Resources Act"	Retrospective risk assessment-based monitoring of water, biota, pollutants
Urban Waste Water Directive	**Forurensingsforskriften (2004)** "Pollution Act"	Polluted material, wastewater treatment
REACH	**REACH-forskriften (2008)** «REACH Act»	Production and use of chemicals above a defined annual tonnage
Directive 2001/83/EC	**Legemiddelforskriften (2010)** «Medications Act»	Risk assessment of pharmaceuticals for human use
Veterinary Medicines Product Regulation	**Forskrift om legemidler til dyr (2022)** «Animal Medications Act»	Risk assessment of pharmaceuticals for veterinary use

Norway is, in the words of the OECD, an "*environmental frontrunner*", with good air and water quality, advanced low-carbon energy, and extensive investment in green research and development. However, the same report also criticises its aging and often non-compliant wastewater treatment system, high material consumption, and limited protection of natural areas ("Norway's environmental performance," 2022; OECD, 2022).

Norway's economic strength supports a high standard of living for the majority of its citizens in the Nordic Welfare Model, with an extensive welfare state and access to universal healthcare. As part of this system, the Norwegian government collects extensive data on social, population, environmental, and medical statistics, including sales of medications. Available datasets stretch back far into the 20th century (Nordic Statistics, 2022; Sommerschild et al., 2021b; Welch et al., 2022b), and are made relatively openly available to researchers, providing a valuable case study for assessing the interactions between human populations and pharmaceutical pollution.

Likewise, well-characterised potential scenarios of future national demographics and are valuable for bounding uncertainty over how the world and its people will develop in the future (Duinker and Greig, 2007). Norway's relatively well-characterised existing scenarios provide, then, a useful resource for forecasting risk in various possible futures.

Demographics and Development

Norway's Statistics office (SSB) predicts the country's population will probably rise to over 5.9 million by 2050 and 6.2 million by 2100, driven mainly by positive net migration. Estimates are presented as three possible scenarios for population growth. The most plausible is "main alternative" (MMM), based on plausible assumptions for fertility, life expectancy and immigration. Two further scenarios, high growth (HHH) and low growth (LLL), are unlikely but provide a deterministic bounding of the uncertainty intrinsic in these projections (Thomas and Tømmerås, 2022). Historic pharmaceutical consumption and forecasting studies figures have shown growth in consumption of selected pharmaceuticals is likely to exceed population growth (Van Boeckel et al., 2014; van der Aa and Kommer, 2010), but population growth remains an important driver of consumption.

Likewise, the number of elderly people (>70 years old) in Norway is expected to almost double by 2060, exceeding 25% of the total by 2100. An ageing population is likely to present more health issues and therefore consume more pharmaceuticals. van der Aa and Kommer (2010) in the Netherlands and Tränckner and Koegst (2010) in Germany predicted significant growths in API consumption and subsequent emission exposure due to population aging. Similarly, measured growth in consumption of prescription pharmaceuticals in Norway has been linked to an ageing population (Norwegian Pharmacy Association, 2023), so it seems likely future demographic change will drive *some* increase in overall consumption of pharmaceuticals. However, given the multi-dimensionality of population demographic structures, and the types and quantities of pharmaceuticals consumed by people of different ages and genders, relating consumption directly to demographics was omitted from this work (Welch et al., 2023).

86% of Norway's population is served by wastewater treatment plants (WWTPs) (SSB, 2021), but the sophistication of treatment techniques follows a clear gradient between the urbanised south-east and rural areas in the west and north of the country. Cities generally have a number of more advanced plants, employing sequential mechanical, chemical and biological treatment to remove pollutants, but more rural areas use a simple mechanical filtration approach, partly due to concerns over efficacity in lower temperatures. 70% of total Norwegian WWTP capacity is discharged to fjords and the ocean via undersea pipes, where it is expected strong dilution will mitigate the risks of environmental impact; inland, however, a number of WWTPs discharge to rivers (Berge and Sæther, 2020).

No study assessing the potential impacts of the new, recast Urban Wastewater Treatment Directive on Norway has yet been published. However, the proposal has been criticised by European water industry groups as potentially unrealistic, and placing excessive focus on "end of pipe" removal rather than tackling the source of the issue (EurEau, 2023). What the eventual revision will require, and the extent to which it will be complied with in Norway are yet uncertain, but it seems probable that investment in treatment will continue and removal of pollutants will increase, albeit unevenly.

Norway's development, climate, regulations, population demographics and minimal pharmaceutical manufacturing infrastructure limit its exposure to the extremely high environmental concentrations of APIs seen in some other nations (Welch et al., 2022b; Wilkinson et al., 2022). Likewise, Norway is among the countries least vulnerable to climate impacts and toxic pollution risk (Bouzas-Monroy et al., 2022; Marcantonio et al., 2021; Welch et al., 2022b). Although the need for adaptation and mitigation in Norway should not be understated, it can also provide a valuable test-case for environmental studies, thanks to its

developed environmental regulatory apparatus and high-quality open access governmental data (Norwegian Digitalisation Agency, 2022). As a developed nation with strong environmental regulation, Norway exports its environmental risks in some sectors to poorer nations (Abbasi et al., 2020). It is then only fair that Norway also export best practice in risk assessment.

2.4 Pharmaceuticals Pollution, from the Present to 2050

The Future of Pharmaceutical Risk

The 21st century presents a series of unprecedented risks to human society (IPBES, 2019). Global environmental change (GCC) – chiefly climate change – is not a herald of the apocalypse. Nor, however, is it something we can just ignore. GGC's consequences will be – and are currently being – felt around the world, across the anthroposphere and ecosphere. According to Persson et al.'s (2022) reassessment of the boundaries of safe human exploitation of the planet (Steffen et al., 2015), novel entities – including chemical pollutants such as pharmaceuticals – are now outside the planet's safe operating space. How the transgression of this boundary will interact with increasing risk to other aspects of the environment is a critical but deeply uncertain issue.

Pharmaceuticals in the environment – as a subset of the "novel entities" boundary – represent a fairly small portion of mankind's overall impact on the environment (Persson et al., 2022; Steffen et al., 2015), but their effects – and their interactions with other biotic, abiotic and anthropogenic factors – are an important part of the risk profile faced by the earth's ecosystems and wildlife (Côté et al., 2016; Reid et al., 2019). A full consideration is beyond the scope of this work, but a broad summary of potential effects, their drives, and possible outcomes relevant to pharmaceutical pollution is presented below (Table 3).

To forecast the conditions that will drive future environmental risk, climate change researchers developed extensive scenarios that bound the likely development of global warming (IPCC, 2022, 2008; van Vuuren et al., 2012). Scenarios have subsequently been extended to cover socio-economic development (O'Neill et al., 2017), chemical emissions (Desrousseaux et al., 2022; Nagesh et al., 2022) and to the local Scandinavian scale (Pilli-Sihvola et al., 2015), to name but a few.

Table 3: Table of potential drivers of change in pharmaceutical risk in the future, adapted from Bunke et al. (2019).

Driver	Effect	Possible Outcomes
Climate Change	Temperature stress	Increasing stress may drive higher toxicity, increase incidence of health issues and drug consumption in humans
	Ocean acidification	Ocean acidification may be additive/synergistic stressor
	Water scarcity	Lower access to water may decrease dilution of APIs raising exposure, and increase health issues
	More extreme weather events	Extreme weather may cause larger pulses in API exposure, damage infrastructure, increase health issues
	Migration of diseases	Changes in climate envelope of pathogens and vectors (e.g., malaria and mosquitos) may drive increases in use of relevant APIs
	Changes in chemical fate	Increases in temperatures and solar radiation may speed breakdown and metabolism of APIs into less or more harmful chemicals

Demographics	Population ageing	An ageing population will use, on average, more APIs, although consumption of other APIs may decrease
	Population growth	A growing population will use more APIs
	Population health	Worse health, driven by other factors, may drive consumption of APIs
	Urbanisation	Urbanisation may increase access to WWTPs but will also concentrate API emission into smaller areas. More ground sealing will increase flooding and remobilisation of APIs.
	Increased food demand	Increasing food demand from population growth may drive an increase in veterinary and agricultural API use.
Economic	Improved access to APIs	Growth of the welfare state, cheaper APIs, or growing wealth of segments of the population may increase API consumption.
	Offshoring of manufacturing	Offshoring of API manufacture to regions with cheaper costs and less effective regulation may increase manufacturing emission to the environment.
Development	Better WWT technology	Better WWT technology may increase removal of APIs in treatment plants.
	Better manufacturing technology	Better manufacturing technologies may reduce wastage and emission during API production
	Substitution of problematic APIs	APIs may be substituted for similar APIs with lower environmental impacts
	Development of new APIs	New APIs may be developed for existing or new applications, with different toxicity profiles.
	Better drug destruction	Replacement of landfill of pharmaceutical waste with incineration may decrease emission
Societal	Changes in societal values	Changes in societal value of health, the environment, etc. may drive use of APIs and mitigation work
	Legislative changes	Changes in legislation may affect any part of the source-to-outcome pathway
	Development of/education on drug disposal pathways	Better drug disposal pathways, and public education thereof, may reduce emission of APIs to the environment
Environment	Changes in levels of other pollutants	Through mixture effects, increasing/decreasing levels of other pollutants will affect indirect pharmaceutical toxicity
	Other ecosystem stressors	Ecosystem collapse, changes in land use, etc.

In general, however, the potential for these effects to influence the overall pharmaceutical risk landscape introduces a many-dimensional aspect to any assessment. In such a context, where many uncertainties are interacting, the ability to quantify them is more important than ever (Maertens et al., 2022). Probabilistic risk assessment provides that facility.

Bayesian Networks for Environmental Risk Assessment

Thomas Bayes (1701 – 1761) never lived to see a field of statistics take on his name. *Bayesian probability* is built around the practice of interpreting probability as a degree of confidence in an outcome, rather than a random frequency. This systemisation and transparent display of uncertainty has many potential applications in ERA, a pragmatic discipline that relies on an element subjective judgement of probabilities and hazards.

Bayes' most famous contribution to statistics is Bayes' theorem (sometimes law, or rule), which states that the conditional probability of an event A occurring given that B is true (the posterior probability) is equal to the conditional probability of B occurring given that A is true, multiplied by the probability of A occurring, divided by the probability of B occurring (Equation 4).

$$P(\mathrm{A}|\mathrm{B}) = \frac{P(B|A) \times P(A)}{P(B)} \qquad \textit{(Eq. 4)}$$

A: *An event.*

B: *A different event.*

P(): *The probability of a given event or events occurring*

$A \mid B$: *An event conditional on an earlier event.*

In the 1980s, the computer scientist Judea Pearl developed the Bayesian network (BN). Bayesian networks (Figure 8), also known as Bayesian belief networks, are a graphical representation of the probabilistic relationships between variables that allowed the probability of a set of variables to affect the probabilities of the remaining sets (Pearl, 1985). Technically described, a BN is a *directed acyclic graph* (DAG), that is, a graph where nodes (sometimes vertices) are connected by edges (or arcs) representing directional relationships. *Acyclic* refers to the fact that a Bayesian network cannot contain any directed closed loops.

The relationships between nodes are described by Conditional Probability Tables (CPTs), that set the probabilities of each state of a child node (here Node 2) depending on the state of its parent nodes (here only Node 1). CPTs can be constructed based on expert input, generated following an equation, or fitted to data.

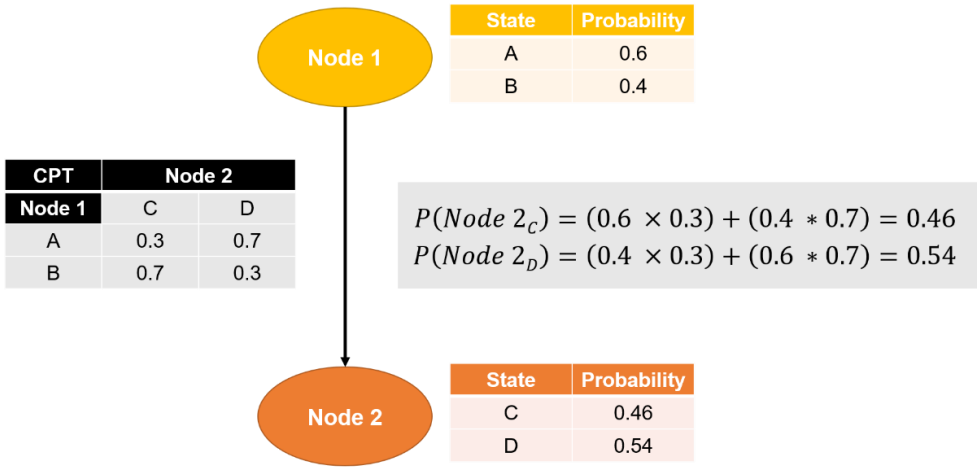

Figure 8: A diagram of a simple Bayesian network, consisting of two nodes linked by an edge representing a conditional probability distribution. The Conditional Probability Table (CPT) gives the probabilities of each state of Node 2, given the state of Node 1. When the network is compiled, the probability of each state of Node 2 is calculated based on the CPT and the probability distribution of Node 1.

Bayesian networks' applications in the assessment of environmental risk were, according to a recent review (Kaikkonen et al., 2021), first exploited in 2007 for the assessment of risks to freshwater fish (Pollino et al., 2007). Although BNs have seen some case-by-case in ERA in the US (Johns et al., 2017; Landis et al., 2017a, 2017b; Mitchell et al., 2021), they have yet to become more broadly accepted by regulators (Kaikkonen et al., 2021). Today, Bayesian

network approaches represent a considerable fraction of implementations of probabilistic environmental risk assessment (Maertens et al., 2022).

Bayesian networks present a number of methodological advantages which predispose them to use in ERA. As probabilistic representations of the possible states of different variables, they are intrinsically well-equipped to deal with variability, and force the user to make explicit decisions about how uncertainty will be quantified in the model (Hart and Pollino, 2008). Likewise, BNs are well-equipped to handle uneven data availability (Hamilton and Pollino, 2012) as is frequently an issue in pharmaceutical ERA (Ågerstrand et al., 2015), and can incorporate expert opinions where empirical data is not available (Pitchforth and Mengersen, 2013).

Bayesian networks may also improve on a tradition of threshold-based interpretation of environmental risk assessment. Although used throughout ERA – including in this thesis – the use of a risk score or quotient representing the exceedance of a threshold concentration, rather than ecotoxicological assessment endpoints and cause-effect relationships has often been criticised (Landis and Chapman, 2011; Mentzel et al., 2022a). Where data is available BNs can be integrated with more developed ecotoxicological approaches, such as Species Sensitivity Distributions (SSDs) (Wepener and O'Brien, 2022). Better integration of these richer datasets and better-defined relationships may also allow more nuanced retrospective assessment of risk based on site and species vulnerability (Andres, S. et al., 2022). This could avoid the current one-out, all-out approach to classifying the chemical quality of water bodies under the WFD. Such an approach classifies a water body with high levels of one pollutant as a body with higher levels of many pollutants (Loga and Przeździecki, 2021) – i.e., as "*not good*". This has been criticised for creating a "perverse incentive" (Water UK, 2014) for managers to avoid mitigating individual risks, as doing so will not stop a body from "failing" (Latinopoulos et al., 2021).

The advantages of BNs in considering multiple stressors and endpoints have also been highlighted (Landis, 2021; Sperotto et al., 2017), well-suiting them to the multi-scenario, multi-stressor approach envisioned by the ECORISK 2050 project (Welch et al., 2022a).

Bayesian networks applications to environmental issues, including risk assessment, have however identified some limitations. Bayesian network design is vulnerable to a number of quandaries (Marcot, 2017), including high sensitivity to state discretisation.

Bayesian networks are also limited by an inability to represent cyclic phenomena or dynamic relationships (Hamilton and Pollino, 2012). However, some techniques have been developed to bypass this issue, such as the use of Object-Oriented Bayesian Networks (OOBNs) for iterating a value by using multiple linked instances of the same BN to represent slices of time (Korb and Nicholson, 2010).

Although Bayesian networks can be an extremely intuitive way to communicate causal relationships between different environment variables with uncertainty (Sperotto et al., 2017), ERA stakeholders have previously communicated that in order for BNs to receive more acceptance, they must model ERA using a framework similar to what assessors are already familiar with, and produce outputs that can be easily compared to deterministic methods (EUFRAM, 2006).

The application of BNs to pharmaceutical ERA has so far been limited. To the authors' knowledge, only one BN has to date been developed assessing the issue. Brandmayr *et al.* (2015) address emissions of metformin (a common anti-diabetes drug) and metoprolol (a common beta blocker) in Germany under a detailed range of health and prescription scenarios. This suggests that pharmaceutical ERA could be fertile territory for the further development of BNs, particularly if lessons learned from their use in other fields can be incorporated.

3. Data and Methods

Papers I-III represent a workflow for the processing and analysis of data to support the characterisation of environmental risk posed by pharmaceuticals to the environment (Figure 9). In Paper I, a method is developed for calculating PECs for roughly 800 APIs. In Paper II, these PECs are matched with toxicity and physico-chemical property data, allowing for ranking, comparison with MECs, and the assessment of the inclusion of wholesale and veterinary sales compared to OTC and human medications only. Finally, in Paper III, a probabilistic method is developed for the assessment of risk of six high-priority APIs selected from Paper III. The effects of various scenarios are compared, using individual API RQ, as well as summed RQ and joint probability of any API RQ exceeding a given threshold.

3.1 Statistical and Graphical Software

The calculation of API sales weights from product wholesales was conducted in Microsoft Access. With this exception, data processing, cleaning, visualization, GIS, and deterministic statistics were conducted in the programming language R. Adobe Illustrator, Inkscape, and Microsoft PowerPoint were also used in the creation of graphics.

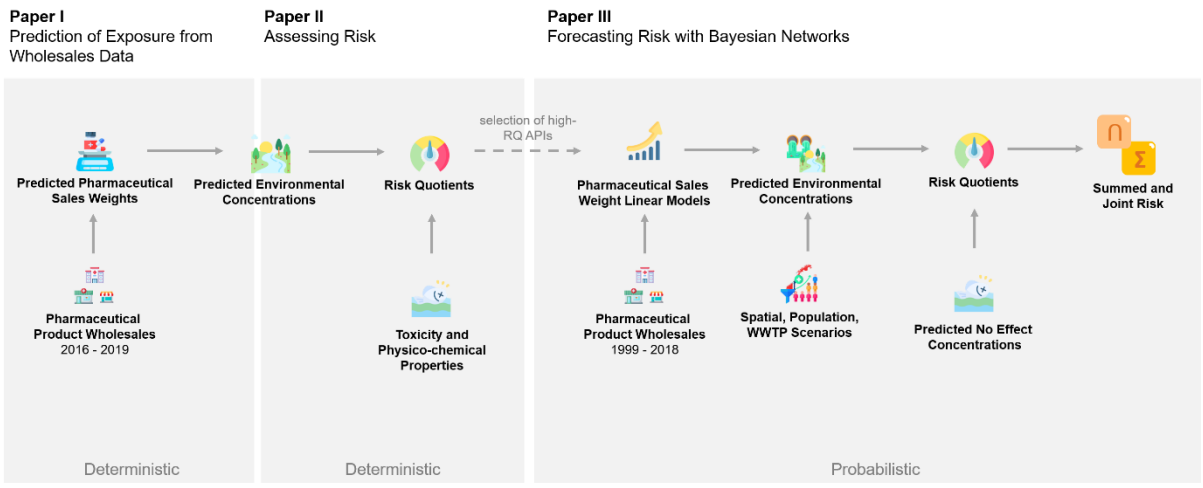

Figure 9: Graphic summary of data and methods used across Papers I - III. Icons courtesy of Freepik.

3.2 Prediction of Exposure from Wholesales Data (Paper I)

The keystone of this thesis is the Norwegian Institute of Public Health's Drug Wholesales Statistics Database (DWSD), a dataset of the retail of pharmaceutical products to pharmacies, merchants, hospitals, and other medical institutions collected since the 1970s (NIPH, 2019). Although similar pharmaceutical datasets are available across Europe, Norway's is relatively unusual in its extensive history and coverage of not only prescription but also over-the-counter (OTC) and veterinary products (Ballarín et al., 2015). Conversely, by comparison to

Europe's larger nations, publicly available data on levels of pharmaceuticals in the environment is limited (Welch et al., 2022c), making sales-based approaches to prediction appealing as a cost-effective adjunct to analytical chemistry studies.

In Paper I, we lay out the methods for predicting environmental concentrations of approximately 800 APIs from Norwegian pharmaceutical wholesales weights between 2016 and 2019 (Figure 10) (Welch et al., 2022c), based on methods developed by Grung et al. (2008). We further compare the resulting wholesales weights and PECs to other literature on the study area to evaluate the agreement between the datasets.

Starting with a dataset of all medicinal products sold in the period, products were first associated with APIs. APIs not of environmental concern (e.g., vitamins, vaccines) were omitted, as were gasses and products with extremely low wholesales. Product API weights were matched from databases or manually determined from documentation online. Product API weight was then multiplied by the quantity of a given product sold to obtain a weight sold per API, per year. Next, the sales weight is multiplied by (1 – WWTP Removal). In the case of this work, no removal from treatment was assumed.

The effective dilution of this weight of APIs in the aquatic environment was calculated by determining the total yearly wastewater production for the population of the studied area (in this case, the whole of Norway). As PECs were calculated on a national basis, per year, 365 days and Norway's population in the given year were used in the denominator. The denominator was also multiplied by a default dilution factor of 10, corresponding to a 1-in-10 dilution of wastewater entering the environment. Solving this equation gave a Predicted Environmental Concentration of each API in the Norwegian surface water environment (Welch et al., 2022c).

$$PEC_{sw} = \frac{API\ sold\ per\ year \times (1 - WWTP\ Removal)}{365 \times Wastewater\ production \times Population \times Dilution\ factor} \qquad \textit{(Eq. 5)}$$

PEC_{sw}: Predicted Environmental Concentration in surface water (g/L, prefixed as appropriate)

API sold per year: Weight of API sold in one year

365: Days in one year

Population: Population of studied area

WWTP Removal: Removal of API in WWTPs. Default 0

Wastewater production: Wastewater produced per person, per day (L)

Dilution factor: Dilution of wastewater upon entering environment. Default 10

Trends in calculated wholesales weights were examined to detect any extreme changes (any year's wholesales weight greater or smaller than 10 times the mean) in order to internally assess our calculations. PECs or wholesales weights, depending on data availability, were compared with similar figures from Felleskatalogen, Grung's 2005 data, and wholesales of products published in NIPH reports (Felleskatalogen, 2022; Grung et al., 2008; Sakshaug et al., 2018, 2013; Sommerschild et al., 2021a). Finally, the dataset of pharmaceutical PECs was made available via an online repository (Welch et al., 2022c).

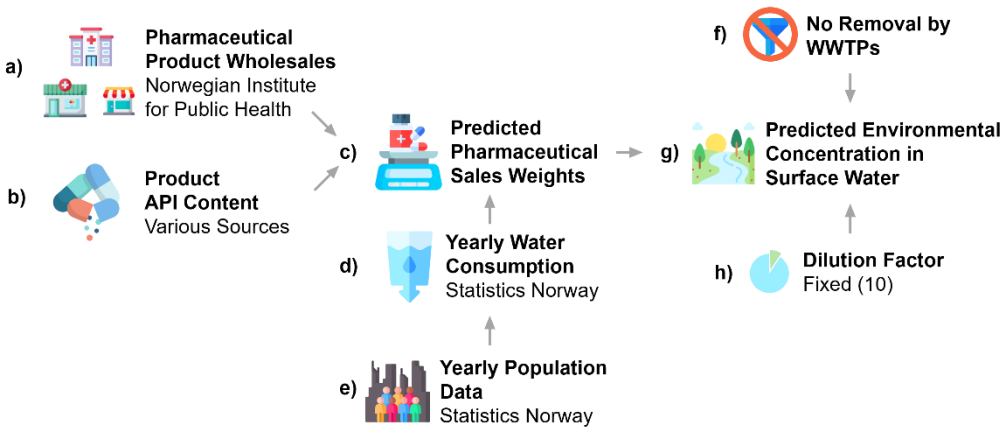

Figure 10: Conceptual diagram of Paper I data sources, workflow and calculation of Predicted Environmental Concentration in surface water. Pharmaceutical produce wholesales (a) are combined with information on product (a) content to (c) predict sales weights. Sales weights are then combined with population (e) – derived yearly water consumption (d) to calculated Predicted Environmental Concentrations in Surface Water (g, Equation 5), assuming no removal by WWTPs (f) and a fixed dilution factor of 10 (h). Icons courtesy of Freepik.

3.3 Assessing Risk (Paper II)

Paper II's estimated PECs were subsequently used to characterise environmental risks posed by the roughly 208 of the roughly 800 non-exempt APIs to the Norwegian freshwater environment (Figure 11). Adapting the regulatory guidelines for API environmental risk assessment in the EU (EMA CHMP, 2006), Risk Quotients were calculated for roughly 200 APIs with publicly available toxicity data (PNECs) sourced from FASS, AstraZeneca and the Joint Research Centre (AstraZeneca, 2017; FASS, 2019; Loos et al., 2018). Likewise, public data on persistence, bioaccumulation, and mobility (experimental if available, otherwise QSAR) was appended to APIs, and the potential for hazard via these properties assessed. Risk Quotients were also calculated with QSAR PNECs from the NORMAN database (provide reference to wen page), but these were not used further in the work due to substantial disagreement between predicted and experimental values.

PECs were compared with publicly available Measured Environmental Concentrations (MECs) compiled by the German Environmental Agency (UBA)'s *Pharmaceuticals in the environment* database (Graumnitz and Jungmann, 2021), to validate predictions against measured values, and detect any overall trends.

PNECs were compiled from the Norwegian Pharmaceutical Specialties website (Felleskatalogen, 2022), AstraZeneca's public environmental data (AstraZeneca, 2017), and the EU's Joint Research Centre (Loos et al., 2018), and used to calculate RQs for the roughly 25% of substances with both an available PEC and PNEC. Computationally modelled PNECs from the NORMAN Lowest PNEC database were also used to calculate an alternative set of RQs (Aalizadeh et al., 2017; NORMAN, 2022). These Provisional PNECs (P-PNECs) were compared to experimental PNECs by calculating Pearson's R (correlation coefficient) and Spearman's rho (rank correlation coefficient).

Persistence and bioaccumulation hazard statements ("low/moderate/high/data deficient") from FASS were also appended to APIs and used to compare their potential hazard driven by factors other than toxicity. Quantitative Structure-Activity Relationship (QSAR) predictions

of persistence, bioaccumulation and mobility were also derived using OPERA (Open (Quantitative) Structure-activity/property Relationship App) where hazard statements were unavailable (EPA, 2018).

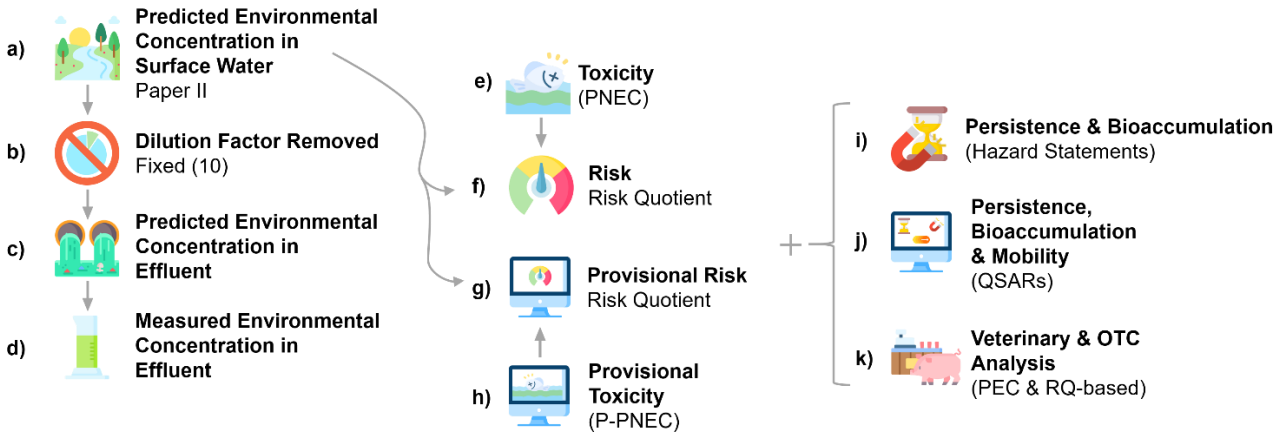

Figure 11: Diagram of workflow, output, calculation of Risk Quotient and Provisional Risk Quotient, additional analyses, and data sources of Paper II. Predicted Environmental Concentrations (PECs) in Surface Water (a) from Paper I are first, with their dilution factor removed (b) to produce PECs in effluent (c), compared with Measured Environmental Concentration data for effluent (d). Then, experimental (e) and provisional (h) toxicity data is used to calculate Risk Quotients (f) and provisional Risk Quotients (g). Subsequently, Risk Quotients are matched with experimental (i) and predicted (j) information on physico-chemical properties to determine an overall risk and hazard profile. Finally, Risk Quotients and Surface Water PECs are compared with and without the addition of veterinary and Over-the-counter (OTC) sales to determine the effects of their inclusion. Icons courtesy of Freepik.

3.4 Forecasting Risk with Bayesian Networks (Paper III)

In order to develop a probabilistic approach to pharmaceutical environmental risk assessment, a Bayesian network was developed to predict toxicity-driven risk, present and future, to Norwegian surface waters (Figure 12). Historic pharmaceutical wholesales for the period 1999-2018 were used following the protocol in Paper I (Welch et al., 2022c) to estimate the relationship between weight sold, population and calendar year for six APIs with high predicted RQs.

An OOBN was constructed in HUGIN Researcher, a Bayesian network development package (HUGIN Researcher 9.3, 2023), to predict risk. Three classes of a framework for calculating wholesales weights and influent, effluent and surface water PECs were created, discretised respectively for low, medium, and high sales weight APIs, to mitigate sensitivity issues. Linear models were fitted to sales data, population, and year, per API. Within each class, the previously fitted linear models were then used to estimate sales of the six APIs in 2020 and 2050, relative to population.

Three population growth scenarios from Statistics Norway were applied in 2050 to three example counties representing rural, semi-urban and urban areas. This resulted in twelve potential sales weight scenarios for each of the APIs, which were subsequently used to predict environmental concentrations, based on an extended version of Paper I's equation (Welch, Grung, et al., 2022) (Equation 2). PEC distributions were first calculated for WWTP influent. PECs in effluent were subsequently calculated based on heavily abstracted removal rates

under existing treatment, and two upgrade scenarios (upgrade of existing worse-than-secondary to secondary, while leaving secondary and tertiary untouched; or full tertiary). Then, receiving water PECs were calculated based on a flat dilution factor from effluent, and RQs calculated per API for these waters.

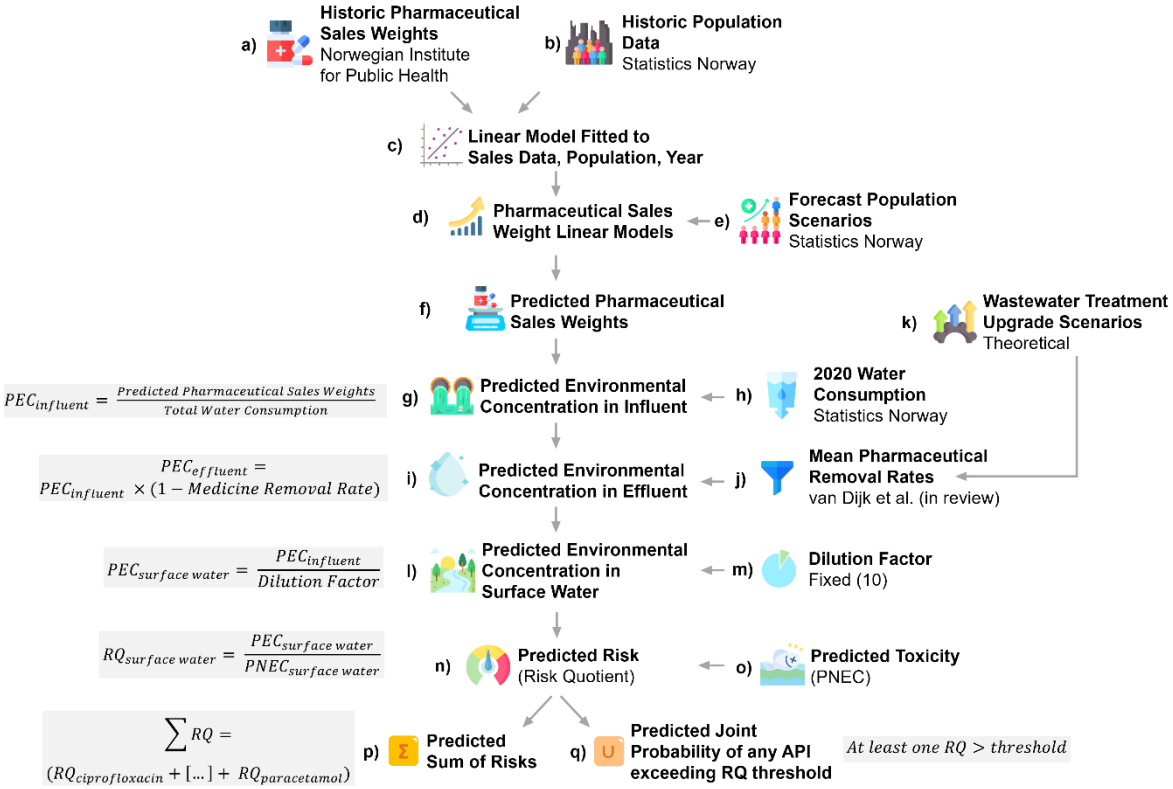

Figure 12: Diagram of data sources, workflow, equations, and output of Paper III. Historic pharmaceuticals sales (a) for 6 Active Pharmaceutical Ingredients (APIs) and population (b) are fitted to a linear model (c), which is then used (d) with a range of population forecast scenarios (e) to predict sales weights (f). These sales weights are subsequently used to calculate Predicted Environmental Concentrations (PECs) in influent (g), based on 2020 water consumption figures (h). PECs in effluent (i) are calculated across various wastewater treatment upgrade scenarios (k) using abstracted removal rates (j), and a PEC in surface water is calculated (l) using a fixed dilution rate of 10 (m). Risk Quotients (RQs) are then predicted, per API and scenario (n), using externally sourced toxicity data (o). Finally, a predicted sum of RQs (p), and the joint probability of RQs exceeding various thresholds (q) were calculated across the APIs for each scenario. Reproduced from Welch et al. (preprint, 2023)

A distribution of Sum of Risk Quotient (ΣRQ) was calculated across the 6 APIs; following Backhaus' assertion (Swedish Chemicals Agency, 2015, 2021) that the assumption of concentration addition (shared mode of action) is a valid, if conservative assumption, even across APIs with different modes of action, no distinction was made across these categories.

As an adjunct to Sum of Risk Quotients, the joint probability of any API exceeding a given RQ threshold was also calculated and compared for each scenario (Figure 13). A low RQ, calculated deterministically, may indicate a low-probability but adverse impact, or a high-probability of minimal impact (Fairbrother et al., 2016). Summed Risk Quotients are more appropriate for the latter scenario, but where ecosystems are exposed to a great many stressors

with a low probability of causing serious adverse effects, environmental degradation is likely to occur.

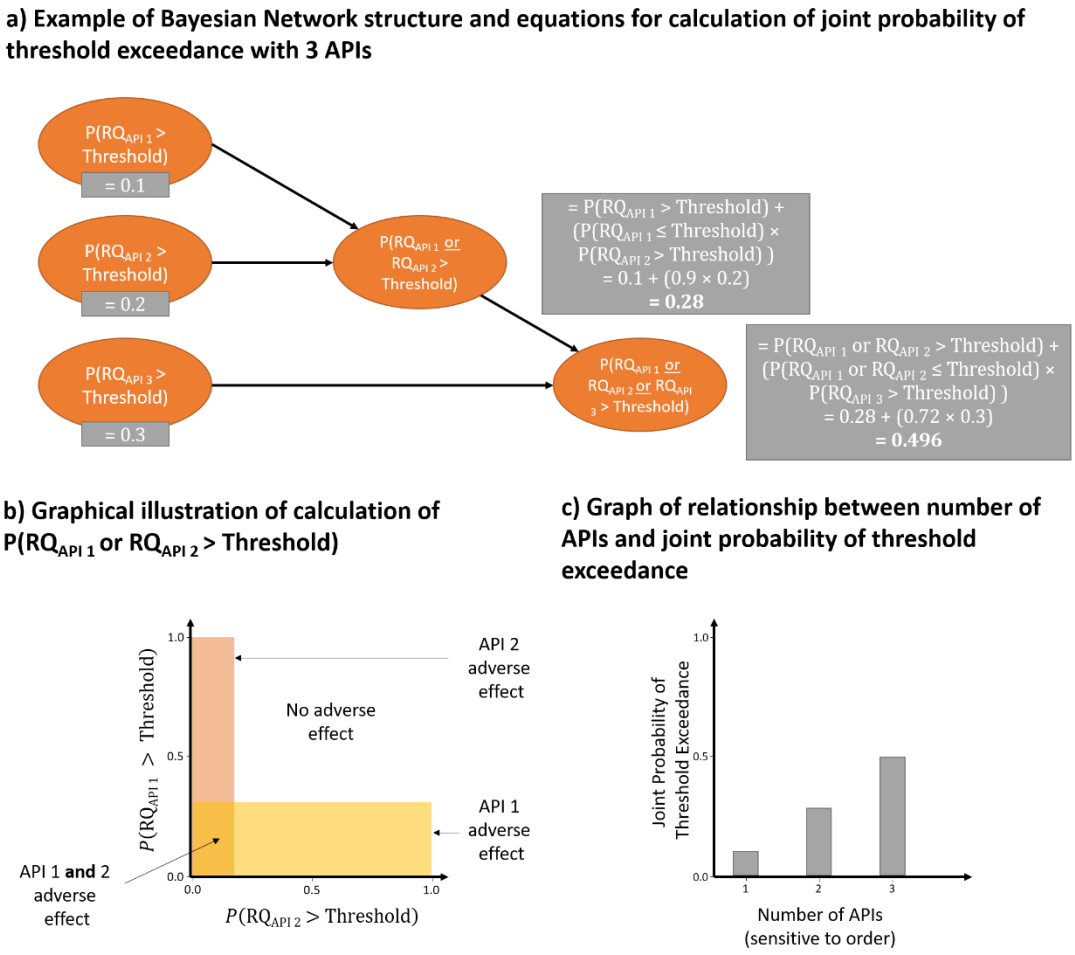

Figure 13: (a) Example, with calculations, of a Bayesian network for calculating the joint probability of exceeding an arbitrary RQ threshold. (b) Graphical illustration of the individual and joint probabilities of an "adverse effect" of APIs 1 and 2 in (a). (c) Graph of the relationship between number of APIs and joint probability of threshold exceedance in (a).

4. Results

4.1 Prediction of Exposure from Sales Data (Paper I)

Roughly 6000 different human medical products and 600 different veterinary medical products were summarised each year, representing 870 unique APIs across the four-year period. In order to evaluate our results, we compared our data to other pharmaceutical sales datasets covering similar time periods in Norway.

A Bland-Altman (or Tukey mean-difference) plot was used to compare our 2018 data to the predictions of the Norwegian pharmaceuticals specialities website Felleskatalogen (Felleskatalogen, 2022), based on commercially collected market data. Agreement between the two datasets was extremely high (mean log difference ≈ 0), although nine APIs fell outside of the 95% Confidence Intervals calculated for the mean difference.

A further Bland-Altman plot was constructed to compare predicted wholesales weights to prescription weights, obtained from the publicly assessable NorPD database, for a panel of seven high-consumption APIs. Overall, prescription data predicted lower sales weights, principally driven by the decongestant xylometazoline (wholesale ~1000 × prescription), but partly also by the OTC-and-prescription painkillers ibuprofen (2.3 ×) and paracetamol (1.5 ×). Conversely, the prescription-only APIs amoxicillin and progesterone predicted a lower wholesales than prescription weight (0.68 and 0.77 ×). Prescription data for these APIs did not distinguish between different routes of administration (oral, injected, vaginal), so we elected to use the highest defined daily dose (DDD) of each API. Amoxicillin had two possible DDDs, 1.5 g (oral) and 3.0 g (injected), while progesterone had three – 90 mg (vaginal), 30 mg (oral) and 5 mg (injected). Consequently, the sales weight derived from oral amoxicillin and oral and injected progesterone was over-estimated.

Ibuprofen, paracetamol and ethinylestradiol wholesales weights were also compared to 2005 predicted sales weights in Grung et al. (2008), and historical NIPH reports, using simple graphs of population-normalised consumption over time. Growth in paracetamol consumption since 2005 appeared plausible and followed NIPH-reported trends. Reported ibuprofen data was less complete, but where data was available for comparison trends appeared to roughly correspond. Ethinylestradiol consumption was less easy to compare due to its presence in a range of combined products, and no conclusion was drawn on agreement between the datasets.

Lastly, 31 APIs were shortlisted as displaying unusual trends in wholesales weights, year-on-year. Of these, plausible explanations – recorded shortages, new authorisations or deregistrations – were found for 26 APIs, leaving 5 unexplained.

4.2 Assessing Risk (Paper II)

MECs recorded in Norwegian WWTPs in 2015-2016 were compared to our PECs for 19 substances in the period 2015-16. In seventeen of these cases, PECs were larger than MECs (by a median factor of 20), while in two cases (the stimulant amfetamine and the antibiotic ofloxacin) PECs were smaller, by a factor of 56 and 1.5 respectively. No significant Spearman rank-correlation was detected.

RQs were calculated for 208 substances between 2016 and 2019. 17 substances were predicted to have an RQ in excess of 1. Seven of these substances were sex hormones, including the highest-risk substance (levonorgestrel), while three analgesics (painkillers), a statin, an antiseptic, an antifungal, and an immunosuppressant were also present. A number of these high-RQ substances also presented hazard due to their physico-chemical properties. Three such APIs had a high potential to bioaccumulate. Six substances had high and five moderate potential to persist in the environment. Four substances were estimated to be very mobile, and three mobile, in the environment.

QSAR provisional-PNECs from NORMAN were available for 428 substances, including 78 which also had experimental PNECs. However, agreement between the two datasets was poor. Provisional RQs were on average 50% higher than experimental values, although this in part may be explained by the static AF of 1000 applied to provisional-PNECs, compared to the more variable AF used for experimental PNECs. Likewise, correlation was low between values (Pearson's $r = 0.301$) and ranking (Spearman's $rho = 0.493$).

Of the 870 available sales weights, 42 substances were available both OTC and under prescription. When OTC sales were excluded, PECs were a mean of 68.5% (median 71.6%) the size of total sale PECs, though this was largely driven by only 8 common OTC medications. For 10 of the 42 APIs RQs could also be calculated and compared. Here 92% of total sales risk came from non-OTC and only six APIs saw RQ increase by more than 10%. Overall, the exclusion of OTC sales had very little effect on risk ranking (*Spearman's rho = 0.99, P < 0.01*).

In 43 cases, human-only and veterinary-and-human (total) sales could be compared. A mean of 84% (median 94%) of PEC value was contributed by human use, driven by only 5 APIs. RQs could only be compared for three APIs, with a mean human contribution of 94%. Here risk ranking was almost identical between the two sets (*Spearman's rho = 0.99. p < 0.01*).

4.3 Forecasting Risk with Bayesian Networks (Paper III)

Discrete distributions of RQs were calculated under each combination of scenario, region, and API. Firstly, wastewater treatment was kept at contemporary efficiency to assess the impact of population growth over time. In an urban county, the distribution of the ΣRQ of all six APIs grew in magnitude between 2020 and 2050, though no variation was seen between the three population growth scenarios. However, in the semi-urban county risk not only grew from 2020 to 2050 under all scenarios but shifted upwards in magnitude from ~30% that RQ > 1000 to ~75% that RQ > 1000 under main and high growth. Meanwhile in the rural county, the highest risk of all population growth scenarios across the counties was predicted in 2050 under high growth. Smaller but nevertheless still large ΣRQ distributions were observed under low and main growth in 2050.

With time period and population growth fixed to 2050 and the main growth scenario (i.e., 1.12 times 2020's population), effects of varying the WWT scenario across the three counties were also modelled. Across all three counties, upgrading treatment to secondary or better produced only a very small reduction in the overall magnitude of the risk distribution. However, an upgrade of all WWT facilities to "best" (85% removal rate), saw a significant reduction in ΣRQ in all cases.

ΣRQs were also compared to the joint probability that any API exceeded a set RQ threshold (of 100 or 500). Both indicators showed a similar pattern in increases with the number of pharmaceuticals contributing to the indicator.

5. Discussion

Pharmaceutical pollution occupies a crowded field of anthropogenic stressors and is part of a complicated interplay of environmental, human, and climatic factors. In this context, the rapid assessment of risk is essential to understanding and managing the problems we face today, and will face in the future (Welch et al., 2022a). The methods and data we present in this thesis are a contribution to ERA that is both cost-efficient, and more capable of reflecting the uncertainties present across the risk landscape.

Our exposure assessment of pharmaceutical pollution is the first such wide-ranging (>800 APIs) exercise Norway, and an unusually broad and longer-term assessment by international standards. PEC-based approaches such as ours are a valuable adjunct to MEC-based prioritisation. Although MEC-based approaches are important tool for assessing

environmental pollution, their cost and overall complexity are key limiting factors, and, particularly in Norway, available data is patchy (Graumnitz and Jungmann, 2021). Detection is limited to a subset of APIs, within certain limits of detection and quantification, and tends to skew towards substances already highlighted as being of concern (Burns et al., 2018b).

The comparison of our approach with similar studies reveals a complicated picture of the technique's use and results. The earliest sales-based exposure predictions for pharmaceuticals were carried out in the 1990s (Stuer-Lauridsen et al., 2000) and predicted generally low concentrations in the aquatic environment (0.5 ng/L – 3 μg/L). Due to limited data PNECs could only be derived for 6 pharmaceuticals, and the study found RQs greater than one for ibuprofen, paracetamol, and acetylsalicylic acid. A single RQ was calculated for "estrogen", a grouping of various estrogens, but this value was below one, as were the remaining two API's.

Since then, similar studies have been conducted across the world, largely in the West. Burns *et al.* (2018b) identified 73 prioritisation studies in their recent review, the majority of which were conducted in France, the US and the UK. Substances identified as the highest priority – based either on exposure or risk – varied considerably between geographical regions. Many sales-based prioritisation studies limit their coverage to 100 or less APIs, and cover only a single year (Besse et al., 2008; Chen et al., 2015; Jones et al., 2002; Ortiz de García et al., 2013; Riva et al., 2015; Schwab et al., 2005). In particular, many of the studies focused on antibiotics but omit estrogens, making a direct comparison difficult. However, Burns *et al.* (2018b) identified that across the 73 studies their review encompassed, diclofenac was the most commonly selected priority pharmaceutical, followed by ethinylestradiol, ciprofloxacin, paracetamol, ibuprofen, carbamazepine, clarithromycin, estradiol, erythromycin and amoxicillin. The methodology across these studies varied considerably. In particular, some studies derived PECs both with and without literature-based WWTP and human metabolic removal rates (Chen et al., 2015; Riva et al., 2015). In general, PECs were found to overestimate MECs of equivalent media, although the degree of overestimation varied considerably between papers (Besse et al., 2008; Burns et al., 2017; Ortiz de García et al., 2013; ter Laak et al., 2010). However, these findings were not unequivocal. A similar comparison of 2016 PECs to MECs was conducted by Burns, Carter, Kolpin, *et al.* (2018a) in two UK rivers. They found that on an average annual basis, PECs calculated for 24 APIs (not including sex hormones) using experimentally-derived WWTP removal rates and river-specific dilution rates *underestimated* MECs for the two rivers by 0.51 and 0.04 respectively.

Perhaps the broadest sales-based risk prioritisation exercise was conducted by Gunnarsson *et al.* (2019), who carried out an analysis of API retail, prescription and hospital sales weights across 22 European countries. The study made similar assumptions of geographically even consumption, no wastewater or metabolic removal, and standardised wastewater production (200 L per person, per day) and dilution (1 in 10). In total, RQs were calculated for 138 APIs. The study found median RQs > 1 for seven APIs in at least one European country. Four APIs – levonorgestrel, ethinylestradiol, estradiol and abiraterone – had median RQs across the countries greater than 10. Three APIs – propranolol, fulvestrant and fluoxetine – had median RQs between 1 and 10. Eighteen APIs had median RQs greater than 1. Gunnarsson *et al.* also calculated PECs with country-specific dilution factors (Keller et al., 2014), typically higher than the (conservative) default value of 10. Under these conditions, only five APIs had a median RQ > 1 in at least one country: levonorgestrel, estradiol, ethinylestradiol, abiraterone and propranolol. A direct comparison to Gunnarsson *et al.*'s (2019) results is not possible, as data on PECs at the national level were not published. However, the list of APIs identified as

having the highest RQs was remarkably similar. Like Gunnarsson, we predicted levonorgestrel, ethinylestradiol, estradiol and abiraterone to be among the highest priority pharmaceuticals.

Comparison between our priority substances and those identified by EU legislation-level screening is also enlightening. There was no crossover between our list of substances with RQ > 1 and the WFD's latest watchlist for union-wide monitoring (European Commission, 2022c). However, the pharmaceuticals in the latest proposed Priority Pollutants amendment (European Commission, 2022d), sets legally binding EQS values for nine pharmaceuticals - ethinylestradiol, estradiol, azithromycin, carbamazepine, clarithromycin, diclofenac, erythromycin, estrone and ibuprofen – four of which also appear on our list of high RQ APIs. Likewise, the recast UWWTD proposes monitoring of 10 pharmaceuticals, including, from our list, diclofenac (European Commission, 2022a).

Although prioritisation at the European level is in itself a valuable guide, Burns *et al.*'s review (2018b) of global risk and exposure-based prioritisation studies concluded that risks are regionally specific, driven by national variation in relevant factors. Wilkinson *et al.*'s global study (2022) of pharmaceutical pollution (i.e. exposure) in rivers found significant, order-of-magnitude variation in many API classes, with Bouzas-Monroy *et al.*'s follow-up study of risk (2022) identifying similarly uneven patterns of risk distribution across different continents. This national variation in risk is evidence of the need for national-level prioritisation exercises such as that conducted across our first and second paper (Welch *et al.*, 2021; Welch, Moe, *et al., accepted*, 2022). Furthermore, our coverage of APIs was unusually broad, as most PEC-based approaches cover 100 or fewer APIs in a single year, and are frequently based only on prescription data (Burns et al., 2018b). By assessing exposure for 800+ APIs over a four-year period, we provide a far more comprehensive, top-down assessment of pharmaceutical pollution in a developed nation. In particular, such a comprehensive approach is less biased by the "Matthew Effect" (Daughton, 2014), the tendency of studies and experimentation to be conducted on known problem chemicals rather than unknown chemicals. Additionally, by calculating sales weights at the product, rather than DDD level, we were able to provide more a more accurate overall measure of pharmaceutical sales weights. This added significantly to the workload of exposure assessment, however. As Europe moves towards a one health paradigm of human and environmental health protection (One Health EJP, 2022), the integration of product API sales weights with existing national sales records could greatly reduce the barrier to more efficient, automated sales weight-based exposure prediction. Were a permanent partnership to be formed between environmental and public health agencies, this data could be published routinely alongside existing sales and environmental data for regulatory, scientific and public use.

As with other studies (Burns et al., 2018b), risk could not be assessed across the roughly 75% of APIs without publicly available toxicity data. This is a commonly recognised limitation of both measured and predicted assessment of pharmaceuticals risk (Ågerstrand et al., 2015), and was not an issue we were able to directly address.

A further limitation of our work was not including the consideration of WWTP removal rates, metabolic removal and conversion of APIs, and receiving-water specific dilution rates. Although in line with similar studies (Gunnarsson et al., 2019) and pharmaceutical ERA guidelines (EMA CHMP, 2006), this likely explained our overestimation of PECs compared to MECs in WWTP effluent (Welch, Moe, *et al., accepted*, 2022). Inclusion of API-specific removal rates has been shown in other studies to reduce the discrepancies between MECs and

PECs (Chen et al., 2015; Riva et al., 2015). However, disregarding these factors was appropriate at the scale and scope of our work, and produced an order of pollutant priority in line with many other global prioritisation exercises (Burns et al., 2018b).

The inclusion of these removal rates could make prioritisation more accurately reflective of the risk management landscape in a given area. However, even these additions to modelling of environmental concentrations may fail to represent the overall risk situation. The assumption that metabolic processes in the body of target organisms or WWTPs simply remove hazardous chemicals is clearly an oversimplification. For example, APIs may be transformed into *more* toxic or otherwise hazardous products by these processes (Li, Sobek and Radke, 2016), or their "removal" may simply involve partition to biosolids that are subsequently released to the environment (i.e. ciprofloxacin in sludge applied to fields (Eriksen et al., 2021)). Under the circumstances, the exclusion of this modelling step remained the most practical and conservative approach, particularly given the additional workload associated with locating relevant figures in the literature for more than 800 APIs. Our final paper, with its reduced scope of 6 APIs, was able to include variations in WWTP removal. However, even here, finding adequate removal data for each of the APIs and treatment levels was not possible, and we elected to use a flat removal rate for each level of treatment across all of the APIs (Welch et al., 2023). Furthermore, the use of such an approach modelled after routes of exposure for human medicinal products may have been inappropriate for the veterinary products in the dataset.

It should also be emphasised that the use of RQ as the primary measure of risk throughout this thesis is a choice of necessity rather than an uncritical endorsement. As stated in the section *Tiered ERA of Pharmaceuticals* RQs are tools for the prioritisation and comparison of risk – and a very specific ecotoxicological definition of risk, at that – across substances or scenarios. A RQ does not in isolation provide a measure of magnitude of effects on actual ecosystems or species (Leeuwen, 2007, Raimondo and Forbes, 2022). However, a large portion of regulatory ecotoxicology, especially in the EU, has been built around the use of RQs to assess pollution risks, which has shaped the data available. Data on pharmaceutical toxicity is particularly difficult to acquire, and more sophisticated approaches to mixture risk, such as Sum of Toxic Units, required information on toxicity tests that was not available during the literature search. As Predicted No Effect Concentrations remain the primary published data on pharmaceutical toxicity, their use was considered appropriate for the scope of our work.

Our novel joint probability of any API RQ exceeding a given threshold approach inherits many of the flaws of the standard RQ approach. However, we believe it adds value to this conventional approach, while requiring no extra data and very little extra work. The joint probability approach is consistent with the Sum of RQs, but recognises the uneven contribution of APIs to overall risk. In particular, any given RQ score can represent a diversity of combinations of adverse event magnitude and probability (Fairbrother, 2016). However, two events from different ends of this spectrum (a high probability, low magnitude event, and a low probability, high magnitude event) would require different management strategies. Under these circumstances, a joint probabilistic risk metric communicates more clearly that adverse effects are likely to occur as the number of stressors increases. In our example (Paper III), our choice of high-RQ APIs made it more difficult to demonstrate a further advantage that would be more apparent with a wider number of lower-RQ APIs. In future work, we would like to address this in the design of our BNs, although the issue of computational complexity increasing non-linearly with number of APIs has yet to be solved.

Against this backdrop of regional variation and uneven ecotoxicological knowledge, BNs were an ideal tool to explicitly characterise uncertainty and explore how PEC-based approaches might be used to predict future environmental risks of pharmaceuticals. Using our deterministic ERA to identify high-priority APIs in Norway, a complex OOBN was constructed to probabilistically ERA these substances (Welch *et al.*, *preprint*, 2023). Although not the first BN to address chemical ERA (Kaikkonen et al., 2021), or the first to address pharmaceutical pollution (Brandmayr et al., 2015), the contribution is, to the authors' knowledge, the most sophisticated BN for pharmaceutical ERA to date, covering exposure *and* toxicity-driven risk of multiple APIs in different spatial, temporal, population growth and WWT scenarios.

Future Perspectives

BN ERA is, at the present moment, a dynamic field, and in the past years alone a number of other studies presenting novel and innovative approaches have been published. In the field of pesticide ERA, where models are more easily available for predicting spatially and ecologically explicit patterns of risk distribution, a number of studies have predicted risk to different taxa at the sub-regional level (Mentzel et al., 2022b; Troldborg et al., 2022). Although perhaps *too* spatially explicit for our approach, the ability to determine the overlaps between the highest-risk areas of pollutant and the most vulnerable species would be a valuable approach for assessing risks to Norwegian nature. By comparison, Landis, Ayre, *et al.* (2017a) were able to model the effects of mercury, in combination with some other chemicals and abiotic factors, on specifically identified and prioritised species and human use endpoints, for the development of adaptive management strategies.

In addition, for a subset of APIs with more readily available toxicity data, it may prove possible to move to a more probabilistic assessment of risk. Our PNEC-based prediction of RQ distributions was a pragmatic choice based on available data, but where probabilistic exposure *and* effect data is available, a fully probabilistic quantification of risk and its uncertainty may be possible (Mentzel et al., 2022a).

In order to develop probabilistic ERA tools that can and will be used by regulators and stakeholders, it is important that they are comprehensible to those without a background in probabilistic ERA (EUFRAM, 2006), and ideally are developed in collaboration with these parties (Voinov and Bousquet, 2010). To date, as a software prototype, development of the OOBN described above has been a primarily internal exercise, but appropriately expanded it could be a useful tool for risk assessors. A number of studies across the environment fields have shown the value of exercises to develop BNs in partnership with experts and stakeholders (Adams et al., 2022; Kelly (Letcher) et al., 2013; Krueger et al., 2012; Laurila-Pant et al., 2019), and this could be extended in the future to the ERA of pharmaceuticals.

Further integration of scenarios for forecasting possible futures would also enhance the applicability of our work. Brandmayr *et al.*'s (2015) BN for emission prediction of metformin and metoprolol is likely too detailed for an ERA at the scope that is envisaged. However, if its consideration of factors influencing API emission and risk can be summarised into broader pharmaceutical consumption scenarios, such as those developed by Nagesh et al. (2022), it could prove a powerful tool for exploring the range of variation possible in future risk scenarios.

Although our consideration of only 6 APIs makes our assessment of mixture and joint toxicity of APIs comparatively small in scale, we believe the approach holds promise for future ERA of mixtures. Despite the considerably different risk profiles of the APIs – sex hormones with low sales weights but high toxicity, and NSAIDs with the opposite – it was possible, using an OOBN based design, to combine individual APIs' RQ distributions. By subsequently calculating both a sum of RQs, and a joint probability of any RQ exceeding a given threshold, a model was developed that was capable in theory of providing both probabilities of a given region and species experiencing unacceptable risk, *and* a broad overview of how the pharmaceutical risk landscape may evolve under different scenarios. Although both these functionalities remain in an early developmental stage, where data for more APIs is available, they may be integrated in the future with current trends in ERA of multiple stressors. This includes the trend towards a Mixture Assessment/Allocation Factor approach, proposed by Backhaus and the Swedish Chemicals Agency (Swedish Chemicals Agency, 2021) and mentioned by name in the recent EU chemical strategy (European Commission, 2020b), which begins with a tier-one assessment of ΣRQ. Likewise, the European Environment Agency European Topic Centre on Health and the Environment (EEA ETC-HE)'s recent proposal for an indicator on chemical risks to ecosystems is built on similar principles to our joint probability of threshold exceedance approach (Andres, S. et al., 2022). With the most encouraging suggestion yet that EU legislation will expand to address mixture toxicity (European Commission, 2020b), the joint and mixture risk approach developed here may find use for probabilistically assessing future risks.

Finally, the predictive approach (Welch et al., 2022c) could be refined to improve the time-efficiency of the process so that future and past wholesales can be used to predict a larger number of MECs. Furthermore, by pairing this data with API-specific transformation and removal statistics, and Norway-specific dilution, it would be possible to reduce the overestimation of concentrations of substances such as paracetamol and diclofenac which are often well-removed by WWTPs (Izadi et al., 2020).

The deterministic approach to the ERA of pharmaceuticals in Norway adds considerably to the state of knowledge on Norway's risk landscape, and the role pharmaceuticals play within it. Furthermore, with the developed OOBN, we add to the evidence that BNs can be a valuable addition to the toolbox of environmental risk assessors, due to their improved ability to quantify and propagate uncertainty (Hart and Pollino, 2008; Moe et al., 2021), and intuitive depiction of relationships between relevant factors. More work is needed to bridge the lack of data, and data availability issues in the ERA of pharmaceuticals (Ågerstrand et al., 2015), but a truly comprehensive understanding of their role in global environmental risk is likely out of our reach (Daughton, 2016). In this context, robust, probabilistic models that treat uncertainty transparently and explicitly are an important tool for the ERA of pharmaceuticals (Hart and Pollino, 2008; Moe et al., 2021).

6. Conclusions

This thesis has developed a set of deterministic and probabilistic methods for the prediction of exposure and subsequent characterisation of pharmaceutical environmental risk, using Norway as a case study. It is shown that although toxicity data availability continues to impair the ERA of pharmaceuticals, calculations of PECs from sales weights can be an effective adjunct to analytical methods. We predict, based on the data available, the that highest RQ APIs in Norway are largely sex hormones and analgesics. Lastly, we forecast probabilistically the joint and combined risk of a subset of APIs under a variety of future scenarios.

The approaches in this paper are intuitive and can be applied in other nations and to other pollutants with similar or better data availability. Although this is hardly the first time pharmaceutical risk is predicted from sales weights, the development of the methodology enables a deterministic overview of pharmaceutical environmental risk in a highly-developed country. Furthermore, the OOBN developed builds a foundation for the Bayesian network-based ERA of pharmaceuticals.

Acceptance of probabilistic methods such as BNs in prospective, regulatory risk assessment of pharmaceuticals is likely to be a slow and complex process. However, the existing adoption of BNs for retrospective environmental risk assessment (Landis, 2021; Mitchell et al., 2021) shows that they can be a valuable tool in protecting real-world ecosystems.

I hope that the work in this thesis will serve as a useful resource for the risk assessors of today and tomorrow. Earth's uncertain future means the risk landscape of tomorrow may look very different to today's, and a robust set of tools capable of handling the uncertainty intrinsic in such a forecast is urgently needed.

7. References

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Paper I: Pharmaceutical pollution: Prediction of environmental concentrations from national wholesales data

DATA NOTE

REVISED Pharmaceutical pollution: Prediction of environmental concentrations from national wholesales data [version 2; peer review: 2 approved, 1 approved with reservations]

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Abstract

The regulation and monitoring of pharmaceutical pollution in Europe lag behind that of more prominent groups. However, the repurposing of sales data to predict surface water environmental concentrations is a promising supplement to more commonly used market-based risk assessment and measurement approaches. The Norwegian Institute of Public Health (NIPH) has since the 1980s compiled the Drug Wholesale Statistics database - covering all sales of both human and veterinary pharmaceuticals to retailers, pharmacies, and healthcare providers.

To date, most similar works have focused either on a small subset of Active Pharmaceutical Ingredients (APIs) or used only prescription data, often more readily available than wholesale data, but necessarily more limited. By using the NIPH's product wholesale records, with additional information on API concentrations per product from, we have been able to calculate sales weights per year for almost 900 human and veterinary APIs for the period 2016–2019.

In this paper, we present our methodology for converting the provided NIPH data from a public health to an ecotoxicological resource. From our derived dataset, we have used an equation to calculate Predicted Environmental Concentration per API for inland surface waters, a key component of environmental risk assessment. We further describe our filtering to remove ecotoxicological-exempt and data deficient APIs. Lastly, we provide a limited comparison between our dataset and similar publicly available datasets for a subset of APIs, as a validation of our approach and a demonstration of the added value of wholesale data.

This dataset will provide the best coverage yet of pharmaceutical sales weights for an entire nation. Moreover, our developed routines for processing 2016–2019 data can be expanded to older Norwegian

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Any reports and responses or comments on the article can be found at the end of the article.

wholesales data (1974–present). Consequently, our work with this dataset can contribute to narrowing the gap between desk-based predictions of exposure from consumption, and empirical but expensive environmental measurement.

Keywords
pharmaceutical pollution, wastewater, wholesale data, predicted environmental concentration

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REVISED **Amendments from Version 1**

The paper has been updated based on the comments and feedback of reviewers. Changes include:

* Removal of the section on potential applications

* Clarification of the choice of model, matrices, and parameters

* Reorganisation of the background data and data availability statement

Any further responses from the reviewers can be found at the end of the article

Plain English summary

Pharmaceuticals, by design, affect human or animal biology, targeting specific organs and biological systems to treat diseases. Pharmaceuticals and their metabolites—partly degraded or transformed ingredients—that reach the environment may have unwanted and long-lasting biological effects on plants, animals, and microbes. This comes in addition to environmental footprint of chemicals that are used during the production of pharmaceuticals. In Norway, a coastal nation of more than five million people, the primary route of pharmaceuticals in the environment is via human consumption. Although some pharmaceuticals can be metabolised in the body and degraded in sewage treatment plants, a proportion reaches rivers, lakes, fjords, and coastal zones.

A better overview of the types and amounts of pharmaceuticals in the environment is important for assessing and managing environmental risk, but measuring their presence everywhere can be resource-intensive and expensive. With limited funds for environmental monitoring and management, a rapid and cost-efficient method for predicting concentrations of pharmaceuticals in the environment should be used to screen for the substances most likely to pose a problem.

In this paper we present such an exercise: we worked with the Norwegian Institute for Public Health's wholesale drugs data, adapting, and translating it from a medical resource to a set of sales weights for each pharmaceutical ingredient. These sales weights were in turn used to predict concentrations of drug pollution in receiving freshwaters. In total, we predicted sales weights and environmental concentrations for almost 900 Active Pharmaceutical Ingredients, from abacavir to zuclopenthixol, sold between 2016 and 2019.

Introduction

Pharmaceutical consumption is widely recognised as an important source of anthropogenic chemicals in the environment (European Commission, 2019; Richardson & Bowron, 1985). In much of the European Union (EU) and the European Economic Area, prospective (prior) environmental risk assessments of pharmaceutical products begin with an exposure assessment. Conservative, or worst-case Predicted Environmental Concentrations (PECs) of active pharmaceutical ingredients (APIs) are calculated by extrapolating from the highest average daily dose of a pharmaceutical, and the proportion of a nation's population taking said pharmaceutical – by default, 1% (EMA, 2006).

More recently, refined approaches have been suggested using pharmaceutical sales data collected by government agencies or market research agencies, to provide a more accurate and comprehensive prediction of environmental concentrations of APIs at the national (Grung *et al.*, 2008) and European (Gunnarsson *et al.*, 2019) level. In some cases, available data is limited to prescription sales, but where available wholesales data provides a far more complete picture of overall consumption.

In this paper, we present a dataset of predicted API consumption PECs based on reported sales weights of pharmaceuticals from a unique public sector source, the Drug Wholesale Statistics database of the Norwegian Institute for Public Health (NIPH, 2019). This source covers all sales of pharmaceuticals and medicines to pharmacies, supermarkets, hospitals, and other healthcare providers, from the year 1974 onwards. We describe (1) the sales data and additional information on pharmaceutical API content for the years 2016–2019, (2) the procedures for converting the sales data from number of packets per product to amount (kg) of each API, and (3) a final dataset of total amount of API sold per year, which can be used for prediction of environmental concentration. Although these methods have only been applied to and evaluated for the years 2016–19, they may also be applicable to past data.

With this dataset, we aim to provide an accurate resource describing sales weights and predicted environmental concentrations of environmentally relevant pharmaceutical products sold across Norway, providing a useful snapshot of pharmaceutical pollution for our and others' work. More advanced modelling approaches, such as ePiE (exposure to Pharmaceuticals in the Environment) (Oldenkamp *et al.*, 2018), have been developed, but are not yet available for Norway, and though prone to over-estimation our approach permits rapid prioritisation of APIs without the need to gather a great quantity of further excretion and removal data.

In particular, it will provide a useful resource for the characterisation of their environmental risk – on which our work is currently ongoing (ECORISK 2050 Deliverable D6.2).

Methods

Classifications and grouping of pharmaceuticals

The classification of pharmaceutical substances for human and veterinary use is standardised by the World Health Organization (WHO) under the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) code system (RRID: SCR_000677). An ATC code (Figure 1a) is a seven or eight character tiered alphanumeric code based on the target organ, therapeutic indication and/or pharmacology, and chemical structure of substances, while a DDD is defined as the average maintenance dose for a drug used in its main indication in adults. The ATC system's widespread global use since the

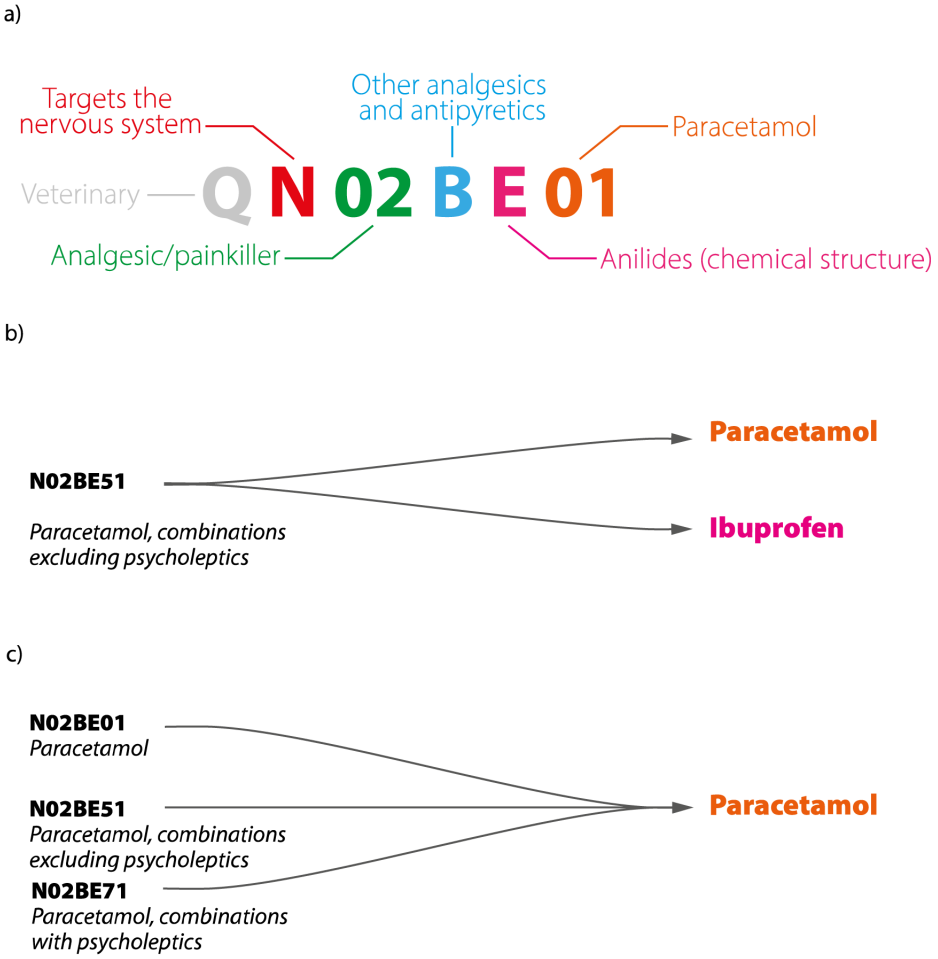

Figure 1. Relationships between APIs and ATC codes. *(**a**) An example of the ATC code for paracetamol taken as an analgesic (N02BE01), (**b**) one ATC code can represent multiple APIs – in this example, N02BE51 represents a combination of paracetamol and ibuprofen, (**c**) one API can have more than one ATC code, paracetamol is represented here by three codes—N02BE01, N02BE51 and N02BE71—corresponding to the forms and indications it is sold under in Norway. API, Active Pharmaceutical Ingredient; ATC, Anatomical Therapeutic Classification.*

1970s make it a useful tool for the broad classification of drugs within the Norwegian Drugs Wholesale Database.

ATC codes serve principally as a tool for drug utilization monitoring and research and are difficult to adapt to a substance-driven ecotoxicological approach. APIs are a more relevant entity for the characterisation of environmental risk, as ecotoxicological information is available for individual APIs rather than pharmaceutical products or ATCs. Under the ATC system, a product is characterised by a single ATC code that can contain multiple APIs, which are taken as a cocktail in the same pharmaceutical product (Figure 1b). Conversely, one API can be used for treatment of diverse disorders of different organs and thereby be associated with different ATC codes (Figure 1c). This complex set of many-to-many relationships between APIs and ATCs poses a distinct challenge for their interconversion, requiring a great deal of manual cross-referencing of products.

Publications of pharmaceutical sales from WHO Collaborating Centre for Drug Statistics Methodology and the NIPH are given in DDDs, limiting their utility for ecotoxicology work. DDDs aid comparison between pharmaceuticals consumption independent of price, package size and strength, but are impractical for ecotoxicological studies in which the weights of APIs sold are needed and are not always available for individual APIs or combinations of APIs.

Consequently, we elected within our dataset to calculate from scratch overall sales weights for each API, as a proxy of the emission of APIs. This required the assessment of each recorded sold product to determine the mass of each API in the product. The calculation of the total API emission per year is based on (1) the strength of the product (*i.e.*, the API concentration in units such as mg/L, mg/g, or mg/pill), (2) the amount of the product sold in one package (in units such as L, g, or no. of pills per package) and (3) the number of

packages sold per year. See Table 1 for a summary of product and API vocabulary.

Active Pharmaceutical Ingredients

Most—more than 50% in 2007—APIs are sold as pharmaceutical salts, with positive or negatively charged ions appended to their structures to increase stability and solubility in water (Bastin *et al.*, 2000; Paulekuhn *et al.*, 2007). Where the given mass of API in a product in fact refers to the salt form, this can lead to over-estimation of the total volume of active substance sold, especially where the ion represents a substantial portion of the overall weight. Information on the salts used in each product was not always listed in the source data, and consequently, we assumed the full given mass of API per product referred to the active ion However, we aim to include an assessment of the effects of salts on PECs in future analyses of the data.

Data sources and management

Sales data for years 2016–2019 were extracted from the Norwegian Drugs Wholesale Database (Figure 2, Figure 3a, Sales data). By contrast to prescription-only records such as

Table 1. Specific definitions of vocabulary used in this paper.

Vocabulary	Definition
ATC code	Anatomical Therapeutic Classification Code, a code classifying APIs or groups of APIs based on their medical use, target human organ, chemical structure, *etc.*
API	Active Pharmaceutical Ingredient, the therapeutic chemical(s) in a pharmaceutical product
Combination drug	A single product containing more than one API
Item	The components of a package, such as individual pills, dispensed sprays of an inhaler, *etc.*
Package	A single sold unit of product, such as a packet of multiple sheets of pills, a flask of liquid, *etc.*
(Pharmaceutical) Product	A specific manufacturer's pharmaceutical, as sold, by unique product ID
Strength	The amount of a given API in an Item, Package or Product
Unit	The unit assigned to a given Strength, such as mg L^{-1}, mg $pill^{-1}$, International Units, *etc.*
DDD	Defined Daily Dose, "the average maintenance dose per day for a drug used in its main indication in adults" (WHOCC, 2018), a standardised unit per ATC code and route of administration used to give a rough estimate of consumption.

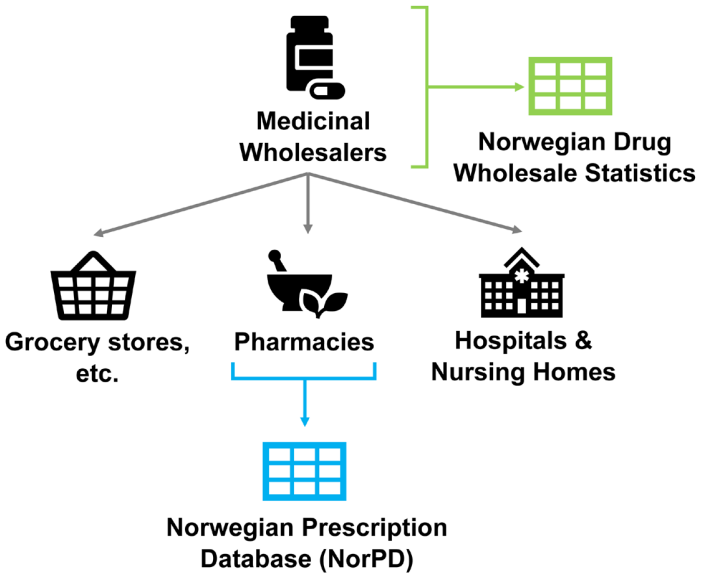

Figure 2. Diagram of information sources to NIPH Norwegian Drug Wholesale Statistics and Norwegian Prescription Database. *Figure reproduced and adapted from Sommerschild et al. (2021a) with permission from the publisher. The Norwegian Prescription Database is, at time of writing, in the process of being renamed to the Norwegian Prescribed Drug Registry.*

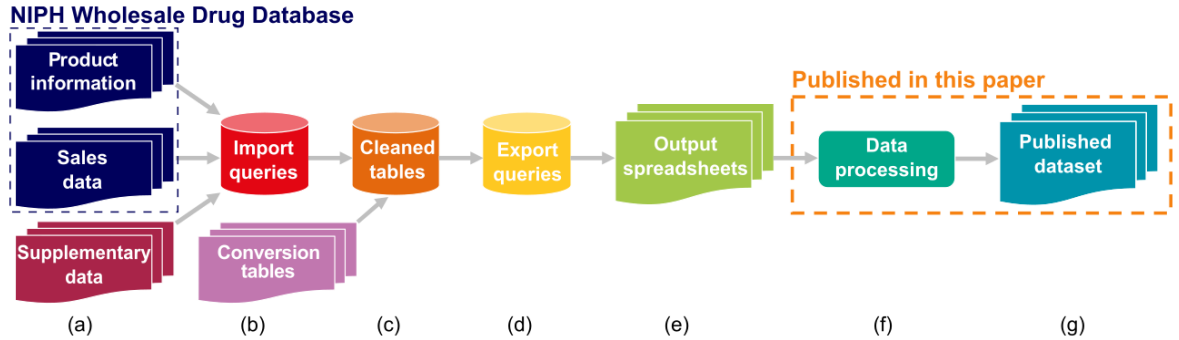

Figure 3. Simplified diagram of data extraction and management pipeline. Sales and product background data (**a**) from NIPH (dashed blue box) and elsewhere was imported into an Access DB via a series of queries (**b**), cleaned with the addition of various conversion tables (**c**), and exported (**d**) into output spreadsheets (**e**). This data was then formatted for analysis in R (**f**) and PECs calculated, and the results output to foreground CSV files (**g**), both of which are available as part of this paper. NIPH, Norwegian Institute of Public Health.

NorPD (Norwegian Prescription Database) this covers all sales to pharmacies, hospitals, nursing homes, and non-pharmacy outlets licensed to sell drugs within Norway, including prescriptions, over-the-counter (OTC) sales, and procurement by medical establishments (NIPH, 2019). In its raw form this dataset consisted of per-product sales, such as a packet containing multiple sheets of pills, or a suspension of liquid medicine.

The Norwegian health system distinguishes between three groups of human prescription medications. Group A and B cover drugs with potential for abuse, such as stimulants, opiates and strong painkillers, while Group C includes drugs minimal potential for abuse but that are still controlled, such as anti-depressants. All other products are available OTC. For the purposes of this analysis, Groups A, B and C were combined. Note that in some cases, an API may be available both on prescription and OTC – for instance, smaller doses of paracetamol can be bought OTC, while larger doses require a prescription (Helsenorge, 2020). The Norwegian Drug Wholesale Statistics and its output "wholesale data" covers both prescription and OTC sales of human and veterinary medications.

In adherence with NIPH's commercial confidentiality requirements, sales in currency values, and commercially sensitive information on the sales of individual manufacturers' products were removed from the final published dataset.

Additional information on individual products that was required for calculating the sales weight per API (Figure 3a, Product information), including number of items per package, strength (concentration of API per item), and associated unit were obtained separately from the centralised NIPH sales database and matched to sales data using internal product codes. In a sizable number of cases, no additional data were available for given products, automatic matching failed, or the data available were inappropriate for use in our workflow. Here records were checked manually against product contents records online, principally the Norwegian pharmaceuticals specialties site Felleskatalogen, the UK Electronic Medicines Compendium, and the US site Drugs.com. Cases where one product contained two or more APIs (combination drugs) were split into separate entries for each API to ensure substances were fully accounted for.

Although efforts were made to include the sales of as many products as possible, products with sales below 1000 packages over the four-year period, except for categories of special interest (antibiotics, sex hormones), were excluded as a time-saving measure. Additionally, gas APIs (such as anaesthetic gases) were likewise excluded.

The two primary data sources, and supplementary product information where gaps were present in the former, were imported into a Microsoft Access database and organised into a related set of tables. The main table types were data tables, conversion tables, and code lists. The main data tables are shown in Figure 4 and described below.

1) t_Product: the description of each pharmaceutical product (identified by product number), including information on the product type and the product amount per package (Table 2)

2) t_Product_API: the concentration of each API per item and the total amount of API per package of the product (Table 3)

3) t_Sales_Product: the number of packages sold per product per year (Table 4)

Information on APIs in a given product was not available in the original data sources but had to be extracted from the ATC codes associated with the sales data (Figure 3a). In some cases, extracted data corresponded directly to an API, but for combination products, and ATC codes where the included APIs were not immediately interpretable, API content was determined, stored, and converted at the individual product level.

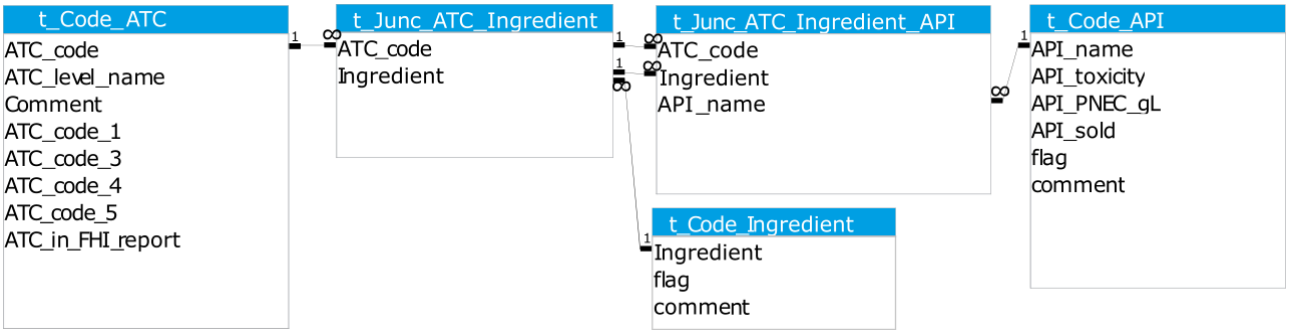

Figure 4. Simplified diagram of database structure: the main data tables. API, Active Pharmaceutical Ingredient; ATC, Anatomical Therapeutic Classification; PNEC, Predicted No-Effect Concentration.

Table 2. Field names, types, and descriptions for the Product Table t_Product.

Field name	Data type	Description
ProductCode	Number	Database internal unique product ID
ProductName	Short Text	Full product name from NIPH records
ProductName_short	Short Text	Product name with medium/dose removed
ATC_code	Short Text	Full ATC Code
ProductDetails	Short Text	Additional medium/dose data from ProductName
ProductType	Short Text	Standardised medium: pill, fluid, *etc.*
ProductGroup	Number	Formulation institution; 1 for manufacture, 2 for compounding pharmacy
DateStart	Date	Unused variable for product registration date
DateEnd	Date	Unused variable for product removal date
PackageQuantityValue	Number	Quantity of medium per package (number of pills, L of fluid, *etc.*)
PackageQuantityUnit	Short Text	Unit of medium per package
Item	Short Text	Unused variable from source data
ConversionFactor	Number	Unused variable from source data
NoOfAPI_PerProduct	Number	Number of APIs in a product
NoOfItemsPerPackage	Number	Unused variable superseded by PackageQuantityValue

NIPH, Norwegian Institute of Public Health; ATC, Anatomical Therapeutic Classification; API, Active Pharmaceutical Ingredient.

Ultimately, for each product (Table 2), the associated API names were extracted from the full ATC name and entered in the table t_Product_API (Table 3).

In most cases the information needed for calculating the amount of API per package (the concentration of API in the product and the amount of the product per package) was available in the original data source (the product information table). In some cases, where this information was not provided, it was still possible to extract the information manually from the product name.

For products where API information could not be found in the included data, it was instead sourced for each individual product from the Norwegian pharmaceutical specialties website Felleskatalogen or Summaries of Product Characteristics (SPCs) from the pharmaceutical specialties websites of other nations (Electronic Medicines Compendium (UK), Pharmaceutical Specialties in Sweden, Medical Online Information Centre (Spain)).

Table 3. Field names, types, and descriptions from the API per Product Table t_Product_API.

Field Name	Data Type	Description
ProductCode	Number	Database internal unique product ID
API_name	Short Text	
StrengthValue	Number	Original strength information from NIPH (not standardised)
StrengthUnit	Short Text	Original strength information from NIPH (not standardised)
API_ConcentrationPerItemValue	Number	Converted API strength value (with standardised unit if possible)
API_ConcentrationPerItemUnit	Short Text	Standardised API strength unit (if possible)
API_AmountPerPackageValue	Number	Calculated API amount value (with standardised unit if possible)
API_AmountPerPackageUnit	Short Text	Standardised API amount unit (if possible)
Comment	Short Text	
Exclude	Short Text	Yes (if record should be excluded from extraction)

NIPH, Norwegian Institute of Public Health; API, Active Pharmaceutical Ingredient.

Table 4. Field names, types, and descriptions from the Product Sales Table t_Sales_Product.

Field Name	Data Type	Description
sYear	Number	Sales year
ProductCode	Number	Database internal unique product ID
PackageAmountSoldValue	Number	Number of packages of a unique product sold
PackageAmountSoldUnit	Short Text	Helper variable used to record counting process

This was also the case for combination products containing two or more APIs, which typically required further work to determine and confirm the APIs present.

The resulting many-to-many relationship between ATC and API (see Figure 1) is represented by the code lists and junction tables shown in Figure 5.

Finally, the information on yearly sales (number of packets) per product was stored in the table t_Sales_Product (Table 4). During data extraction (Figure 3d), this yearly sales information was combined with the calculated amount of API per product package, to obtain the total amount of API per year from the sales data.

Data processing in R

Data extracted from the Access database (Figure 3d) were subsequently exported into flat files (Figure 3e) for calculation of PECs and future analysis. For this purpose, the records were grouped by API and year and the calculated amount sold aggregated by sum. The exported dataset was prepared for analysis and publication in R version 4.1.2 " *Bird Hippie*" (R Core Team, 2021; RRID:SCR_001905). A full list of the R packages used is available as *Underlying data* (Welch *et al*., 2022).

Sales weights per product per year were filtered to remove any zero values, and values for which no units were assigned, representing records for which the API amount could not be calculated. Sales weights were then summed by API, per year, and APIs were filtered according to a list of exemptions from risk assessment on the basis of non-toxicity (as applies to vitamins, vaccines, antibodies, *etc*. (EMA, 2006)). Unique products excluded at each state are illustrated in Figure 6, and the total number of entries input (unique products) and APIs output are summarised in Table 5. The final dataset is published as a comma-separated values (.csv) file.

Graphics. Graphs were rendered in R (see repository for code and packages used (Welch *et al*., 2022)). Diagrams were drawn in Adobe Illustrator (RRID:SCR_010279), with the

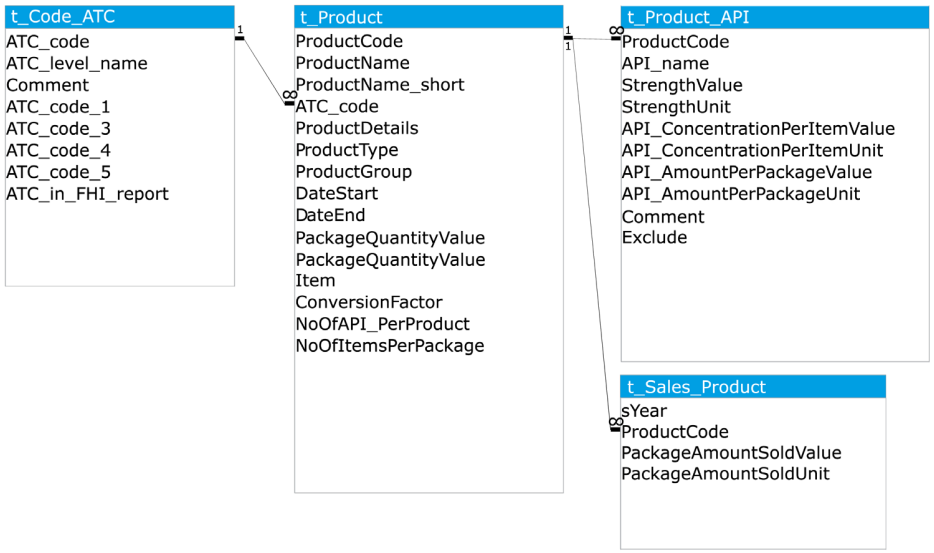

Figure 5. Diagram of code lists and conversion tables. Defines the many-to-many relationships between ATC and API in database. ATC, Anatomical Therapeutic Classification; API, Active Pharmaceutical Ingredient.

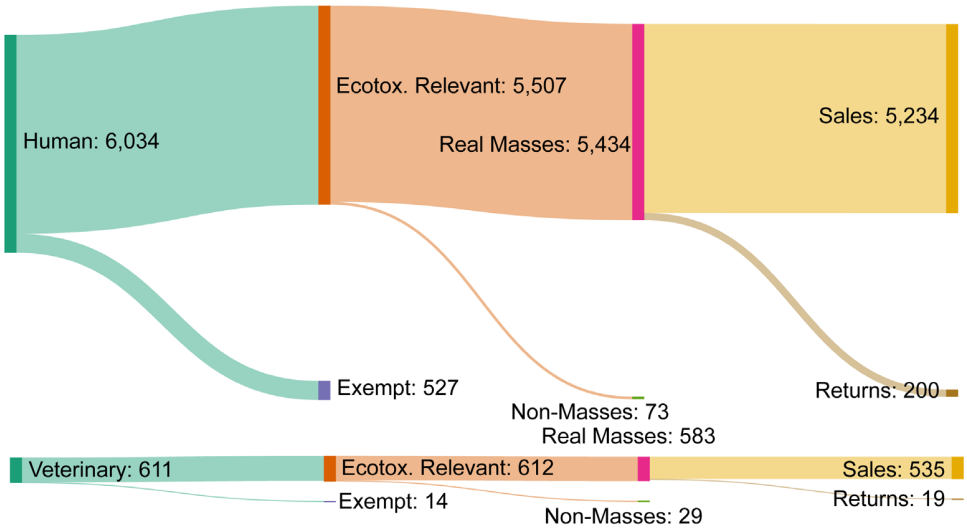

Figure 6. Records retained/removed at each stage of data processing. Count of unique products sold in 2019 retained and removed at each step of data processing (Figure 3f), categorised as human (upper) or veterinary (lower). Stages cover the removal of exempt product types (vaccines, vitamins, etc.), substances with sales recorded in non-mass units (e.g. international units), and negative sales corresponding to the return and disposal of products.

exception of Figure 6, which was rendered by the website SankeyMATIC.

Data evaluation

The predicted sales weights in this dataset were compared to similar datasets gathered by both co-authors in NIPH and other Norwegian agencies (Table 6) in order to detect discrepancies and assess the correspondence between independently calculated PECs. Although the primary output of this data paper is PECs, their limited availability made it more practical to carry out comparisons at the sales weights level, particularly as the choice of variables in the calculation of PECs is a question of judgement and conservatism as well as mathematics.

The choice of datasets for comparison and data evaluation was informed mainly by the scarcity of publicly available data in

Norway, compared to better studied nations such as Germany or Spain. The Grung dataset was chosen for comparison as the only previously published dataset using the same method.

The Norwegian Pharmaceutical Specialties website Felleskatalogen maintains a rolling risk assessment on a yearly basis of pharmaceutical risk, using sales data from a private market research firm. In order to benchmark the completeness and accuracy of our dataset to another party's measurement of the same values, we compared our calculated sales weights to theirs. Due to the data's private ownership, Felleskatalogen's PECs are not archived year-on-year or especially transparent; this makes them a useful resource for comparison, but not a permanent part of the scientific record.

Comparisons were performed using a Bland-Altman plot, also known as a Tukey mean-difference plot (Bland & Altman, 1999), which allows for the visual comparison of two measurements of a single parameter.

Table 5. Table of number of unique human and veterinary products input from starting dataset (Figure 3e) and number of unique API output (Figure 3g), by year.

	Starting dataset entries		Unique APIs
Year	*Human*	*Veterinary*	
2016	5,713	660	804
2017	5,904	655	820
2018	5,991	611	820
2019	6,034	597	831

API, Active Pharmaceutical Ingredient.

Further comparisons were conducted between our dataset and prescription data for a high-use subset of APIs. NorPD is a publicly available resource, comparable to those available in other nations, that can produce reports of drug consumption by age, region, sex, and year across Norway. However, as a record of prescription this database is necessarily more limited than the Drug Wholesale Statistics database; additionally, all sales are recorded only in DDDs, introducing inaccuracy compared to actual quantities sold, and excluding drug formulations for which no DDD has been assigned. A further Tukey mean-difference plot (also known as a Bland-Altman)plot was created to compare prescription and wholesales predicted sales weights.

Lastly, we compared our predicted sales weights to two further analyses based on the same dataset. An analysis of 2005 API sales weights for a panel of 11 APIs was conducted by Grung *et al.* (2008); we selected three high-use APIs with a wide range of constituent ATC codes—paracetamol, ethinylestradiol and ibuprofen—and compared these sales weights with our predictions for 2016–19.

To further benchmark trends in consumption, these sales weights were normalised by dividing the figures by the annual population of Norway. They were then compared to wholesale data published by NIPH – available as PDF reports (Sakshaug *et al.*, 2013; Sakshaug *et al.*, 2018; Sommerschild *et al.*, 2021b) of consumption in DDDs per thousand people per day for a limited range of substances. Although direct comparisons between normalised sales weights and DDD/1000 people/day were not possible, we were able to compare overall trends in consumption to look for disagreement.

Predicted Environmental Concentrations

PECs of individual APIs in the compartment Surface Water were calculated using a modified form (Equation 1) of the standard refined PEC_{sw} equation, with default variables (Table 7), outlined in the EMA's guidelines for pharmaceutical environmental risk assessment (2006).

Table 6. Summary and labelling scheme for datasets used and referenced in this paper.

Label	Source	Type	Output format	Years used (Total coverage)	Reference
Welch	NIPH	Wholesale	g/API	2016–19	DOI: https://doi.org/10.17605/OSF.IO/GMX58
Felleskatalogen	FK	Wholesale	g/API	2018	Felleskatalogen, 2022
NorPD	NIPH	Prescription	DDDs	2016–19 (2004–20)	NIPH, 2021
Grung	NIPH	Wholesale	DDDs & g/API	2005	Grung *et al.*, 2008
NIPH	NIPH	Wholesale	DDDs	2007–19	Sakshaug *et al.*, 2013; Sakshaug *et al.*, 2018; Sommerschild *et al.*, 2021b

NIPH, Norwegian Institute of Public Health; NorPD, The Norwegian Prescription Database; API, Active Pharmaceutical Ingredient; DDD, Defined Daily Dose.

Table 7. Table of PEC_{sw} equation default variables and parameters.

Component	Unit	Description
g of API sold	*g year*$^{-1}$	The total weight (g) of an API sold in a year
WWTP removal	*unitless*	The proportion of the API removed at WWTP (default of 0)
365	*days year*$^{-1}$	The number of days in a year
Wastewater consumption	*L person*$^{-1}$ *day*$^{-1}$	The average wastewater consumption (L) of the population of a given area per day
Population	*persons*	The population of a given area
Dilution factor	*unitless*	The ratio of dilution between WWTP effluent and receiving waters (default of 10)

PEC, Predicted Environmental Concentrations; API, Active Pharmaceutical Ingredient; WWTP, Wastewater Treatment Plant.

As no specific bodies of water are specified in the guidelines, the model is assumed to apply to all relevant freshwater bodies, *i.e.*, rivers and lakes. In Norway, where a significant proportion of WWTP (Wastewater Treatment Plant) outflow is to saltwater fjords, the omission of marine modelling is a limiting factor, but is in-line with current practice in Norway.

Likewise, metabolism of APIs in the human body was assumed to be 0 as a worst-case scenario for all APIs. Although this may overestimate PECs, the assumption that metabolism of an API intrinsically removes the overall volume of ecotoxicologically active substance entering the environment may also underestimate the effects of metabolites (Farré *et al.*, 2008).

Equation 1.

$$PEC_{SW} = \frac{API\ sold \times (1 - WWTP\ Removal)}{365 \times Wastewater\ consumption \times Population \times Dilution\ factor}$$

PEC, Predicted Environmental Concentrations; API, Active Pharmaceutical Ingredient; WWTP, Wastewater Treatment Plant.

As mentioned, the standard equation estimates sales weights from the maximum dose of a given API and the proportion of people in a population taking that API. By contrast, by using our dataset of pharmaceutical wholesales we can input a more exact figure for consumption across the entire population of Norway. Default values for removal in wastewater treatment plants (0% removal) and dilution factors (dilution to 1 part in 10 upon entering receiving waters) were retained as worst-case assumptions, potentially contributing to overestimation of PECs. In particular, the assumption of 0% removal biases the dataset towards overestimating concentrations of well-removed APIs.

In addition, the default dilution factor of 10 has been criticised as potentially not covering especially low-flow conditions in European rivers (Link *et al.*, 2017). In Norway, the coast and sea are the primary receivers of Norwegian treated wastewater (Berge & Sæther, 2020); information on dilutionfactors is difficult to locate, but one report (Källqvist *et al.*, 2002) suggested coastal WWTP outflow pipes are situated at sufficient depth and distance to achieve dilution rates of 50–75.

PECs were individually calculated per API, per year, using information on yearly average wastewater generation and Norwegian population, obtained from Statistics Norway and included as *Underlying data* (Welch *et al.*, 2022).

Identification and grouping of APIs

To aid in the contextualisation and machine reading of the dataset, additional data were collected and appended to API sales data. Firstly, standard InChIKeys, a short, unique string based on molecular structure, were, where possible, found for all APIs (Heller *et al.*, 2015) using the R package webchem (Szöcs *et al.*, 2020) (RRID:SCR_017684) to look up API names via the Chemical Translation Service (Wohlgemuth *et al.*, 2010) (RRID:SCR_014681).

Additionally, APIs were sorted into single categories based on function and/or target organ (antidepressant, respiratory, antibacterial, *etc.*), adapted from ATC classifications and sourced from Felleskatalogen, Drugs.com, and WHOCC for Drug Statistics records. A short description of the type and application of APIs was also included, based principally but not exclusively on use in Norway.

Data evaluation

Comparison with Felleskatalogen data

Figure 7 summarises agreement between the two datasets for the year 2018. A mean difference (blue line) extremely close to zero on the y-axis indicates little average difference between calculations. However, a number of substances below the lower red line (95% CI) indicate potential errors in either our or Felleskatalogen's calculations (Table 6). In total, Felleskatalogen sales weights are available for 203 APIs, of which 193 have available toxicity data in the form of Predicted No Effect Concentrations (PNECs), while our dataset contains sales weights for 821 APIs, 255 of which have available PNECs.

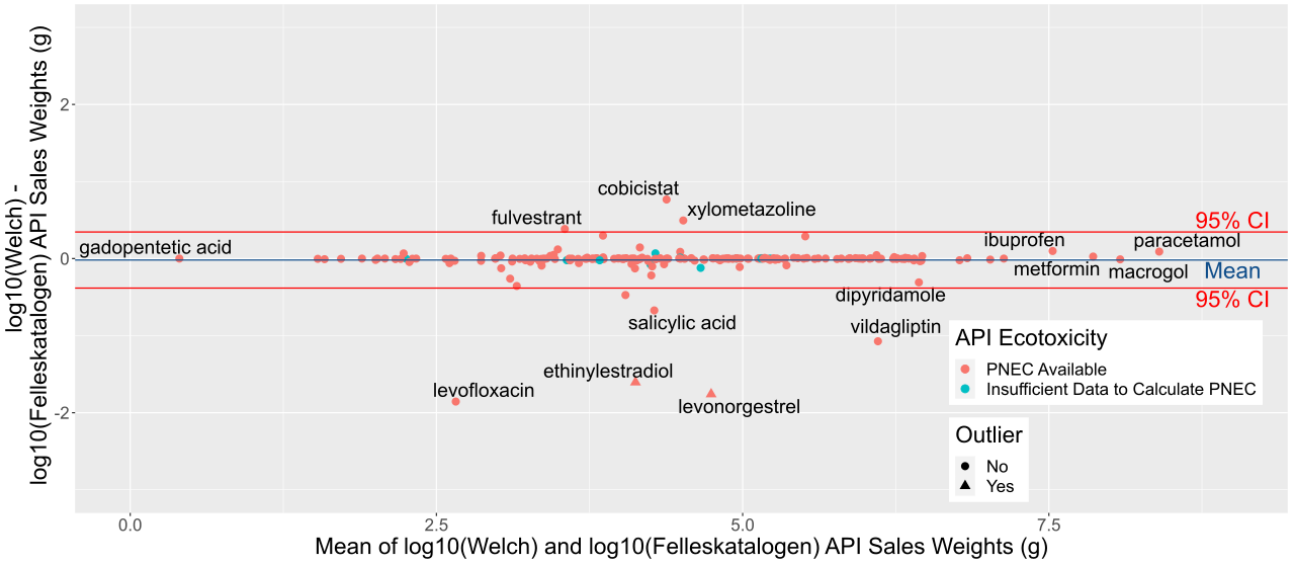

Figure 7. Comparison between NIPH-derived and Felleskatalogen Predicted Environmental Concentrations datasets, for sales in 2018. Bland-Altman or Tukey mean-difference plot of difference (y axis) and mean (x axis) of log10-transformed sales weight data from our and Felleskatalogen sources. Blue line marks mean difference, and red 95% Confidence Intervals. A substance with no difference between the two predicted weights would fall on the 0 line on the y axis. NIPH, Norwegian Institute of Public Health; API, Active Pharmaceutical Ingredient; PNEC, Predicted No-Effect Concentration.

Of these, discrepancies between figures for ethinylestradiol and levonorgestrel are due to the mistaken substitution of milligrams (mg) for micrograms (mcg or µg) for one combination product containing levonorgestrel and ethinylestradiol in Felleskatalogen's data source and have consequently been excluded from summary statistics. Differences in sales of salicylic acid may be due to its presence in a number of non-medical skin products not included in NIPH data, and/or from the combination of the weights of salicylic acid and 5-aminosalicylic acid, treated as separate APIs in our data. The discrepancy for levofloxacin between our data (5.4 × 10 g) and Felleskatalogen (3.9×10^3 g) is likely due to the exclusion of eye drops containing the antibiotic from the NIPH source data, while no explanation was found for the difference in vildagliptin, 3.7×10^4 g compared to 4.4×10^6 g.

Comparison with prescription data

To assess the value of our dataset compared to NorPD (Table 6), we compared predicted sale weights for six substances (Table 8) present in both datasets, a selection of common human, veterinary, over the counter (OTC) and prescription APIs, for the year 2019 (Figure 8).

Comparing wholesale and prescription sales weights for these substances (Table 8), it can be seen that on average, prescription data predicted lower sales weights for APIs, but this was driven by the decongestant xylometazoline, whose sales weight was predicted to be around 1000 times higher than prescription weight. The OTC and prescription painkillers paracetamol and ibuprofen had a sales weight of roughly 1.5 times and 2.3 times wholesale than prescription.

The prescription-only APIs metoprolol and atorvastatin showed strong agreement between wholesale and prescription weights (<10% difference), while amoxicillin and progesterone were predicted a 45% and 28% higher prescription weight than sales weight. In both cases, this is likely due to the difficulty of distinguishing the appropriate DDD to use with prescription data, as it does not distinguish between routes of admission at the ATC code level, and the highest DDDs for these substances are 2–3 times higher than the lowest.

Comparison with Grung *et al.*, 2008 and NIPH Wholesale Report Data

Predicted sales weights, normalised by population, were also compared to earlier (recorded in 2005, published in 2008) (Table 6) predictions and (non-comprehensive) published trends in consumption by DDD. Comparing our predictions of paracetamol sales weights to those in 2005 (Figure 9) shows a plausible growth in normalised consumption, the majority of which is driven by growing consumption in plain paracetamol over time.

Consumption of ibuprofen (Figure 10) is also driven by the consumption of ibuprofen as a painkiller (variously classified as M01AE01 (oral/rectal/injected) and M02AA13 (topical)). Drawing direct comparisons between different combinations of the API is difficult due to changes in API encoding, patchy

Table 8. Panel of human and veterinary drugs selected for comparison between our dataset and NorPD. Where multiple DDD values were possible for one ATC code, the highest value was used. Codes beginning with Q correspond to veterinary applications. Inj. refers to injected forms of drug, vag. to vaginal.

API	Description	Availability	ATC Codes	DDD	Notes
Paracetamol	Human painkiller	OTC & Prescription	N02AJ06 N02BE01 N02BE51	3.0 g (oral) 3.0 g (oral) 3.0 g (oral)	High consumption
Ibuprofen	Human painkiller	OTC & Prescription	M02AA13 C01EB16 M01AE01	N/A 0.03 g (oral) 1.2 g (oral)	High consumption
Xylometazoline	Human nasal decongestant	OTC & Prescription	R01AA07 R01AB06	0.8 mg (nasal) N/A	High consumption
Amoxicillin	Human & vet. antibacterial	Prescription	J01CA04 J01CR02 QJ01CA04	1.5 g (oral) 3 g (inj.) 1.5 g (oral) 3 g (inj.) N/A	Significant consumption
Progesterone	Human & vet. sex hormone	Prescription	G03DA04 QG03DA04	30 mg (oral) 5 mg (inj.) 90 mg (vag.) N/A	High consumption
Atorvastatin	Human statin	Prescription	C10AA05 C10BA05	20 mg (oral) N/A	2nd most used prescription
Metoprolol	Human beta blocker	Prescription	C07AB02	0.15 g (oral)	9th most used prescription

NorPD, The Norwegian Prescription Database; API, Active Pharmaceutical Ingredient; DDD, Defined Daily Dose; ATC, Anatomical Therapeutic Classification; OTC, over the counter; N/A, not applicable.

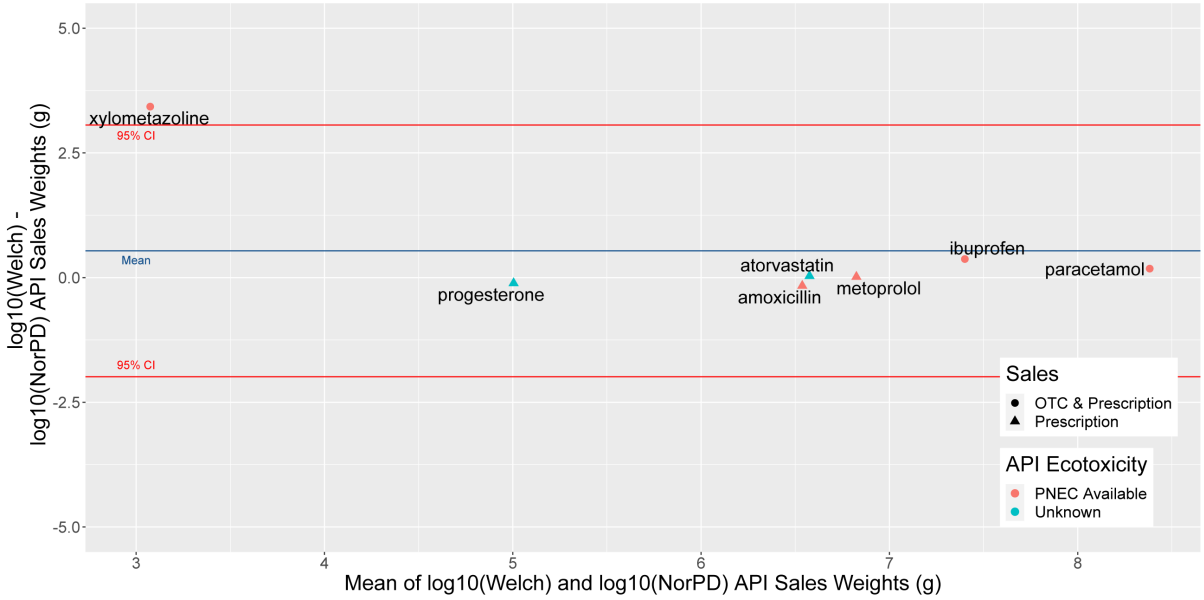

Figure 8. Bland-Altman or Tukey mean-difference plot of difference (y axis) and mean (x axis) of log10-transformed sales weight data from our and NorPD sources for six selected APIs in 2019. Blue line marks mean difference, and red 95% Confidence Intervals. A substance with no difference between the two predicted weights would fall on the 0 line at the centre of the y axis. NorPD, The Norwegian Prescription Database; API, Active Pharmaceutical Ingredient; OTC, over the counter; PNEC, Predicted No-Effect Concentration.

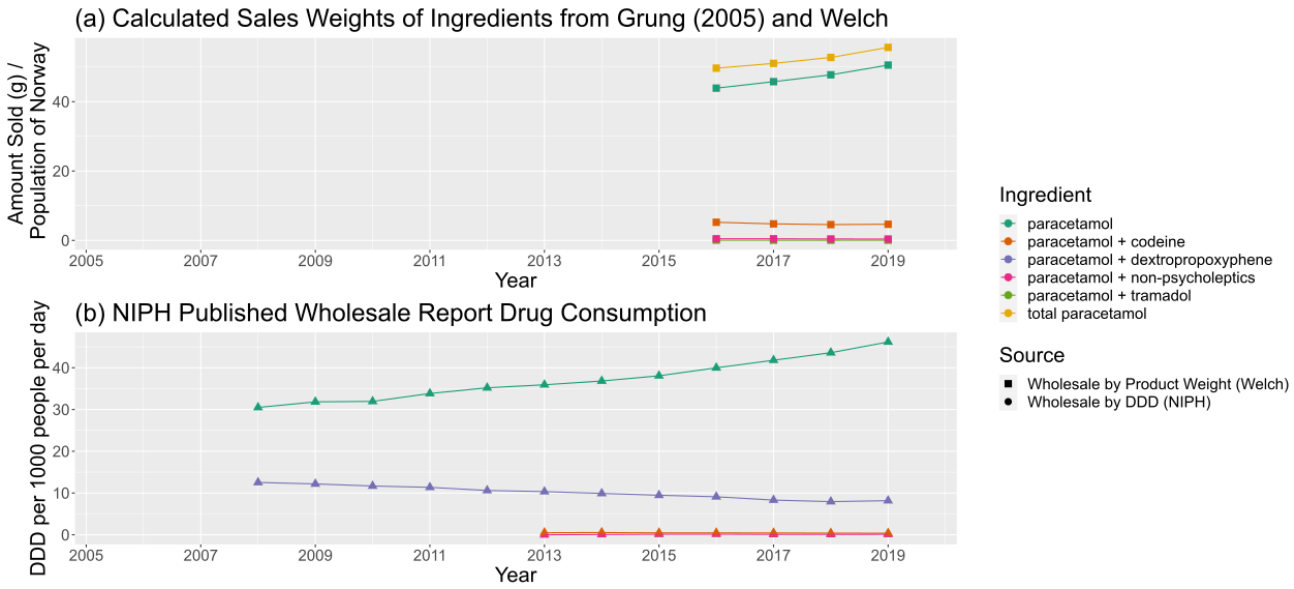

Figure 9. Comparison of predicted sales data sources for paracetamol and paracetamol-containing products. (**a**) Calculated sales weights, by ingredient, for products containing paracetamol in 2005 and from 2016–19, normalised by annual population of Norway. (**b**) Consumption of paracetamol-containing products by ingredient from NIPH published reports, in DDD per 1000 people per day. The combination "paracetamol + non-psycholeptics" corresponds to combinations of paracetamol with caffeine, acetylsalicylic acid, or ibuprofen. For a more complete description of data sources, refer to Table 6. NIPH, Norwegian Institute of Public Health; DDD, Defined Daily Dose.

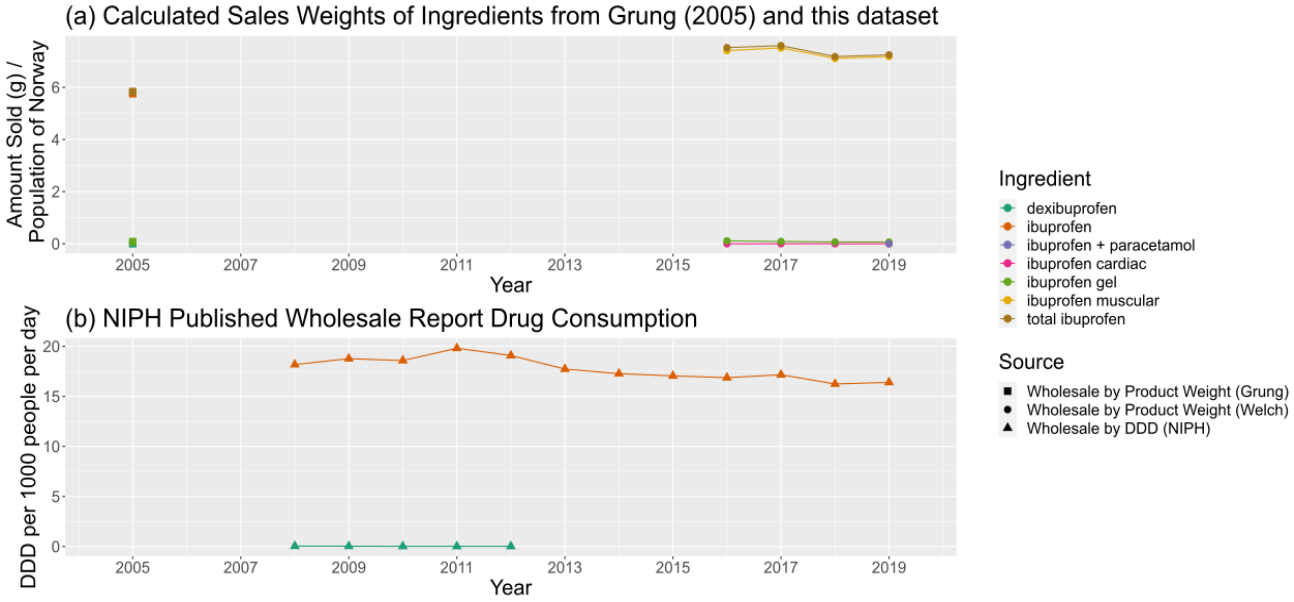

Figure 10. Comparison of predicted sales data sources for ibuprofen and ibuprofen-containing products. (**a**) Calculated sales weights, by ingredient, for products containing ibuprofen in 2005 and from 2016–19, normalised by annual population of Norway. (**b**) Consumption of ibuprofen-containing products by ingredient from NIPH published reports, in DDD per 1000 people per day. For a more complete description of data sources, refer to Table 6. NIPH, Norwegian Institute of Public Health; DDD, Defined Daily Dose.

data availability in Wholesale Reports, and the disappearance of dexibuprofen, an enantiomer of ibuprofen. Nevertheless, in overall trends, a similar pattern of overall decline offset by a small bump in 2017 can be observed.

Interpreting individual sales patterns for ethinylestradiol, also known as EE, is harder than the above due to the wide range of combination contraceptives and hormone therapies. An overall trend of decline in consumption in Figure 11a can be seen, driven by small decreases in constituent consumption, but in Figure 11b it is less apparent whether the trends of different compositions balance each other out. Historical data on ethinylestradiol consumption was largely absent in Wholesale Reports before 2016 (Sakshaug *et al.*, 2013; Sakshaug *et al.*, 2018), except in the case of vaginal rings, where consumption was given in units sold in one report and DDD in the next, making comparisons difficult. Nevertheless, trends for individual combinations that appear in both datasets – EE and levonorgestrel (in fixed static doses), vaginal rings containing EE and etonogestrel, and EE and cyproterone showing corresponding trends.

Checking for extreme changes

In addition to the above comparisons of our data with similar datasets, we elected to compare sale weights by API internally to detect outliers. Sale weights per year were compared to a mean weight over the sales period, and APIs for which at least one year's sales weight was more than 10 times greater than the mean were highlighted. The substances are graphed in Figure 12.

This shortlist covered two APIs with exclusively veterinary use (altrenogest and toceranib) and 29 exclusively human APIs. All of the APIs were available exclusively via prescription, except for cyclizine. Registration and deregistration dates were checked, across the APIs, to determine if changes in consumption could be explained by regulatory status. As products, and therefore product API content tend to remain consistent over the 2016–19 period, the above changes are expected to represent actual changes in consumption. However, it was considered prudent to check medical and pharmacy literature for possible explanations, nevertheless (Table 9).

Stark changes largely corresponded with recorded changes in marketing authorisation (23 substances, 74.1%). Use in some APIs appears to result from shortages in supply (three, 12.5%), while the remaining five (16.1%) were not immediately explicable. These latter substances were then re-checked in source data, no errors were found between years. In three cases, where 2018 sales weights were available from both our and Felleskatalogen data (osimertinib, gadobenic acid and edoxaban), both predictions were in close agreement (<10% difference between values). Beyond the (de)registrations and supply issues listed above, changes in use may be driven by public advertising campaigns, medical lobbying, or relevant press stories.

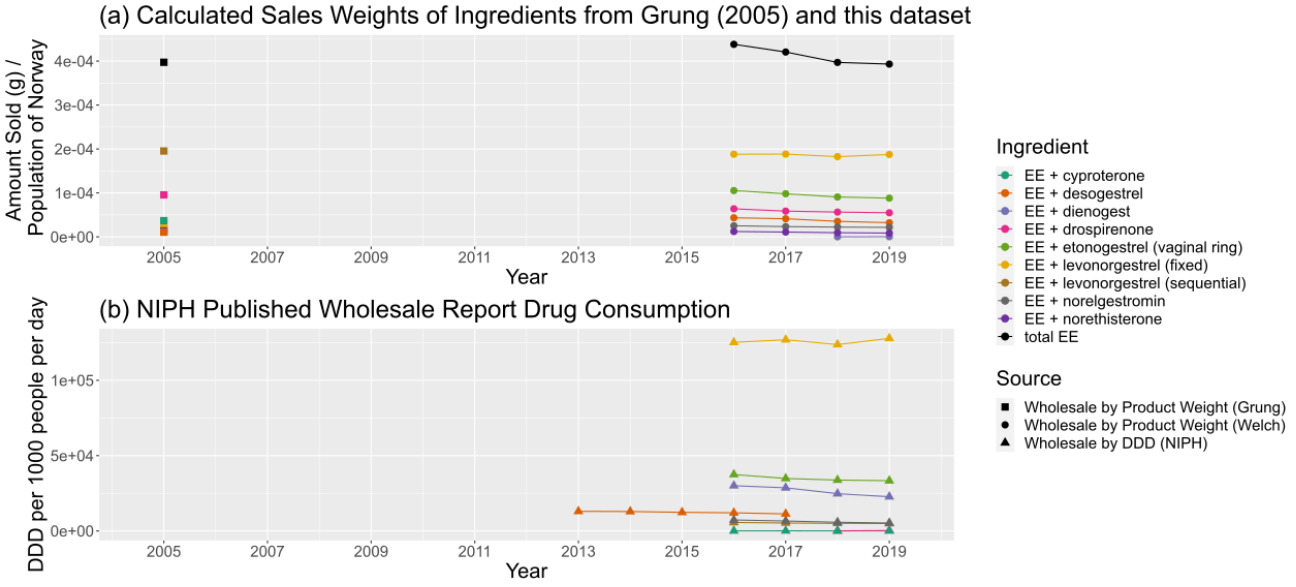

Figure 11. Comparison of predicted sales data sources for ethinylestradiol and ethinylestradiol-containing products. (**a**) Calculated sales weights, by ingredient, for products containing EE in 2005 and from 2016–19, normalised by annual population of Norway. (**b**) Consumption of EE-containing products by ingredient from NIPH published reports, in DDD per 1000 people per day. Fixed and sequential ingredients refer to a course of pills of either a fixed dose, or a changing (sequential) dose. For a more complete description of data sources, refer to Table 6. NIPH, Norwegian Institute of Public Health; DDD, Defined Daily Dose; EE, ethinylestradiol.

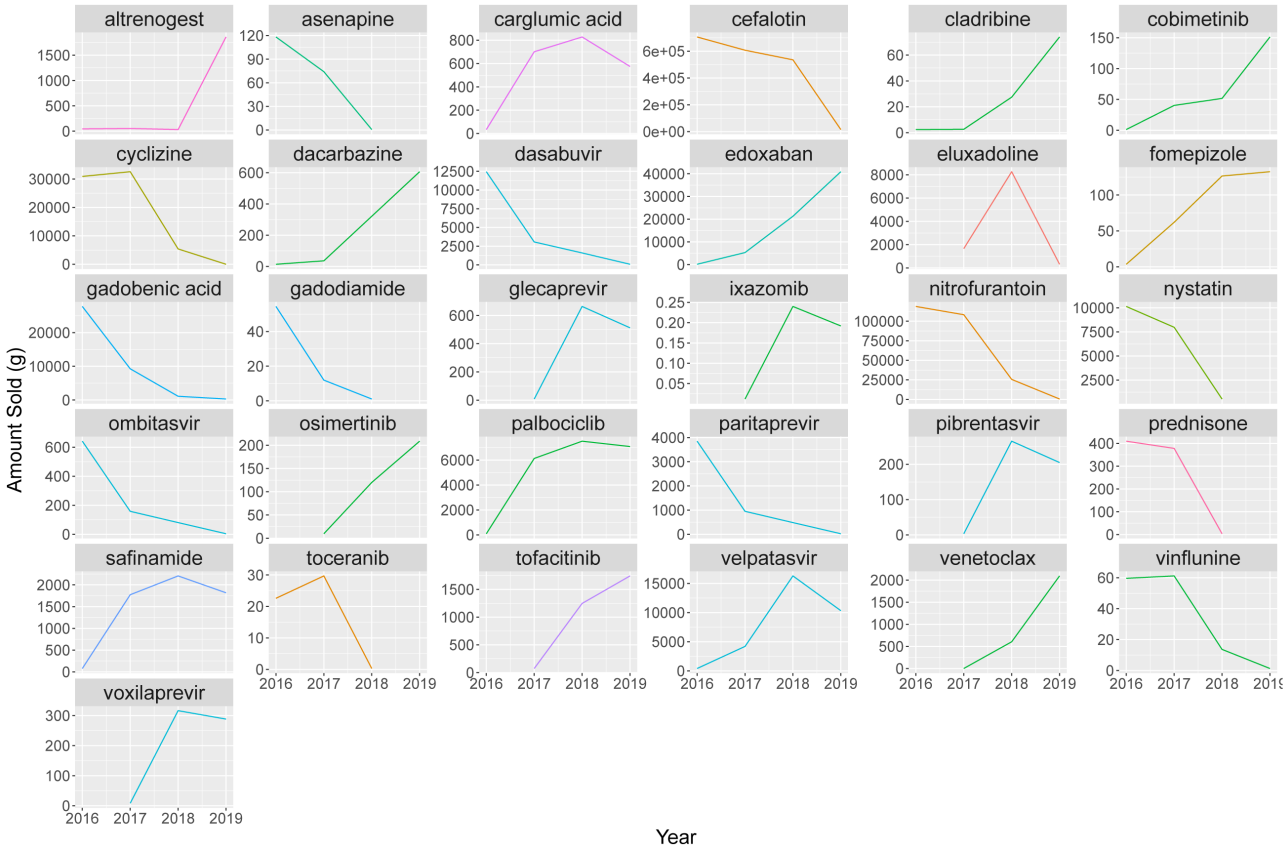

Figure 12. Calculated sales weights 2016–2019 for APIs where at least one year's weight is 10x bigger or smaller than the mean API sales weight. A total of 31 APIs were shortlisted under this criterion; see Table 9 for further details. Coloured by type. API, Active Pharmaceutical Ingredient.

Table 9. Shortlist of APIs where at least one year's weight is 10× bigger or smaller than the mean.

API name	Type	Description	Comments
altrenogest	sex hormone	veterinary birth control	New formulation ("Altresyn Ceva" authorised in Norway 2018 (Statens legemiddelverk, 2022)
asenapine	antipsychotic	atypical antipsychotic for schizophrenia and bipolar disorder	Sole product ("Syncrest") deregistered 2017 (Felleskatalogen, 2022)
carglumic acid	metabolic	carbamoyl phosphate synthetase inhibitor for hyperammonaemia	Two products, one of which ("Ucedane") was first authorised in June 2017 (Felleskatalogen, 2022)
cefalotin	antibacterial	beta-lactam cephalosporin antibiotic	Shortage of cefalotin in Norway recorded 2019 (Antibiotika.no, 2019)
cladribine	antineoplastic	antimetabolite and immunosuppressant for multiple sclerosis and leukaemia	Authorised August 2017 (Felleskatalogen, 2022)
cobimetinib	antineoplastic	mitogen-activated protein kinase inhibitor for melanoma	Authorised November 2015 (Felleskatalogen, 2022)
cyclizine	antiemetic	piperazine antihistamine for nausea relief from motion sickness, vertigo	Cause of change unknown
dacarbazine	antineoplastic	alkylating agent for skin cancer and lymphoma	Authorised March 2017 (Felleskatalogen, 2022)
dasabuvir	antiviral	antiviral used in combination for treatment of hepatitis C	Manufacturer withdrew application for dasabuvir/ombitasvir/paritaprevir/ritonavir in 2016 (Nye Metoder, 2016); however, ritonavir is also available alone

API name	Type	Description	Comments
edoxaban	antithrombotic	Factor Xa inhibitor for clotting reduction for strokes, atrial fibrillation, DVT	Authorised June 2015 (Felleskatalogen, 2022)
eluxadoline	antidiarrheal	treatment for diarrhoea from IBS	Authorised as reimbursable prescription 2017, withdrawn from market 2019 (Statens legemiddelverk, 2017; Felleskatalogen, 2022)
fomepizole	antidote	antidote to methanol and antifreeze poisoning	Cause of change unknown
gadobenic acid	diagnostic agent	gadolinium contrast agent used for magnetic resonance imaging	Cause of change unknown
gadodiamide	diagnostic agent	gadolinium contrast agent used for magnetic resonance imaging	Deregistered 2018 (Felleskatalogen, 2022)
glecaprevir	antiviral	protease inhibitor used in combination with pibrentasvir for hepatitis C	Glecaprevir/pibrentasvir ("Maviret") Authorised July 2017 (Felleskatalogen, 2022)
ixazomib	antineoplastic	proteasome inhibitor for multiple myeloma	Authorised November 2016 (Felleskatalogen, 2022)
nitrofurantoin	antibacterial	antibiotic for bladder infections	Shortage recorded from 2018–2021 (VG, 2019)
nystatin	antifungal	topical antifungal	Cause of change unknown
ombitasvir	antiviral	antiviral taken with paritaprevir and ritonavir for hepatitis C	See dasabuvir
osimertinib	antineoplastic	tyrosine kinase inhibitor for non-small cell lung cancer	Authorised February 2016 (Felleskatalogen, 2022)
palbociclib	antineoplastic	selective cyclin-dependent kinase inhibitor for breast cancer	Authorised November 2016 (Felleskatalogen, 2022)
paritaprevir	antiviral	combination treatment for hepatitis C	See dasabuvir
pibrentasvir	antiviral	antiviral used in combination for hepatitis C	See glecaprevir
prednisone	steroid	corticosteroid and immunosuppressant for many immune and allergic disorders	Shortage recorded 2019 (Statens legemiddelverk, 2019)
safinamide	dopaminergic	MAO inhibitor for Parkinson's	Authorised February 2015 (Felleskatalogen, 2022)
toceranib	antibacterial	receptor tyrosine kinase inhibitor for canine cancers	Deregistered 2019 (Felleskatalogen, 2022)
tofacitinib	immunosuppressant	treatment for arthritis, ulcerative colitis	Authorised March 2017 (Felleskatalogen, 2022)
velpatasvir	antiviral	NS5A inhibitor for hepatitis C	Sofosbuvir/velpatasvir ("Epclusa"), Sofosbuvir/velpatasvir/voxilaprevir ("Vosevi") authorised July 2016 (Felleskatalogen, 2022)
venetoclax	antineoplastic	treatment for leukaemia	Authorised December 2016 (Felleskatalogen, 2022)
vinflunine	antineoplastic	alkaloid derivative for bladder cancer	Cause of change unknown
voxilaprevir	antiviral	protease inhibitor for hepatitis C	See velpatasvir

API, Active Pharmaceutical Ingredient; DVT, deep vein thrombosis; IBS, irritable bowel syndrome; MAO, monoamine oxidase; NS5A, nonstructural protein 5A.

Ethics and consent

Ethical approval and consent were not required.

Data availability

Open Science Framework: Pharmaceutical pollution: Prediction of environmental concentrations from national wholesales data. https://doi.org/10.17605/OSF.IO/Y74FW (Welch *et al.*, 2022).

The following files were used in the creation of this work. All foreground data is included, as is background data publicly available or created by the authors.

A published summary of NIPH wholesale data can be found at https://www.fhi.no/en/publ/2021/drug-consumption-in-norway-2016-2020/; in addition to the contact details of relevant NIPH personnel.

Background (Input) Data	Format	Source	Description	Availability
t830_Product_API_sold_per_ year	CSV	Authors'	Processed NIPH Wholesale data	Commercially restricted
NO_EN_API_names	CSV	Authors'	English-Norwegian names for a subset of APIs	In Repo
API_toxicity_2019	Excel	Authors'	Ecotoxicological status of all drugs sold 2016-19 in Norway	In Repo
Felleskatalogen_PEC _PBT_2018	Excel	Felleskatalogen/ Farmastat AS	Drug toxicity, persistence and bioaccumulation, Norway, 2018	Commercially restricted
InChI_Shortlist	CSV	Authors'	InChIKeys corresponding to APIs studied	In Repo
WW_per_PD_2015_2020	Excel	Statistics Norway	Wastewater consumption per person per day in Norway 2015–2020	In Repo
Pop_1951_2021	Excel	Statistics Norway	Mainland Norwegian population on 1 Jan per year 1951–2021	In Repo
NorPD_API_Subset	Excel	NIPH / NorPD	Sample of API prescription data, 2016–2019	In Repo
DDD_conversion_factors	Excel	WHOCC	DDDs from WHOCC ATC/DDD Index	In Repo
API_desc_short	Excel	Authors'	APIs with broad categories and short description	In Repo
Report_DDD_Trends_Subset	Excel	NIPH	Data extracted from reported sales (in DDD) of a subset of APIs	In Repo
Grung_2005_PECs	Excel	(Grung*et al.*, 2008)	2005 PECs for various APIs calculated from NIPH wholesale data	In Repo
Code				
Data_Pipeline.Rmd	R Markdown	Authors'	Full code used in the processing of data	In Repo
Foreground (Output) Data				
sales_by_API_year_processed_ 2022-08-16_16.24	CSV	Authors'	Final data	In Repo

Acknowledgments

We thank Solveig Sakshaug of NIPH (retired) for her assistance with the Drug Wholesale Statistics database, and Petra Mutinova of NIVA for her work on product API data.

The Norwegian Drug Wholesale Database and Norwegian Prescription Database are funded by the Norwegian Institute for Public Health, a subsidiary of the Norwegian Ministry of Health and Case Services.

Anatomical Therapeutic Codes are maintained and administered by the World Health Organization's Collaborating Centre for Drug Statistics Methodology.

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Open Peer Review

Current Peer Review Status: ✔ ? ✔

Version 2

Reviewer Report 13 February 2023

https://doi.org/10.21956/openreseurope.16279.r30494

✔ **Rosa Maria Marce**
Department of Analytical Chemistry and Organic Chemistry, Faculty of Chemistry, Campus Sescelades, Universitat Rovira i Virgili, Tarragona, Spain

The article describes how the Predicted Environmental Concentration (PEC) of the active pharmaceutical ingredient (API) can be estimated from the whole sales data of pharmaceuticals products. The study includes almost 900 APIs used in human and veterinary medicine and covers the annual sales in Norway during the period 2016-2019.

The first part, the calculation of sales weights of each APIs per year is well described and the way they calculate it is much more correct than the data obtained in some published studies only based on prescription. As regards the second part, the evaluation of PECs is an issue of increasing interest and after the revisions I considered that it is well presented and clearly discussed. In my opinion, based on the way manuscript is presented and the valuable information included, the manuscript should be approved.

Is the rationale for creating the dataset(s) clearly described?
Yes

Are the protocols appropriate and is the work technically sound?
Yes

Are sufficient details of methods and materials provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Occurence of pharmaceuticals in the enviroment. Risk assessment of

chemicals.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 26 September 2022

https://doi.org/10.21956/openreseurope.16279.r30101

Gerd Maack
German Environment Agency (UBA), Dessau-Roßlau, Germany

I have no further comments to the revised version of the manuscript.

Is the rationale for creating the dataset(s) clearly described?
Yes

Are the protocols appropriate and is the work technically sound?
Yes

Are sufficient details of methods and materials provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Environmental Risk Assessment of Pharmaceuticals. Authorization of Pharmaceutical Products. Endocrine Disruption

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 28 June 2022

https://doi.org/10.21956/openreseurope.15234.r29467

?

Ad M. J. Ragas
Department of Environmental Science, Radboud Institute for Biological and Environmental Sciences, Radboud University, Nijmegen, The Netherlands
Caterina Zillien
Department of Environmental Science, Radboud Institute for Biological and Environmental Sciences, Radboud University, Nijmegen, The Netherlands

Summary of the article

Welch *et al*. 2022 describes a methodology to convert national wholesales data of almost 900 APIs used in human and veterinary medicine into a dataset that can be used to estimate environmental exposure data. The resulting dataset covers annual wholesales from Norway for the period 2016 – 2019 and provides a comprehensive overview of API sales for an entire country. The different sources to obtain the data and their scopes and limitations are well described and compared to each other.

General impression

This is a nice data note on a highly relevant topic. The note explains how whole sales data of pharmaceutical products can be used to predict environmental concentration of Active Pharmaceutical Ingredients (APIs). The first part of this exercise is interesting, i.e. the step from wholesales data of pharmaceutical products to the amount of API that is sold. This is also the part that is being validated; or at least comparisons are made with other studies, adding to the trustworthiness of the method. The second part of the method, i.e. the prediction of the PEC (and any references made to prioritization and PNECs) are less convincing. The PEC is estimated in a very rudimentary way; hardly the state-of-the-art. The predictions are also not explicitly compared to measured values and thus not validated. We suggest removing this part from the manuscript.

Points of concern:

- The authors correctly mention that some APIs are salts. Where the PNEC is typically reported as the amount (i.e., weight) of the active ion, products typically report the weight of the salt. This can result in errors. The authors mention this, but they do not explicitly state how they dealt with this issue. Do the API weights that they report refer to the salt or to the active ion? And how did they deal with different salts that have the same active ion? The authors should be more explicit about their implicit assumptions on this point.

- To derive the PEC, no API-specific excretion was considered. This results in the overestimation of PEC but is not mentioned explicitly in section 'Predicted Environmental Concentrations'. This is one of the reasons, we suggest removing the whole section on PECs and to focus on the estimation on the API sales weights.

- The section on Potential Applications is rather speculative. It does not belong in a methods section. We're not familiar with the formal structure of a data note, but it seems more

appropriate to put this type of argument in a reflection/discussion section.

- For your international audience, it would be great if the titles of the datasets on the repository were in English.

- Not all data (i.e., the NIPH wholesales data) used in the data note seem to be publicly accessible. As such, it is difficult to reproduce the results. We don't find this a huge problem, but we're not sure whether this is in line with the publication policy of the journal.

Specific comments

P1: more prominent groups -> please specify;

P1: We doubt whether all readers will know the difference between market-based and sales-based assessments;

P1: Is ecotoxicological-exempt the same as data deficient?

P2: Human biology -> what about the veterinary pharmaceuticals?

P2: but doing so everywhere -> doing what everywhere? I assume measuring, but this is not explicitly stated;

P2: Somewhere you should explain in a bit more detail what the difference is between wholesales data and prescription data. Figure 2 nicely captures this.

P6: The main data tables are shown in Figure 4 -> the tables in Figure 4 have different names than the main data tables listed in the text.
Confusing.

P6: the associated API names associated were…

P8: validating sales data is definitely not enough to “quality-assure PECs”. Please remove or reformulate.

P9: Please add a more explanatory caption. What does “non-masses”, “real masses” and “returns” refer to?

P9: The Norwegian Prescription Database (NorPD), the Norwegian Prescription Database…

P11: Numbers in text are reported in a lot of detail. I suggest using a scientific notation to avoid the suggestion of too much accuracy.

P12: Remove Figure 7b. It adds little to no new information.

P12: More dated -> do you mean more recent?

P14/15:The legend of Figures 9-11 is not particularly clear. Numbers are also difficult to compare.

Can you find a different, more transparent way of presenting these results?

P16: Table 9: Nice example of how this data can be used to detect interesting trends (and/or mistakes).

P17: Some of the names of the data files could be a bit more user-friendly so that the reader immediately understands the content.

Is the rationale for creating the dataset(s) clearly described?
Yes

Are the protocols appropriate and is the work technically sound?
Partly

Are sufficient details of methods and materials provided to allow replication by others?
No

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Human and ecological risk assessment of chemicals, particularly pharmaceuticals.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 21 Aug 2022

Sam Welch

Thank you for your quick and comprehensive feedback on our paper. I've revised the paper in response to a number of your suggestions, and I'll attempt to respond to them all below.

General impression

This is a nice data note on a highly relevant topic. The note explains how whole sales data of pharmaceutical products can be used to predict environmental concentration of Active Pharmaceutical Ingredients (APIs). The first part of this exercise is interesting, i.e. the step from wholesales data of pharmaceutical products to the amount of API that is sold. This is also the part that is being validated; or at least comparisons are made with other studies, adding to the trustworthiness of the method. The second part of the method, i.e. the prediction of the PEC (and any references made to prioritization and PNECs) are less convincing. The PEC is estimated in a very rudimentary way; hardly the state-of-the-art. The predictions are also not

explicitly compared to measured values and thus not validated. We suggest removing this part from the manuscript.

The PEC is indeed calculated in a rudimentary way; unfortunately, with 800+ APIs over four years and limited time this seemed like the best compromise to make the data publicly available. I would also note that more precise modelling tools, such as Oldenkamp et al.'s ePiE are not yet set up for Norway. Our approach is crude, but we're limited by the tools we have available, while removing the PECs entirely would make this data paper no longer an ecotoxicological resource. I've expanded the discussion in the introduction more to cover these questions, but I believe too much discussion would, again, be out of the scope of a data note.

Points of concern: **The authors correctly mention that some APIs are salts. Where the PNEC is typically reported as the amount (i.e., weight) of the active ion, products typically report the weight of the salt. This can result in errors. The authors mention this, but they do not explicitly state how they dealt with this issue. Do the API weights that they report refer to the salt or to the active ion? And how did they deal with different salts that have the same active ion? The authors should be more explicit about their implicit assumptions on this point.**

I've attempted to clarify this in the methods section, but in essence: when clear data on the salt form of an API was available, we factored it into our concentration. When it wasn't, we assumed the full weight corresponded to the active ion.

To derive the PEC, no API-specific excretion was considered. This results in the overestimation of PEC but is not mentioned explicitly in section 'Predicted Environmental Concentrations'. This is one of the reasons, we suggest removing the whole section on PECs and to focus on the estimation on the API sales weights.

Acquiring or developing API-specific excretion factors for 800+ APIs was beyond the scope of this paper. This does potentially lead to overestimates of risk, especially for well-metabolised APIs, but as it's also possible for metabolites to be more toxic, or transformed back into toxic products in the environment, we believe modelling excretion as negligible provides a safest worst-case approach. I've added a summary of this to the section of Predicted Environmental Concentrations .

The section on Potential Applications is rather speculative. It does not belong in a methods section. We're not familiar with the formal structure of a data note, but it seems more appropriate to put this type of argument in a reflection/discussion section.

This is a reasonable point. I've removed the section to keep the paper streamlined – it was an inclusion from an earlier version of the paper and wasn't described in the data note guidelines. We'll cover applications further in an upcoming paper, and they're also mentioned in the Deliverable D6.2 linked in the introduction.

For your international audience, it would be great if the titles of the datasets on the repository were in English. I've updated the names of all data sets to English. **Not all data**

(i.e., the NIPH wholesales data) used in the data note seem to be publicly accessible. As such, it is difficult to reproduce the results. We don't find this a huge problem, but we're not sure whether this is in line with the publication policy of the journal.

The author's guidelines state: "Data notes must describe research data generated and owned by the authors." We've published all the foreground data, generated by the project (Figure 3f & g), some publicly available data, but no background data owned by other parties/under commercial confidentiality. I've updated the Data availability section to make it more explicit which data we are and aren't able to publish.

Specific comments *Responses to the following comments have been limited to save space, but they have all been addressed.*

P14/15:The legend of Figures 9-11 is not particularly clear. Numbers are also difficult to compare. Can you find a different, more transparent way of presenting these results?

I've spent some time considering alternative ways to display the data, but ultimately, I feel these graphs allow comparison between multiple datasets without creating a false conception of closeness. Sales in DDD/1000/day and kg are not directly comparable, especially across different combination ATC codes, but trends map to each other, and sales are plausible taking into account growth in consumption since 2005. **Are sufficient details of methods and materials provided to allow replication by others? –** No In our view, the question of replication (of results) by others is not strictly relevant for a data note. The "methods" are provided as R codes. However, the "materials" would correspond to background data owned by others (NIPH) which cannot be published here. Therefore, the "results" (the foreground data published here) cannot be replicated by others.

Competing Interests: No competing interests were disclosed.

Reviewer Report 22 June 2022

https://doi.org/10.21956/openreseurope.15234.r29470

?

Gerd Maack
German Environment Agency (UBA), Dessau-Roßlau, Germany

The data for this manuscript is part of a larger project and utilize the unique Norwegian Wholesale Statistic database.

However, the text is quite difficult to read, as it misses an overall red line, especially for readers

not involved in the project and those who did not read the project report.

One example of this is the data evaluation. For me, it is not clear why the author chose the data and publications they compared the results of this project to. Grung *et al.* (2005) and the Felleskatalogen data are very likely not known to anyone outside of Norway. Here a better explanation would have been needed.

Finally, all the effort of building the database and extracting the data should end in using the database and producing results. The results, presented here are, in my opinion, not really representative. The criteria chosen, where at least one year's weight is 10x different than the mean, is at minimum unique. I would have expected a bigger evaluation and more results. What is with e.g. the Top Ten of the highest consumption in Norway? What is with the usual suspects like Metformin, Ibuprofen, Diclofenac, etc....? Or with substances which are known to display an environmental risk?

I, therefore, find this manuscript is not really suitable for indexing.

Some detailed comments.

1. Grung (2005) In Figure 9 -11 Grung (2005) is cited, which is not in the references and also not mentioned in the text.

2. Dilution factor - In table 7 the PECsw equation default variables, used in the EMA guideline, are described. In the respective text, it is mentioned that the default dilution factor of 10 is quite conservative. This might be correct for Norway with the unique combination of large fjords and a small overall population. However, the water exchange in some fjords might be quite low, due to the length and the shape and therefore hardly any tidal currents and already in the Olso region, it is probably a different matter. Especially in other parts of Europe, this is clearly not correct. See therefore the public press of the effluent concentration in British rivers and e.g. Link *et al*.[1] for rivers in Germany.

3. Independent of the above, an exposure scenario, where the effluent is discharged directly into the marine environment is not included in the EMA guideline.

4. Comparison with prescription data - Individual active ingredients are sold both as OTC-products and as prescription products, depending on form and strength. This is missing in the discussion on the gap between prescription and sales data.

5. Checking for extreme changes - Reasons for differences can also be an adverb campaign for new generics (increasing consumption) or a similar adverb campaign of a competitor (decreasing consumption)

References

1. Link M, von der Ohe PC, Voß K, Schäfer RB: Comparison of dilution factors for German wastewater treatment plant effluents in receiving streams to the fixed dilution factor from chemical risk assessment.*Sci Total Environ*. 2017; **598**: 805-813 PubMed Abstract | Publisher Full Text

Is the rationale for creating the dataset(s) clearly described?
Yes

Are the protocols appropriate and is the work technically sound?
Yes

Are sufficient details of methods and materials provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Environmental Risk Assessment of Pharmaceuticals. Authorization of Pharmaceutical Products. Endocrine Disruption

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 21 Aug 2022

Sam Welch

Thank you for your quick and comprehensive feedback on our paper. I've revised the paper in response to a number of your suggestions, and I'll attempt to respond to them all below.
The data for this manuscript is part of a larger project and utilize the unique Norwegian Wholesale Statistic database.

However, the text is quite difficult to read, as it misses an overall red line, especially for readers not involved in the project and those who did not read the project report. I've rewritten part of the abstract and introduction, and I hope our intentions – to calculate PECs from Norwegian drug sales, and publish them – are clearer now.

One example of this is the data evaluation. For me, it is not clear why the author chose the data and publications they compared the results of this project to. Grung *et al.* (2005) and the Felleskatalogen data are very likely not known to anyone outside of Norway. Here a better explanation would have been needed. Pharmaceuticals sales data is not generally publicly available, in Norway or elsewhere, and both predicted and measured environmental concentration data for Norway are similarly scarce, compared with better-studied nations such as Germany. Grung et al. (2008) was the only previously published ecotoxicological exercise conducted with the Norwegian Wholesale Database, so we wanted to ensure that the sales weights we calculated were consistent with expected growth in consumption since 2008. Likewise, Felleskatalogen represents the only public source of PECs for APIs in Norway, but as far as we know their results are not archived year-on-year and are not transparent. As Felleskatalogen PECs are predicted using sales data

from a private market research firm, this represented one of the few options we had to check for agreement between two sources of the same data. I've attempted to clarify these points in the section Data evaluation.

Finally, all the effort of building the database and extracting the data should end in using the database and producing results. The results, presented here are, in my opinion, not really representative. ORE guidelines request that data notes omit analysis and focus on describing the data and its collection/creation, so we believe an analysis would be out of scope. **The criteria chosen, where at least one year's weight is 10x different than the mean, is at minimum unique. I would have expected a bigger evaluation and more results. What is with e.g. the Top Ten of the highest consumption in Norway? What is with the usual suspects like Metformin, Ibuprofen, Diclofenac, etc....? Or with substances which are known to display an environmental risk?** As above, as a data note more in-depth analysis would be out of scope for the paper. Checking for extreme variation in sales weights was an internal quality-control process for us to assess potential issues in our data, but we elected to include a summary of this covering APIs where considerable changes are present but caused by market factors.

I, therefore, find this manuscript is not really suitable for indexing. We hope that our explanations above will prove that the manuscript is suitable for publication in ORE after all, when considering the definition and scope of a Data Note.

Some detailed comments.

1. **Grung (2005) In Figure 9 -11 Grung (2005) is cited, which is not in the references and also not mentioned in the text.**

Updated to 2008.

1. **Dilution factor - In table 7 the PECsw equation default variables, used in the EMA guideline, are described. In the respective text, it is mentioned that the default dilution factor of 10 is quite conservative. This might be correct for Norway with the unique combination of large fjords and a small overall population. However, the water exchange in some fjords might be quite low, due to the length and the shape and therefore hardly any tidal currents and already in the Olso region, it is probably a different matter. Especially in other parts of Europe, this is clearly not correct. See therefore the public press of the effluent concentration in British rivers and e.g. Link *et al*.[1] for rivers in Germany.**

As this study is limited to predicting environmental concentrations in Norway, I believe the comment stands. I've found minimal measured or modelled Dilution Factors for Norwegian surface waters, marine or freshwater, which is why we elected to use the default figure of 10. As a side note, fjord-releasing WWTP in Norway typically release effluent from a pipe located low and far from the coast. I've added a brief discussion of the choice of DF, including the paper you reference, to the relevant section in Methods. **Independent of the above, an exposure scenario, where the effluent is discharged directly into the marine environment is not included in the EMA guideline.** This is an issue with the EMA guidelines, but not one we had the capacity to address in this work. I've added a brief discussion of modelling of saltwater to the section on Predicted Environmental Concentrations.

1. **Comparison with prescription data - Individual active ingredients are sold both**

as OTC-products and as prescription products, depending on form and strength. This is missing in the discussion on the gap between prescription and sales data.

I've clarified the language around this in Methods: Data sources and management.

1. **Checking for extreme changes - Reasons for differences can also be an adverb campaign for new generics (increasing consumption) or a similar adverb campaign of a competitor (decreasing consumption)**

This is potentially the case, although I doubt it was an important driver compared to the already identified regulatory factors, and I've therefor not mentioned it in the test. **Is the rationale for creating the dataset(s) clearly described? - Yes Are the protocols appropriate and is the work technically sound? - Yes Are sufficient details of methods and materials provided to allow replication by others? - Yes Are the datasets clearly presented in a useable and accessible format? - Partly** We've attempted to improve the presentation of the published dataset by rendering names in English and with more frequent reference to the data processing pathway depicted in Figure 3.

Competing Interests: No competing interests were disclosed.

Paper II: Predicting Environmental Risks of Pharmaceuticals from Wholesales Data: An Example from Norway

Environmental Toxicology
& Chemistry

Predicting Environmental Risks of Pharmaceuticals from Wholesales Data: An Example from Norway

Journal:	*Environmental Toxicology and Chemistry*
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Mandatory Keywords:	pharmaceuticals, risk assessment, aquatic toxicology, computational toxicology, risk ranking
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Abstract:	Environmental Risk Assessment (ERA) of pharmaceuticals relies on available measured environmental concentrations, but often such data are sparse. Predicted Environmental Concentrations (PECs), calculated from sales weights, are an attractive alternative, but often cover only prescription sales. We aimed to rank, by environmental risk in Norway, around 200 Active Pharmaceutical Ingredients (APIs) over 2016 to 2019, based on sales PECs. To assess the added value of wholesale and veterinary data we compared exposure and risk predictions with and without these additional sources. Finally, we aimed to characterise the persistence, mobility, and bioaccumulation of these APIs. We compared our PECs to available Norwegian measurements, then, using public Predicted No Effect Concentrations, we calculated Risk Quotients (RQs), and appended experimental and predicted persistence and bioaccumulation. Our approach overestimated environmental concentrations compared to measurements for 18 of 20 APIs with comparable predictions and measurements. 17 APIs had mean RQs > 1, indicating potential risk, while the mean RQ was 2.05 and median 0.001, driven by sex hormones, antibiotics, the antineoplastic abiraterone, and common painkillers. Some high-risk APIs were also potentially persistent or bioaccumulative (e.g. levonorgestrel (RQ = 220) and ciprofloxacin (RQ = 56), potentially persistent), raising the possibility of impacts beyond their RQs. Exposure and risk were also calculated with and without over-the-counter sales, showing prescriptions explained 70% of PEC magnitude. Likewise, human sales, compared to veterinary, explained 85%. Sales-predicted environmental concentrations provide an efficient option for ERA, designed to overestimate compared to analytical techniques, and potentially held back by limited data availability and an inability to quantify uncertainty, but nevertheless, an ideal initial approach for identification and ranking of risks.

1. Introduction

1.1. Pharmaceuticals in the Environment

The potential for pharmaceuticals to negatively impact humans and wildlife is, at this point, well known and extensively studied in the scientific community, although still less so than more prominent groups (Maack et al., 2022). relatively little of this information has been globally translated into regulation (Miarov et al., 2020; Schaub & Braunbeck, 2020; Sumpter et al., 2022). Pharmaceuticals sold and prescribed for both human and veterinary use have been detected across the range of human-dominated continents (Beek et al., 2016; Wilkinson et al., 2022) and even in the Arctic (Kallenborn et al., 2008) and Antarctic (González-Alonso et al., 2017), across groundwater, marine and fresh surface waters, drinking water (Benotti et al., 2009) and terrestrial matrices (Patel et al., 2019).

By design, pharmaceuticals are capable of biologically relevant effects at low concentrations, and studies have shown both sublethal effects and mortality in lab studies at environmentally relevant levels (Caldwell et al., 2012; Flaherty & Dodson, 2005) across a wide variety of pharmaceutical classes. Understanding of direct and indirect mechanisms of action varies between types and species, making it difficult to extrapolate data from effects in humans to other species. Although many target receptors are highly evolutionarily conserved across species (Arnold et al., 2014), different species, and different life stages, can respond to different APIs in unpredictable ways (A. R. Brown et al., 2014).

Despite this variability, grouping pharmaceuticals by broad organ/system target and mode of action remains a convenient and accessible way to generalise effects. Below, we summarise the state of understanding of the effects of some of the best studied groups.

Pharmaceutical sex hormones, principally employed as contraceptives and as part of hormone therapies have been shown to disrupt fish reproduction in laboratory (Nash et al., 2004) and experimental field studies (Harris et al., 2011; Kidd et al., 2007) at environmentally relevant

concentrations, and linked to observed fish sexual disruption in rivers downstream of WWTPs, (Jobling et al., 1998; Mills & Chichester, 2005). However, drawing direct causative links between a given API and an environmental effect remains difficult.

Anti-depressants are the second most common prescribed class of medications after statins (McDonald, 2017), and typically function by preventing the reuptake of the neurotransmitter serotonin. Serotonin is a heavily evolutionarily conserved substance responsible for a broad range of effects including mood, memory, pain, and immune defence, and anti-depressants have been shown to affect behaviour and reproduction in a range of fish (McDonald, 2017) and aquatic invertebrates (Estévez-Calvar et al., 2017; Gonzalez-Rey & Bebianno, 2013), as well as developmental effects in amphibians and fish (Conners et al., 2009; Foran et al., 2004).

Antibiotics, meanwhile, have received a great deal of public and scientific attention as drivers of antimicrobial resistance (Kovalakova et al., 2020) but a number of such substances have also shown environmental toxicity to standard test taxa. Direct toxicity is largely limited to prokaryotic algae and cyanobacteria (González-Pleiter et al., 2013), but some toxicity to plants, invertebrates and fish has also been shown (Isidori et al., 2005; Kovalakova et al., 2020; Yang et al., 2017).

Environmental toxicity has also been found in other therapeutically important groups of APIs (Active Pharmaceutical Ingredients). Statins, a class of drug widely prescribed to lower blood cholesterol, have shown toxicity to aquatic plants (Brain et al., 2006), invertebrates (Dahl et al., 2006; Neuparth et al., 2014; Ribeiro et al., 2015) and fish (Ellesat et al., 2010; Estey et al., 2008; Ribeiro et al., 2015; Thorpe et al., 2004). Analgesics acting via the cyclooxygenase pathway, most famous among them paracetamol, diclofenac, and ibuprofen, are toxic to various aquatic species at high concentrations (around 1 to 100 µg/L) (Cleuvers, 2003, 2004; Nunes et al., 2014). However, toxicity data available across and within drug groups can be inconsistent and difficult to access (Ramström et al., 2020), limiting attempts to understand the overall pharmaceutical risk landscape, beyond individual substances.

1.1. Environmental Risk Assessment of Pharmaceuticals in Europe

Environmental risk assessment (ERA) of human pharmaceuticals in the EU is administered by the European Medicines Agency (EMA), which is empowered to conduct a single authorisation procedure that recommends a pharmaceutical product for marketing in the EU, Iceland, Liechtenstein, and Norway (EMA, 2018).

Under current guidelines, last updated in 2008, all new substances brought to market are required to either conduct an ERA or provide evidence that no such risk assessment is required (EMA CHMP, 2006). Significant changes to the ERA of chemicals across the EU are planned, including a movement to a single assessment per substance regardless of manufacturer and application, under the European Green Deal, but relevant legislation has yet to be passed or implemented (van Dijk et al., 2021).

To streamline the process, this risk assessment is conducted on a tiered basis (Figure 1a), where early phases examine potential for risk under conservative assumptions, while later phases use more realistic assumptions. In summary, at Phase I a Predicted Environmental Concentration (PEC) based on the predicted percentage of a given population using a drug ("Market penetration") and the maximum daily dose of the drug is used to predict a conservative PEC.

If this PEC is below an action limit of 0.01 µg/L, then no further assessment is needed, but if this limit is exceeded a further Phase II assessment is conducted, comparing toxicity and interactions with the environment, predicted from a panel of standardised lab studies, to regulatory thresholds. Additionally, if necessary, a refined PEC can be calculated using more nuanced measures of interactions with the body and environment, and, depending on the individual characteristics, assessments of risk in specific matrices (sediment, sewage treatment plants, groundwater) and to specific taxa (microbes) can be triggered (EMA CHMP, 2006).

At phase I, a log K_{ow} (n-octanol-water partition coefficient, a measure (ascending) of a molecule's lipophilicity) threshold of 4.5 triggers the assessment of persistence and bioaccumulation. Should

the API proceed to phase II, these will be further assessed. Persistence screening, based on the EU TGD (EC, 2003) uses a battery of tests to determine whether the chemical is likely to be degraded by various abiotic and biotic processes over reasonable periods, while bioaccumulation is typically assessed by testing the ratio between the API in fish and the API in water in a stable spiked environment. Where either of these parameters are found to be potentially problematic, this is noted in an API's risk assessment, but neither are factored into the numerical descriptor of risk, or any regulatory decision-making. That said, concentrations of pharmaceuticals in the environment are increasingly regulated under the Water Framework Directive, and draft Environmental Quality Standards for the APIs including azithromycin, diclofenac, estrone, estradiol and ethinylestradiol (EC, 2011a, 2011b, 2011c) have been set, which by design as retrospective ERA account for persistence.

Risk, defined as the probability of an API exceeding a threshold of toxic effect, is calculated by dividing the PEC for a given area by a Predicted No Effect Concentration (PNEC), based the lowest concentration at which chronic or acute adverse effects are found to fish, algae, and daphnia, divided by an assessment factor of 3 to 1000, depending on data availability and test duration. As a matter of convention, any RQ < 1 is generally assumed to be of negligible importance, while exceedances indicate a potential issue. However, as with persistence and bioaccumulation above, no cost-benefit comparison is conducted, as the medical benefit to humanity is judged to outweigh any environmental impact.

Over the fifteen years that this ERA requirement has been in force, reaction to it has been mixed. New risk assessments are required only where it cannot be shown that a substance authorisation would contribute no *additional* risk, so many generally high-consumption substances, such as carbamazepine and paracetamol (Burns et al., 2018), have not, in some cases had ERAs triggered, while newer APIs, even those with much lower consumption, must still be assessed.

Conversely, for those substances where ERAs have been conducted, little or no data is made publicly available, with no ability for researchers to audit the data used in the assessment (Ågerstrand et al.,

2014, 2015; Oelkers & Floeter, 2019). Meanwhile, the battery of tests used has been criticised as originally designed to assess the toxicity of industrial chemicals to an extremely limited range of species (Brandt et al., 2015; Gunnarsson et al., 2019), and thus insufficient to assess the risk posed by API toxicity, let alone the more complex ecologically-mediated effects of antibiotics (Boxall et al., 2012). In Norway, where WWTPs principally—69% of capacity in plants of over 2000 population equivalents—discharge to saltwater ecosystems (EEA, 2022), the freshwater species used in standard tests may be insufficient for estimating risk from pharmaceutical pollution. In the TGD, a default additional Assessment Factor of 10 is given for extrapolating from freshwater to marine ecosystems (EC, 2003), but this has been criticised by the EU's own expert committee on ecotoxicology (EC CSTEE, 2002).

Across other sides of the multi-stakeholder table, both the pharmaceutical industry and European NGOs have criticised the current state of ERA as too broad, not well equipped to prioritise drugs based on chemical properties and mode of action, and lacking transparency, with large portions of toxicity data still proprietary and not in the public domain (European Environmental Bureau, 2018; Snape & Owen, 2019). In 2018 the EMA released a set of draft guidelines for public consultation that build on the prior guidelines and address specific mechanisms of toxicity (endocrine disruption) and reduce the need for environmental fate testing, but there is as yet no timeline for if or when these will replace the guidelines currently in force (EMA, 2018), despite the growing importance of environmental sustainability in the EU's plans for pharmaceuticals, and its ambitions to reach a toxic free environment (EU, 2020, 2021).

In response to this lack of risk assessments for common drugs, and the relative abundance of prescription and sales data available, several parties have conducted desk studies, aiming to predict the emissions, exposure and effects of pharmaceuticals to the environment from already existing data (Dong et al., 2013; Grung et al., 2008; Gunnarsson et al., 2019; Guo et al., 2016; He et al., 2020; Jelic et al., 2011). Even desk studies, however, can prove patchy, focusing on different metrics of

potential impact, including exposure, hazard and risk and different models, but with a geographical reach largely limited to the developed West, Japan and China (Burns et al., 2018). A key issue in this approach remains the culture of commercial confidentially in the pharmaceutical industry, which runs directly counter to the academic imperative to make data and methods transparent and readily available, and a great deal of data that is nominally publicly available (Daughton, 2016) might more properly be called grey literature.

Although a wide range of pharmaceutical substances can be easily detected in aquatic ecosystems with modern analytical chemistry (Patel et al., 2019), the extensive diversity of pharmaceutical substances and potentially affected ecosystems, and the necessarily pre-emptive nature of pharmaceutical risk assessment have created an enduring need for the conservative prediction of pharmaceutical environmental concentrations in the environment for regulatory and policy purposes.

Comparisons of sales and prescription-derived exposure predictions to measured exposure have shown its promise as an efficient approach in a number of settings: Burns et al. (2017) found good agreement between PECs and MECs (Predicted and Measured Environmental Concentrations) for 95 APIs in one of the two urban rivers studied in York, UK, while Letsinger & Kay (2019) observed that for 24 APIs with PECs and MECs available, predictions (PEC_B in their work) overestimated both mean and maximum MECs but nevertheless provided a useful tool for prioritisation.

More refined tools, that predict environmental concentrations based on an extensive set of hydrological, demographic and WWTP parameters (T. Austin et al., 2022; Oldenkamp et al., 2018), have been developed, but do not currently include the Norwegian mainland. Furthermore, inclusion of over-the-counter (OTC) sales is rare, particularly on a larger scale (T. J. Austin et al., 2021), potentially leading to underestimates of emissions even where environmental behaviour and fate is well-parameterised. Thus, in Norway, where MECs are rare, models of pharmaceutical emissions are crude, but sales data is high-quality and centralised by public authorities, the existing PEC_{SW} (PEC in

Surface Water) prediction equation represents an ideal first-line tool for prediction and prioritisation.

1.2. Norway in 2019 and beyond

Norway is a highly developed and largely sparsely populated nation in the North of Europe, with mainland habitation ranging from the more temperate and urban south to the arctic north. Norway's population in 2019 was 5.33 million, 82.6% of whom lived in urban settlements. At present day, roughly half of Norway's population lives in Østlandet, in the south-east of the nation, of which 1.01 million live in the Oslo greater urban area, Norway's capital and densest, most populous city. Distribution of water treatment technology is also uneven across the country, with basic mechanical filtration giving way to large-scale advanced, tertiary treatment plants in the south (Berge & S. Sæther, 2020).

State population projections predict a population of over 5.9 million by 2050, and the number of elderly (>70 years old) to double from 670,000 today to 1.4 million (Statistics Norway, 2020). Concurrently, under the high global warming Representative Concentration Pathway 8.5 ("*Business as usual*"), Norway's climate is predicted to change drastically by 2100. Average temperature is expected to increase by around 4.5 °C, and precipitation by 18%, as extreme rainfall events become more common and snow cover shrinks (Hanssen-Bauer et al., 2017).

Norway's economy and way of life is built on marine and freshwater ecosystems, producing an estimated 13,000 million EUR and 600 million EUR in measured ecosystem services respectively per year (Skre, 2017). Of Norway's biodiversity, last documented by the Norwegian Red List for Species in 2015, 14% of threatened species were found in fresh and saltwater ecosystems, and a further 32% in wetlands, coasts, and floodplains (Henriksen & Hilmo, 2015).

Norway's development, climate, regulations, population demographics and minimal pharmaceutical manufacturing infrastructure limit its exposure to the extremely high environmental concentrations of APIs seen in some other nations (Wilkinson et al., 2022). However, its high degree of centralised

data collection, and relatively well-characterised environment make it an ideal testbed for assessing the effectiveness of sales-based approaches.

1.3. Aims

In this paper, we present a top-down method for the ranking of API environmental risk. We build upon a dataset of predicted environmental concentrations (PECs) in surface waters based on national wholesale data for Norway (2016-2019), recently published by Welch et al. (2022). (1) To assess the accuracy of PECs by comparison with available measured environmental concentrations (MECs) for Norway. (2) To calculate risk quotients (RQ) for each API by combining PECs with publicly available environmental toxicity values (PNECs), and make a ranking risk of APIs by risk quotients. (3) To refine the risk characterisation of APIs by inclusion of other chemical properties (persistence, mobility, bioaccumulation). (4) To evaluate the added value of additional information sources and their potential effects on the risk characterisation.

2. Methods

2.1. Software and Data

All data processing and analyses were conducted in Base R 4.2.1 "Shake and Throw" and RStudio 2022.07.1 Build 554. Packages used are summarised in the software repository available below.

API sales weight data in Norway for the years 2016 – 2019 was obtained from a processed and cleaned form of the Norwegian Institute for Public Health's Norwegian Wholesale Drug Database (Welch et al., 2022). PEC_{SW} were calculated there using the standard refined PEC_{SW} equation (Equation 1) outlined in the EMA's guidelines (EMA CHMP, 2006).

$$PEC_{SW} = \frac{API\ sold \times (1 - WWTP\ Removal)}{365 \times Wastewater\ production \times Population \times Dilution\ factor} \quad \text{(Eq. 1)}$$

PEC_{SW} equation with default variables and parameters: API weight sold per year (g), proportion removed in WWTPs (default of 0), days per year (365), wastewater produced per person per day

(default of 200 L), population of area or country, dilution factor of effluent in receiving waters (default of 10).

These data were paired with PNECs and bioaccumulation and persistence hazard statements from the Norwegian pharmaceutical specialities website Felleskatalogen (2022), and further PNECs made available by AstraZeneca (2017) and the EU Joint Research Centre (Loos et al., 2018). Norwegian MECs compiled by the German Environment Agency's Pharmaceuticals in the Environment database (Baz-Lomba et al., 2016; Graumnitz & Jungmann, 2021; Paruch et al., 2017; Plósz et al., 2010; Rodriguez-Mozaz et al., 2020; Vasskog et al., 2008) were used in validation. Lastly, quantitative structure-activity relationship (QSAR)-predicted mobility, bioaccumulation and persistence from OPERA (EPA, 2018), and predicted "provisional PNECs" from the NORMAN ecotoxicology database (Aalizadeh et al., 2017; NORMAN, 2022; von der Ohe et al., 2011) were used to characterised the biotic and abiotic properties of APIs where experimental data were not available..

Where necessary, data was translated from the original language to English. Felleskatalogen Norwegian language Persistency and Bioaccumulation key phrases, typically following a format of "[API name] was found to have a [low/moderate/high/data deficient] [persistence/bioaccumulation] were translated into an ordered categorical variable by matching key phrases (low, moderate, etc.) and replacing the statement with their English equivalent. Norwegian API names were also manually matched with English API names.

2.2. Calculation of Environmental Risk

Comparison of Predicted and Measured Environmental Concentrations

PECs were compared with available Norwegian MECs for wastewater influent and effluent samples, as available surface water MECs were of limited applicability. Of the available MECs, data were limited to single sample analyses of parent substances with valid date values and literature credibility rated as "good" by the database maintainers. In order to draw more direct comparisons,

PECs for wastewater treatment plants (PEC_{WWTP}) were calculated from PEC_{SW} by removing the dilution factor of 10 from the equation, in effect multiplying PEC_{SW} values by 10.

Predicted No-Effect Concentrations

Toxicity data was obtained in the form of Predicted No-Effect Concentrations for 257 substances from the Norwegian Pharmaceutical Specialties website Felleskatalogen (2020). These PNECs were originally calculated by the Swedish Pharmaceutical Specialities website, FASS.se (2019), where full equations and constituent test data were given; however, this data could not easily be converted into a machine-readable format and hence Felleskatalogen's more accessible but less transparent dataset was used. In any case, a full account of the toxicity data's origin is impossible, as the studies that produced said data are often not publicly available.

In addition, this data was supplemented with PNECs made publicly available by AstraZeneca (AstraZeneca, 2017), for seven APIs: atenolol, lidocaine, metformin, mepivacaine, naproxen, omeprazole, and tamoxifen, and six PNECs calculated by the EU's Joint Research Centre (Loos et al., 2018), for azithromycin, clarithromycin, diclofenac, erythromycin, estradiol and ethinylestradiol. Where more than one value was available for a PNEC, the lowest was used.

Risk Quotients

Predicted risk per API per year were calculated as simple Risk Quotients (or Risk Characterisation Ratios) following the standard ecotoxicological method (Equation 2; EMA CHMP, 2006)

$$RQ_{Surface\ water} = \frac{PEC_{Surface\ water}}{PNEC} \quad \text{(Eq 2.)}$$

In accordance with standard practice for pharmaceutical environmental risk assessment, RQ > 1 was used as a threshold above which substances are considered to pose a potential risk to the environment.

QSAR Predicted No-Effect Concentrations

As access to experimental toxicity data was limited to around 25% of APIs, we used modelled PNECs (EC, 2003; NORMAN, 2018), referred to in the source literature as provisional or P-PNECs, as an alternative for initial screening and prioritisation of APIs. These P-PNECs were calculated by the database authors following standard TGD guidelines for predicted acute toxicity tests across three taxa, with an Assessment Factor (AF) of 1000 applied to the most sensitive species by the database authors (EC, 2003; NORMAN, 2018).

Comparing Risk Quotients and Prioritisation

Simple comparisons between risk quotients based on experimental and QSAR PNECs were conducted by calculating Pearson's R (correlation coefficient) between the two sets of values (Rodgers & Nicewander, 1988). Likewise, Spearman's rho (rank correlation coefficient) was used to compare ranking of APIs using various subsets of data.

2.3. Dataset Overview

On average, 820 PECs were calculated per year across the four-year period, of which roughly 25% also had PNECs available, and 52% had QSAR PNECs (Table 1).

3. Results

3.1. Comparison with Measured Environmental Concentrations

Nineteen APIs had both PECs and WWTP MECs for the 2015-16 period (Figure 2): the stimulants methylphenidate and amfetamine, the beta blockers metoprolol and atenolol, the antibiotics trimethoprim, tetracycline, sulfamethoxazole, ofloxacin, metronidazole, clindamycin, clarithromycin, ciprofloxacin, cefalexin, and azithromycin, the anti-epileptic carbamazepine, the anti-depressant citalopram, the antihistamine fexofenadine, the local anaesthetic lidocaine and the erectile dysfunction therapy sildenafil.

In fifteen cases, PEC_{WWTPs} over-estimated compared to MECs (by a median factor of 20), ranging from a 2800-fold overestimation in the case of metoprolol to a 3.6-fold overestimation for azithromycin. The stimulant methylphenidate, the antidepressant citalopram, and the antibiotic tetracycline were within one order of magnitude, while no API other than the previously discussed metoprolol was more than two orders of magnitude greater. In two cases, the PEC was lower than MECs: the stimulant and drug of abuse amfetamine (56-fold underestimation) and the antibiotic ofloxacin (1.5-fold).

A Spearman rank-correlation test was conducted on the 19 comparable median PEC-MEC sets. No significant correlation was found between either EC rankings (Rho = 0.18, p = 0.46). The small sample size of comparable RQs (6) precluded Spearman's test, but briefly: both RQs ranked ciprofloxacin as by far the highest-risk API, but disagreed on the order of the remaining five.

3.2. Characterising Risk Quotients, Persistence, Mobility & Bioaccumulation

Risk Quotients were calculated for 208 substances across the 2016 to 2019 period. The substances with the 20 highest average RQs over this period are displayed in Table 2, while overall the average RQ of all remaining 188 was 0.24, the minimum 6.9E-8 and the maximum 0.41. Likewise, the persistence classes of the remaining substances were 117 high, 34 moderate, 24 low, and 13 uncertain; the bioaccumulation classes 11 high, 174 low, and 3 uncertain; and the mobility classes, predicted by QSAR, were 63 very mobile, 21 mobile and 104 not mobile.

By far the highest risk quotient was seen for the progestogen and androgen levonorgestrel, driven by its inclusion in a wide range of contraceptive products and its chronic reproductive toxicity to fish above 0.0001 µg/L, and presenting a higher RQ than all other APIs' RQs added together. Levonorgestrel has also found to be potentially persistent in biodegradation tests (FASS, 2019a), although its potential to bioaccumulate and predicted mobility are low.

Six further sex hormones were represented in the top 20 APIs, the estrogens ethinylestradiol and estradiol, and the progestogens norethisterone, etonogestrel, desogestrel and drospirenone, with

RQs ranging from 0.47 to 19. Exposure driven largely by use in birth control drugs and implants, chronic reproductive toxicity has likewise been found at low concentrations in fish. Potential for bioaccumulation amongst these APIs is generally low except for ethinylestradiol, and predicted potential for mobility raises no cause for concern, but five of the APIs, estradiol being the only exception, are potentially persistent or slowly degraded in the aquatic environment.

The antineoplastic (or anti-cancer) APIs abiraterone and fulvestrant feature also in the top 20. Abiraterone, a treatment for testicular cancer that acts not only as inhibitor of the production of androgens including testosterone but also as an estrogen agonist, has shown reproductive chronic fish toxicity at nanogram per litre levels, while fulvestrant, a selective estrogen receptor degrader taken for some breast cancers effects reproduction at even lower concentrations, but is sold at a fraction of the quantity.

Two antibiotic APIs are also present, ciprofloxacin, a broad-spectrum fluoroquinolone, and amoxicillin, a beta-lactam antibiotic. Standard toxicity tests for environmental risk assessments include no explicit assessment of toxicity to bacteria, and consequently toxicity is driven by chronic effects to fish, while toxicity data available for amoxicillin was limited to a single study of algal toxicity (Andreozzi et al., 2004).

The presence of the analgesic cyclooxygenase (COX) inhibitors, ibuprofen and diclofenac (non-steroidal anti-inflammatory drugs, or NSAIDs), and the analgesic paracetamol, is largely driven by their extremely high sales weights. Each of the APIs is consistently among the greatest sales weights each year. Paracetamol toxicity in the microgram/l range was driven by chronic toxicity to *Daphnia magna*, while ibuprofen toxicity in the same range results from its effects on green algae. Paracetamol is slowly degraded in the environment, but no other parameters were found to be cause for concern. Diclofenac was flagged as moderately persistent, and mobile; no information on the taxa driving its PNEC could be found.

Mycophenolic acid, a common immunosuppressant prescribed for organ transplants and autoimmune disorders, also showed high risk, driven by its high sales for its class and chronic reproductive toxicity to fish in the 100-ng/l range. The API was also found to be potentially persistent in the environment, and further, predicted to be mobile.

The remaining constituents of the top 20 represented a diverse range of APIs. Chlorhexidine, used yearly in the hundreds of kilos as an antiseptic and disinfectant, poses significant risk due to its acute toxicity to algae (Environment and Climate Change Canada, 2017) and is potentially persistent, while the antifungal terbafine is chronically toxic to algae, and potentially bioaccumulative. Simvastatin, the second most heavily consumed statin in Norway, showed chronic toxicity to *Daphnia* in lab studies, while dronedarone, Norway's principle antiarrhythmic, was chronically toxic to green algae, as well as potentially persistent. Nicotine, predicted to pose low risk using a PNEC driven by *Daphnia* toxicity (Roder Green et al., 2014; Savino & Tanabe, 1989; Valcárcel et al., 2011), is likely underestimated due to the inclusion of only strictly medical sales in this work. Moreover, this API is predicted to be highly mobile in aquatic environments, raising the potential for it to rapidly move through surface water bodies and potentially into groundwater.

Risk Quotients, Persistence (both experimental and QSAR-based), and QSAR mobility (Log_{OC}) were compared (Figure 3) to illustrated patterns of risk across different parameters of interest. Bioaccumulation factors (EPA, 2018) were omitted from graphs but can be summarised thusly: only one substance was predicted to bioaccumulate, with a Bioaccumulation Factor in excess of 8000 (very bioaccumulative): the antineoplastic mitotane. As no experimental data was available, it was not possible to compare this prediction to an empirical number. Four APIs were predicted to be potentially persistent – desloratadine, an antihistamine, sertraline and vortioxetine, antidepressants, and biperiden, an antiparkinson agent. Of these, desloratadine has been demonstrated to be potentially persistent, but no other comparisons can be drawn.

QSAR-predicted Log_{OC} were within applicability domains and calculated for 482 APIs. 316 substances were classified as very mobile (vM, $Log_{OC} < 3$), 97 as mobile (M, $4 < Log_{OC} < 3$), and 69 as not mobile. Although mobility assessment is not as of yet included in current or planned ERA of human or veterinary pharmaceuticals (EMA, 2018; EMA CHMP, 2006; Regulation (EU) 2019/6, 2022), assessment of mobility has been proposed for inclusion in REACH assessment (Berger et al., 2018), and has recently undergone public consultation (EU, 2022). Thus, it seems reasonable to assume it will at some point be considered in regulatory ERA of pharmaceuticals.

Table 3The predicted mean RQ across the 4 years, and experimental PNEC availability across the 20 API types containing the most APIs are summarised in Table 3. In total, APIs were classified into 57 types, with a minimum number of constituents of 1, a maximum of 110 and a mean of 15.3. Availability of PNECs across all types was poor, with 14 classes (covering 67 APIs) having no data available, and only 7 classes (56 APIs) having 50% or more data. Availability in groups containing highest risk substances, such as antineoplastics, analgesics and sex hormones are notably poor, raising the possibility that overall risk is significantly underestimated due to their omission – though without knowing how much these substances would drive overall risk, drawing firm conclusions would be premature.

3.3. QSAR-Predicted Toxicity as a Supplement to Test Data

As an alternative to limited available PNECs, QSAR lowest PNECs (p-PNECs) generated by Aalizadeh *et al.* (2017) from the NORMAN ecotoxicological database were also used to screen and rank APIs (Figure 4a) (NORMAN, 2018, 2022). We were able to match 428 APIs to provisional PNECs (roughly 50%), 78 of which also had experimental PNECs, permitting comparisons between results (Figure 3b, c). Correlation between the two datasets was poor, with provisional RQs on average 50% higher than standard RQs, and low positive correlation between both values (Pearson's r = 0.301) and rankings (Spearman's rho = 0.493) of RQs. Ultimately this discrepancy is likely based on the narcosis and physicochemical-parameter based prediction tools used in the source data (Aalizadeh et al., 2017), compared to the receptor-driven toxicity (Coors et al., 2022; Gunnarsson et al., 2019) of most APIs, especially high risk sex hormones.

3.4. Wholesale-Prescription and Human-Veterinary Risk and Exposure

Norway's Wholesale Pharmaceutical Database is an unusual resource in its inclusion of not only prescription but also over-the-counter and institutional use of medications, and coverage of both human and veterinary products. PECs, and, where possible RQs, were compared between total, all-inclusive sales weights and prescription sales weights only, to assess the impact of the inclusion of wholesales.

In total, of the 870 APIs for which sales weights were calculated, 72 were available OTC and 840 under prescription. Of these, 42 substances are available both OTC and under prescription. On average, PECs excluding OTC sales were 68.5% (median 71.6%) the size of total sale PECs, but this difference was largely driven by a handful of APIs: the stimulant caffeine (0.001%), the imidazole antifungals ketoconazole and econazole (7% and 20%), the progesterone receptor-modulating sex hormone and emergency contraceptive ulipristal (83%), the anti-acne drug benzoyl peroxide (21%), the laxative bisacodyl (25%), the antihistamine meclozine (32%), and the antifungal amorolfine (43%).

RQ calculations were only possible for 10 of these APIs, giving an average contribution of prescription sales to total sale risk of 92%. Of the constituents, only acetylsalicylic acid (aspirin), diclofenac, miconazole, paracetamol, ibuprofen and the disinfectant, antiseptic and mouthwash chlorhexidine saw an increase of more than 10%, and RQ overall increased by 19.4 across the nine substances. Prioritising APIs by RQ gave an extremely similar order both with and without the addition of OTC sales (*Spearman's rho = 0.99, P < 0.01*).

Likewise, of the 870 APIs 793 were sold for human use and 120 for veterinary use, while 43 are available for both. Of these APIs, only one, methylrosaniline, an antiseptic and disinfectant also known as Solvent Violet 9, is coded as being available over the counter.

Of the 43 dual-purpose APIs, on average 84% (94% median) of PECs' value was contributed by human use. As with the previous comparison, this is driven by only a small proportion of APIs, principally the antibiotics oxytetracycline (4%) and benzylpenicillin (39%), the NSAID meloxicam (8%), the anthelmintic ivermectin (25%), and the sedative dexmedetomidine (39%). Consequent effects on risk could only be calculated for 3 of these, giving a 94% average (92% median) contribution across the antibiotic amoxicillin (91%), the antiseptic chlorhexidine (99%) and the antifungal miconazole (92%). Again, prioritisation based on human data only gave an almost identical order to human and veterinary data (*Spearman's rho = 0.99. p < 0.01*).

4. Discussion

4.1. Comparison of Predicted Environmental Concentrations to Measurements

By design conservative, it is not, perhaps, a surprise that where PECs and MECs were available for the same substances, PECs generally represented an overestimate compared to detected levels in WWTP influent and effluent, although comparing concentrations for the same year was not typically possible. Our findings are broadly in line with other works comparing MECs and PECs (Burns et al., 2017; Letsinger & Kay, 2019), and are likely driven by a combination of factors. Conservative choices of WWTP removal and metabolism parameters will drive overestimates of inputs, especially where

APIs are well-metabolised, or removed – although there remains the potential for APIs to be (back-)transformed into toxic chemicals in the environment (Celiz et al., 2009). Likewise, Norway's complicated hydrological landscape is likely not well captured by a default dilution factor of 10, although very little observational data is available (Keller et al., 2014). Finally, our use of sales data collected at the wholesale level assumes total consumption of purchased pharmaceuticals, when variation in sales to the public, patient adherence (M. T. Brown et al., 2016) and expiry of products mean this is unlikely to be the case.

A handful of exceptions existed to this trend of overestimation. Firstly, amfetamine, a prescription stimulant in enantiomeric mixture, is relatively uncommon in Norway, and is more often sold in Norway as only the right-handed enantiomer dexamfetamine, alone or as the prodrug lisdexamfetamine. Unfortunate, distinguishing between these in the source analysis was not possible (Baz-Lomba et al., 2016), which may contribute to the stark discrepancy between predicted surface water and measured influent concentrations Furthermore, recreational and other illicit uses of amphetamine, and its prodrug methamphetamine, are likely to drive measured concentrations in Norwegian wastewaters, but are difficult to account for in a model based solely on licit sales.

Ofloxacin, with a PEC in the lower ranges of observed effluent MECs, is also a racemic mixture – of levofloxacin and dextrofloxacin – the biologically active former of which is sold more commonly alone. As with amfetamine, it seems probably the discrepancy observed here is caused by the current inability of our model to account for racemic mixtures in prediction.

Covering only 20 of the 870 unique APIs studied (2.3%), it is difficult to generalise conclusions from the MECs compared to the entire dataset. However, the patterns seen here largely depict overestimates of environmental concentrations, in keeping with the model's conservative assumptions, and the choice of the most conservative parameters for metabolism and WWTP removal (EMA CHMP, 2006). APIs were also ranked by environmental concentration and RQ using measured and predicted values. The generation of significant results were limited by small available

sample sizes for comparison, but nevertheless divergences between the two sets of rankings were apparent.

4.2. Characterising Risk, Persistence, Mobility & Bioaccumulation

Predicted API risk, persistence, mobility and bioaccumulation, summarised across Table 2, Figure 3 and Table 3 were characterised by a general patchiness of data, with experimental or QSAR-based parameters generally available for less than 50% of APIs.

Where risk could be considered – roughly 25% of APIs with PECs – 17 substances had RQs in excess of 1, indicating an exceedance of PNECs. Six of these APIs, including levonorgestrel, by far the riskiest (RQ ≈ 220) of the substances, were sex hormones, characterised largely by progestogenic and estrogenic mode of action and adverse effects on fish reproduction at low concentrations. Data were, however, poor both within and across type groupings, a concerning prospect where so many substances in each type share similar modes of action. A discussion of toxicity would be incomplete without also mentioning that PNECs based on risks of anti-microbial resistance (AMR) proposed by Bengtsson-Palme and Larsson (2016) are 3 to 50 times smaller than current PNECs, and consequently the inclusion of AMR as a driver of risk would likely change outcomes significantly.

Data availability was similarly poor for both experimental and predicted persistence and bioaccumulation of APIs, as well as predicted mobility. A number of high-risk APIs, such as levonorgestrel and ciprofloxacin, were potentially persistent, but extrapolating parameters such as persistence and bioaccumulation into an overall quantification of risk is difficult despite the inclusion of screening thresholds throughout the official ERA process (Figure 1).

Seven APIs: terbafine, mycophenolic acid, naproxen, paracetamol, amoxicillin, ibuprofen, and ciprofloxacin showed a potentially concerning combination of high risk (RQ > 1) and mobility (Log K_{OC} < 4). These substances' predicted mobility means they may be more able to circulate in the environment and enter additional compartments such as groundwater; there is also some evidence that APIs with higher K_{OC} values are removed less efficiently from WWTPs (Douziech et al., 2018),

although some of these APIs are known to be removed well (e.g. paracetamol, ibuprofen, >90%) with existing treatment technologies (Al Qarni et al., 2016; Smook et al., 2008; Wojcieszyńska & Guzik, 2020), contributing to an overall uncertain picture of how K_{OC} will affect the environment.

4.3. Use of QSAR-predicted PNECs

The supplementation of scarce toxicity data with QSARs met with limited success (Figure 4), comparisons between provisional PNECs and PNECs for the same API suggesting the QSAR PNECs used have less value as a tool for predicting the highly specific toxicity of many pharmaceuticals. Without access to predicted toxicity values based on the interaction of APIs with specific receptors, predicting risk from QSARs gives results wildly at odds with experimentally derived PNECs. Consequently, we elected not to proceed in risk characterisation using these predicted values, but the general approach may be more applicable as QSARs are refined for pharmaceutical toxicity.

4.4. Effects of inclusion of Over-the-counter and veterinary data

On average, 70% of PECs calculated were attributable to prescription medications only (Figure 5). Likewise, 85% of PEC magnitude was explained by human medications (Figure 6). While their full inclusion drove very little change in overall predicted risk, both at the individual API level and overall, this is principally an effect of limited toxicity data, and we would expect to see a larger and more significant effect as PNEC availability approaches 100%.

4.5. Future work

A number of expansions of the work described here are foreseen but were beyond the scope of this paper.

The Norwegian Institute for Public Health's original source data used for the calculation of PECs, the Norwegian Wholesale Drug Database, records sales at the month and county level (Sommerschild et al., 2021), meaning it may be possible to efficiently localise predictions. At the present stage, an inability to distinguish between emissions in the more densely populated and developed south of the country, as well as seasonal patterns in consumption and hydrology, may limit the specificity of

our predictions. Furthermore, as veterinary, and human drugs are considered jointly under our current models, no allowance is made for variation between urban and agricultural pathways into the aquatic environment. In the future, we hope to develop a geographically explicit approach that permits these factors to be incorporated into modelling.

Quantification of Uncertainty

Uncertainty was difficult to directly quantify in our output dataset of Risk Quotients, as the collection methods used on drug sales are difficult to assess, applying nominally to a sample size equal to the population. Likewise, single worst-case values were used in the calculations of PECs and combined with threshold PNECs in the calculation of Risk Quotients. We aim, in future work, to quantify the contribution of different sources of uncertainty more carefully for a subset of APIs, potentially using hierarchical Bayesian approaches (Wolf & Tollefsen, 2021).

Combined Risk of Pharmaceuticals

Given the current debate over the scientific appropriateness and pragmatic value of various approaches to predict combined, mixture or cumulative risk, we elected to exclude such an exercise. Nevertheless, given the common and at times *opposed* modes of action (for instance, fish feminisation *and* masculinisation by different sex hormones) of different APIs, the combined effects of APIs on wildlife are likely to remain an important area of study and discussion for some time.

Present ERA of pharmaceuticals fails to consider combined effects entirely, but a number of proposals exist to account for increased risk. These include the simple sum of Risk Quotients (Rorije et al., 2022) where all constituents of a mixture are known, the employment of a Mixture Assessment Factor that permits each chemical in a matrix only a tiny share of the worst-case mixture complexity (Swedish Chemicals Agency, 2015), or summing Toxic Units that quantify effects to different taxa. Compared to the two former, the sum of Toxic Units is a more scientifically correct approach, but also by far the most data-dependent (OECD, 2018). As data and methodology become more mature it may be more practical to conduct such wide-ranging assessments of combined

toxicity, but within the scope of this work we chose to limit our consideration to the prioritisation of single substances.

5. Conclusions

Based on our findings, the pharmaceutical environmental risk landscape in contemporary Norway is dominated by a small number of high-risk APIs playing crucial roles in maintaining modern standards of life and healthcare, in particular contraceptives, many of which are also persistent, bioaccumulative and/or mobile. However, the lack of PNECs for many APIs, as well as data on persistence, bioaccumulation and mobility make it difficult to give a comprehensive overall impression of the issue of pharmaceutical pollution in Norway.

QSAR approaches hold some promise as a supplement to slow and expensive laboratory testing, but the data used for comparison in this paper diverged considerably from experimental findings, suggesting they may not yet be mature enough to assess the complex, receptor-driven toxicity of APIs.

Lastly, we found a relatively small impact of the inclusion of over-the-counter and veterinary sales on risk, compared to the prescription human approach taken in many similar studies. However, this is likely to be skewed by the data scarcity discussed above.

Consequently, efforts to further understanding and mitigation of API pollutants in Norway will ideally focus on filling data gaps, either through the publication of existing risk assessment data, mechanism-specific computational approaches, or, where unavoidable, further testing. More specific endpoints, such as for development of anti-microbial resistance, may also need to be employed.

In addition, better models of pharmaceutical transport and dispersal from source to the environment, as have been developed for other areas of Europe, will likely prove invaluable in

refining prioritisation of APIs, and identifying key points where loads of high-risk APIs can be most efficiently and efficaciously intercepted.

Finally, once these data gaps are filled, a more considered assessment of the risks of mixtures of pharmaceuticals can be attempted, under a variety of present and future conditions, finally allowing risk assessment to contribute to prevention, rather than cure.

6. References

6.1. Figures

Figure 1: Flow diagram of (a) full tiered ERA of human medications in the EU (after EMA CHMP, 2006), and (b) a condensed adaptation of the protocol applied in this work.

Figure 2: PECs (red dots) from 2016, and median MECs for WWTP influent (blue squares) and effluent (green triangles), with minimum and maximum (vertical bars), based on data from the German Environment Agency's Pharmaceuticals in the Environment Database for 2015 and 2016 (Graumnitz & Jungmann, 2021), for 20 APIs, on a log10 scale. Theoretical PECs in WWTPs are obtained by multiplying PEC_{SW} by removing the dilution factor of 10; and thus are 10 times higher than PEC_{SW} values.

Figure 3: Maximum Risk Quotient (107 APIs) (a) and predicted mobility (Log Koc) (456 APIs) (b) by API, coloured by Persistence threshold: not enough data available (NA), not persistent (nP), low persistence, moderate persistence and potential persistence (P), and high persistence, based on Felleskatalogen experimental hazard statements (solid points) where available, and EU thresholds applied to QSAR biodegradation where not (asterisks, hollow points). APIs with a missing or negligible RQ (< 0.01, 763 APIs) or Log K_{oc} (> 6, 414 APIs) are placed on the graph axis; 56 APIs have a predicted persistence statement, and 814 do not. Dashed lines indicate RQ > 0.1, 1, 10 and 100 (x axis), and Log K_{oc} < 3 and 4 thresholds. APIs with a RQ > 1, LogK_{OC} < 3, or potential persistence (QSAR) / high persistence (experimental) are labelled.

Figure 4: (a) Risk screening based on NORMAN QSAR PNECs (NORMAN, 2022) for 428 APIs based on 2019 PECs; (b) plotted correlation for 78 APIs between QSAR and experimentally predicted RQs; (c) Tukey Mean difference (QSAR - experimental) plot of difference between RQs against mean of RQ for 78 APIs. APIs labelled where RQ > 10 (a) or where space permits (b, c)

Figure 4: Predicted Environmental Concentrations for 42 APIs and Risk Quotients for 10 of these sold both OTC and on prescription, sorted by total PEC. Values for prescription sales alone are shown by red circles, those from prescription and OTC sales (wholesale) by blue arrows. All variables are plotted on log10 scales. The standard regulatory thresholds of PEC > 0.01 ug/L and RQ > 1 are indicated with a dashed line.

Figure 5: Predicted Environmental Concentrations for 43 APIs and Risk Quotients for 3 of these sold in 2019 both for human and veterinary application, sorted by total PEC. Values for human sales alone are shown by red circles, those from human and vet sales by blue arrows. All variables are plotted on log10 scales. The standard thresholds of PEC > 0.01 ug/L and RQ > 1 are indicated with a dashed line.

6.2. Tables

Table 1: Total number of APIs with PECs per year, and substances of which have PNECs. PNECs from FASS.se (2019b), AstraZeneca (2017) and the JRC (Loos et al., 2018) , QSAR PNECs from NORMAN (2022).

Table 2: Top 20 APIs (of 208) sorted by average Risk Quotient (2016-2019). Bioacc. (Bioaccumulation) hazard statements are translated from Felleskatalogen (Felleskatalogen, 2022) and FASS guidelines (FASS, 2012), where "low" corresponds to BCF < 500 or log D_{ow} (at pH7) < 4, and "high" to BCF ≥ 500 or log D_{ow} (at pH 7) ≥ 4. Likewise, "high" persistence indicates DT_{50} > 120 (OECD 308) or no ready or inherent biodegradation (OECD 301/302B/302C), "moderate" DT_{50} ≤ 120 or inherent biodegradation, and "low" DT_{50} ≤ 32 or ready biodegradability. Mobility is classified based on OPERA (EPA, 2018) QSARs of log carbon adsorption coefficient (log K_{oc}) as either "very Mobile" if log K_{oc} < 3, "Mobile" if log K_{oc} < 4, and otherwise "not Mobile". NA indicates that a QSAR within the applicability domain could not be calculated.

Table 3: Predicted mean Risk Quotient by the 20 most common API types, grouped into bins by one order of magnitude. APIs for which no experimental PNEC was available to calculate RQs are recorded in the No Data column, and as a percentage of the total in the column Missing. Predicted No Effect Concentrations were compiled from publicly available FASS, AstraZeneca and JRC data (AstraZeneca, 2017; FASS, 2019b; Loos et al., 2018); pPNECs were not considered.

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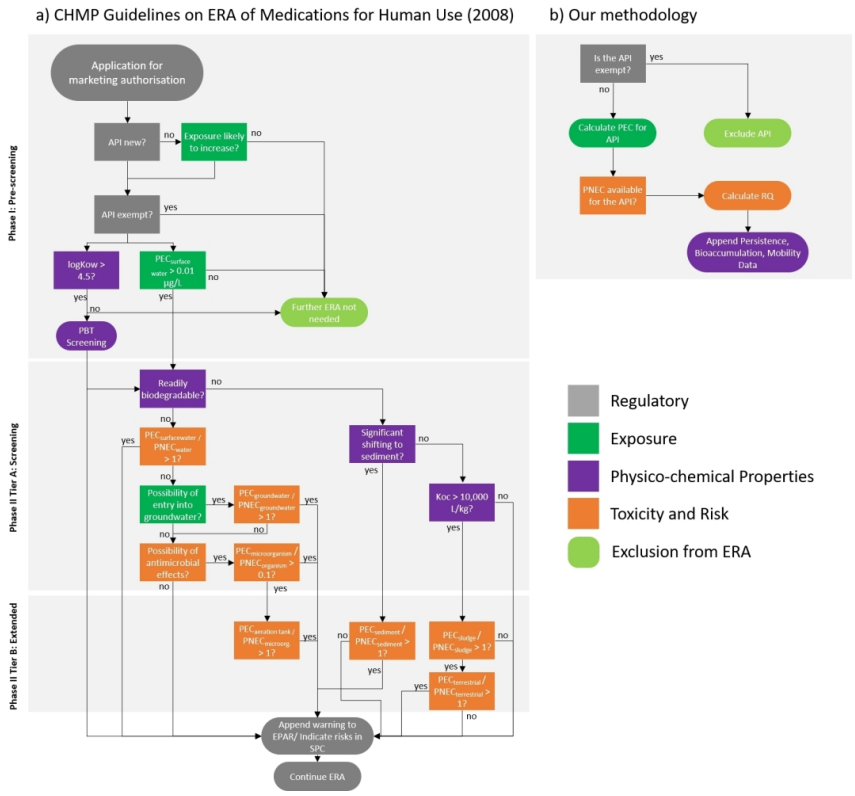

Figure 1: Flow diagram of (a) full tiered ERA of human medications in the EU (after EMA CHMP, 2006), and (b) a condensed adaptation of the protocol applied in this work.

321x280mm (150 x 150 DPI)

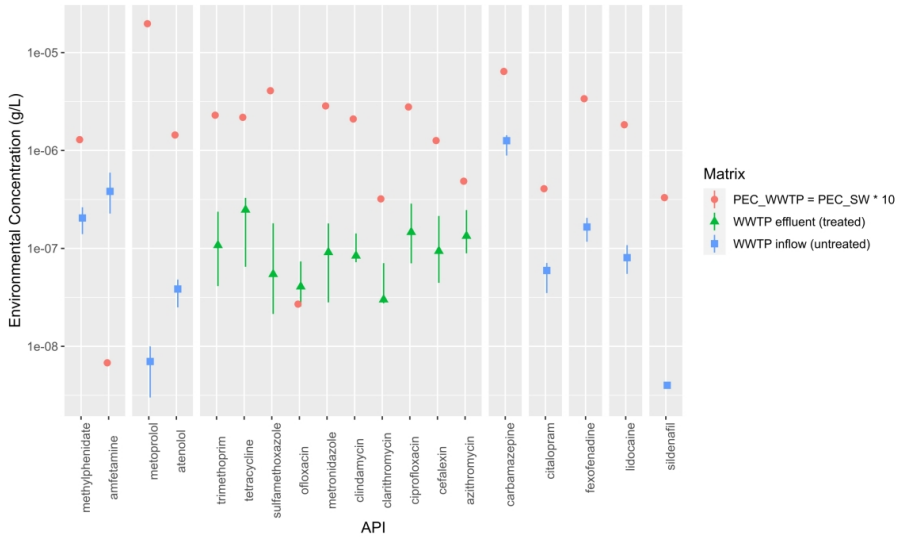

Figure 2: PECs (red dots) from 2016, and median MECs for WWTP influent (blue squares) and effluent (green triangles), with minimum and maximum (vertical bars), based on data from the German Environment Agency's Pharmaceuticals in the Environment Database for 2015 and 2016 (Graumnitz & Jungmann, 2021), for 20 APIs, on a log10 scale. Theoretical PECs in WWTPs are obtained by multiplying PECSW by removing the dilution factor of 10; and thus are 10 times higher than PECSW values.

250x150mm (300 x 300 DPI)

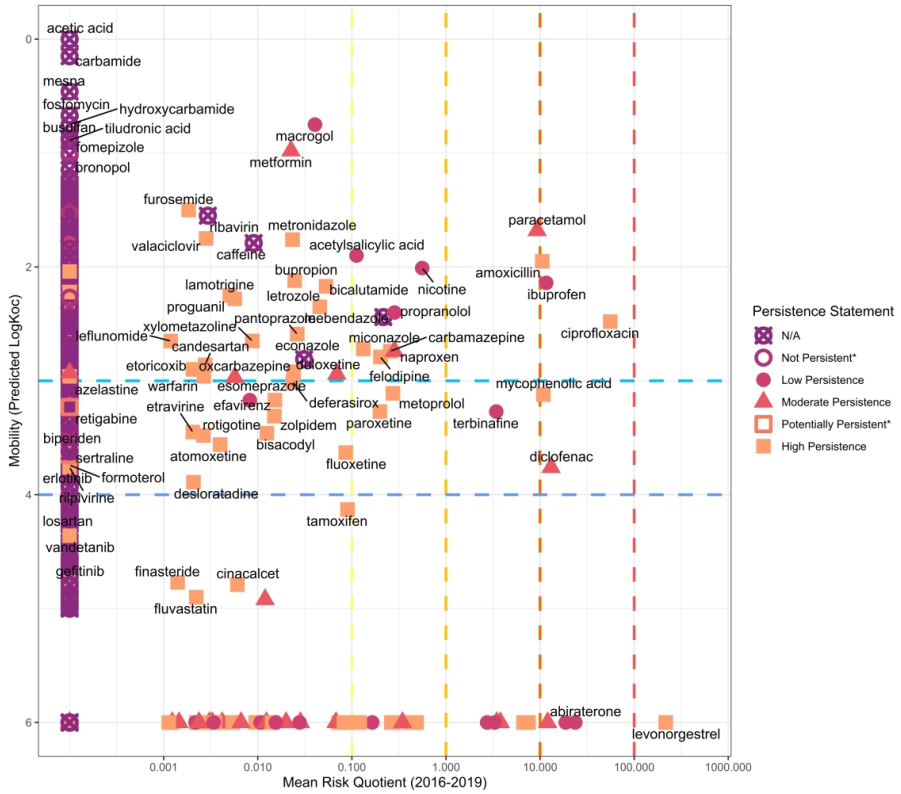

Figure 3: Maximum Risk Quotient (107 APIs) (a) and predicted mobility (Log Koc) (456 APIs) (b) by API, coloured by Persistence threshold: not enough data available (NA), not persistent (nP), low persistence, moderate persistence and potential persistence (P), and high persistence, based on Felleskatalogen experimental hazard statements (solid points) where available, and EU thresholds applied to QSAR biodegradation where not (asterisks, hollow points). APIs with a missing or negligible RQ (< 0.01, 763 APIs) or Log Koc (> 6, 414 APIs) are placed on the graph axis; 56 APIs have a predicted persistence statement, and 814 do not. Dashed lines indicate RQ > 0.1, 1, 10 and 100 (x axis), and Log Koc < 3 and 4 thresholds. APIs with a RQ > 1, LogKOC < 3, or potential persistence (QSAR) / high persistence (experimental) are labelled.

250x219mm (300 x 300 DPI)

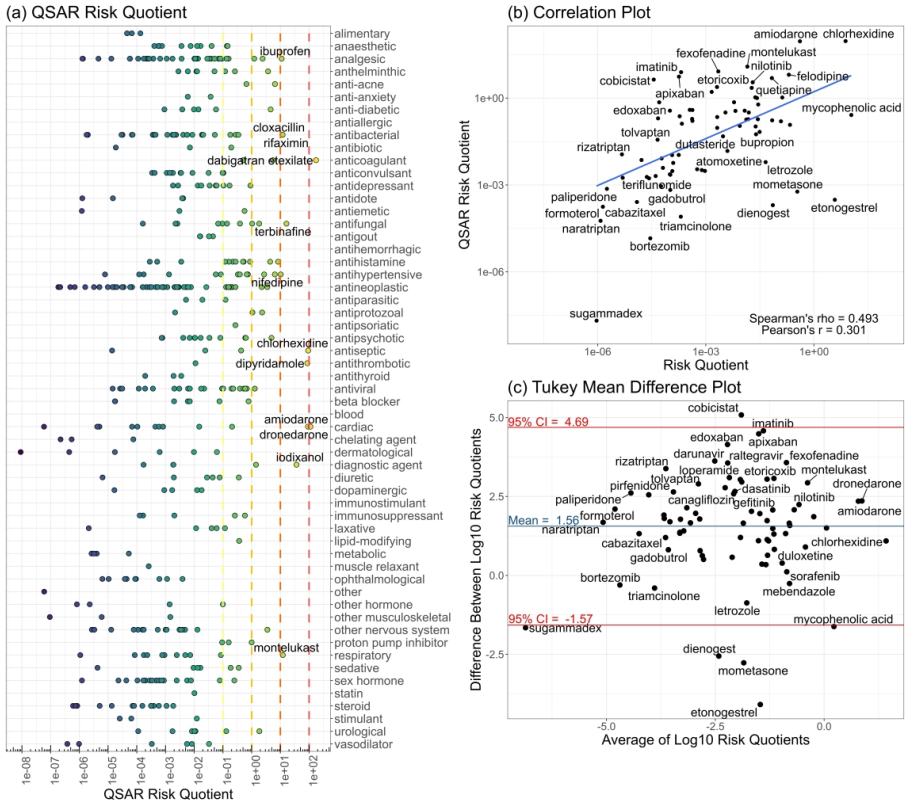

Figure 4: (a) Risk screening based on NORMAN QSAR PNECs (NORMAN, 2022) for 428 APIs based on 2019 PECs; (b) plotted correlation for 78 APIs between QSAR and experimentally predicted RQs; (c) Tukey Mean difference (QSAR - experimental) plot of difference between RQs against mean of RQ for 78 APIs. APIs labelled where RQ > 10 (a) or where space permits (b, c)

450x399mm (300 x 300 DPI)

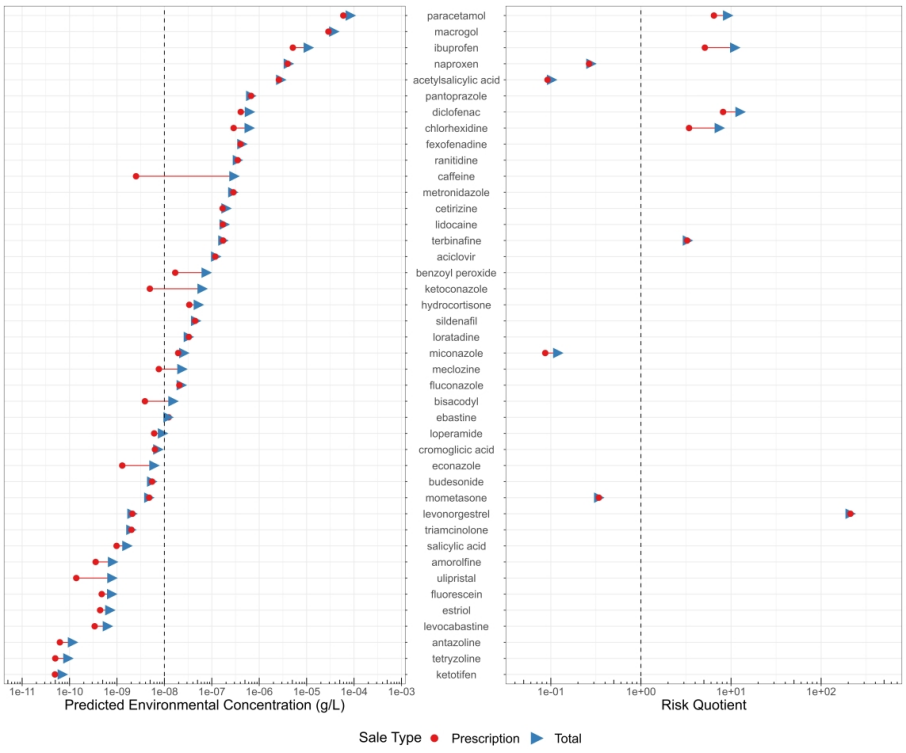

Figure 5: Predicted Environmental Concentrations for 42 APIs and Risk Quotients for 10 of these sold both OTC and on prescription, sorted by total PEC. Values for prescription sales alone are shown by red circles, those from prescription and OTC sales (wholesale) by blue arrows. All variables are plotted on log10 scales. The standard regulatory thresholds of PEC > 0.01 ug/L and RQ > 1 are indicated with a dashed line.

450x399mm (300 x 300 DPI)

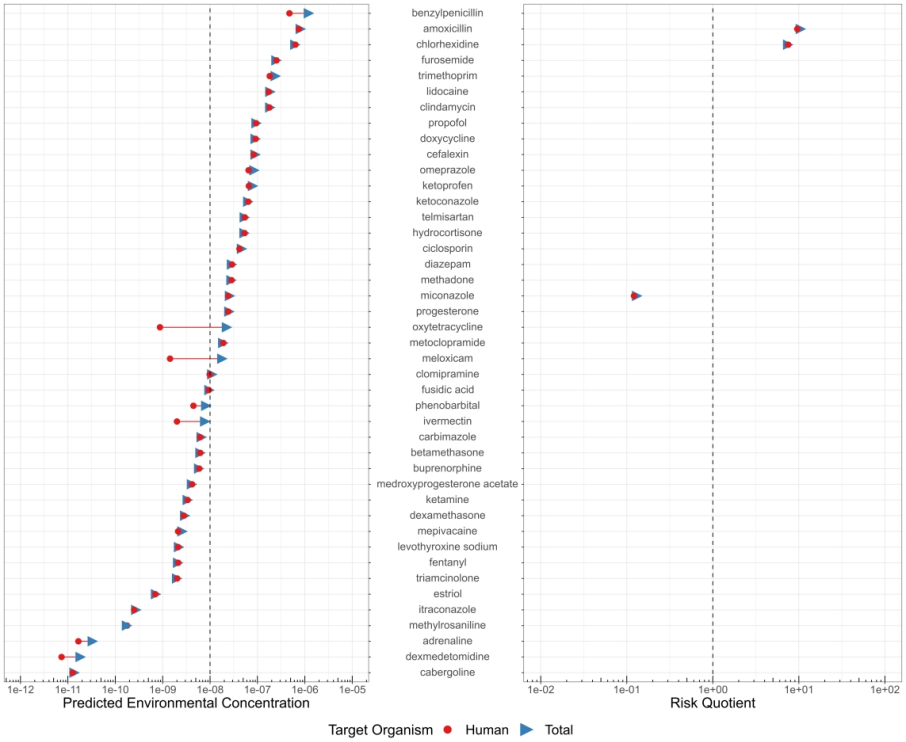

Figure 6: Predicted Environmental Concentrations for 43 APIs and Risk Quotients for 3 of these sold in 2019 both for human and veterinary application, sorted by total PEC. Values for human sales alone are shown by red circles, those from human and vet sales by blue arrows. All variables are plotted on log10 scales. The standard thresholds of PEC > 0.01 ug/L and RQ > 1 are indicated with a dashed line.

450x399mm (300 x 300 DPI)

	PECs	PNECs	QSAR PNECs
2016	805	204	424
2017	821	205	420
2018	821	202	422
2019	832	201	428

API	Type	PEC (µg/L)	PNEC (µg/L)	RQ	Bioacc.	Persistence	Mobility
levonorgestrel	sex hormone	2.2×10^{2}	1.0×10^{4}	220	low	high	nM
ciprofloxacin	antibacterial	2.8×10^{0}	5.0×10^{2}	56	low	high	vM
abiraterone	antineoplastic	3.1×10^{1}	1.3×10^{2}	24	high	low	nM
ethinylestradiol	sex hormone	6.6×10^{3}	3.5×10^{4}	19	high	low	nM
diclofenac	analgesic	6.5×10^{0}	5.0×10^{1}	13	low	moderate	M
estradiol	sex hormone	4.8×10^{2}	4.0×10^{3}	12	low	moderate	nM
ibuprofen	analgesic	1.2×10^{2}	1.0×10^{1}	12	low	low	vM
amoxicillin	antibacterial	8.2×10^{0}	7.8×10^{1}	11	low	high	vM
mycophenolic acid	immunosuppressant	7.4×10^{0}	6.8×10^{1}	11	low	high	M
paracetamol	analgesic	8.6×10^{2}	9.2×10^{1}	9.3	low	moderate	vM
chlorhexidine	antiseptic	6.3×10^{0}	8.4×10^{1}	7.5	low	high	NA
norethisterone	sex hormone	3.3×10^{2}	5.0×10^{3}	6.7	low	high	nM
etonogestrel	sex hormone	1.0×10^{2}	2.7×10^{3}	3.8	low	moderate	nM
desogestrel	sex hormone	9.3×10^{3}	2.7×10^{3}	3.5	low	moderate	nM
terbinafine	antifungal	1.8×10^{0}	5.3×10^{1}	3.4	high	low	M
simvastatin	statin	6.6×10^{0}	2.0×10^{0}	3.3	low	low	NA
fulvestrant	antineoplastic	1.6×10^{2}	5.7×10^{3}	2.7	low	low	NA
nicotine	other nervous system	1.4×10^{0}	2.4×10^{0}	0.56	low	low	vM
dronedarone	cardiac	2.0×10^{0}	4.0×10^{0}	0.49	low	high	NA
drospirenone	sex hormone	1.1×10^{1}	2.3×10^{1}	0.47	low	high	NA

	Risk Quotient							
Type	> 100	> 10	> 1	> 0.1	< 0.1	No Data	**Total**	**Missing**
antineoplastic		1	1	1	22	85	110	77%
antibacterial		2		1	8	63	74	85%
analgesic		2	1	2	6	48	59	81%
antiviral					19	29	48	60%
sex hormone	1	2	3	1	3	24	34	71%
antihypertensive				1	7	23	31	74%
other nervous system				1	4	21	26	81%
respiratory					10	14	24	58%
anticonvulsant				1	6	16	23	70%
steroid				1	6	16	23	70%
antihistamine					4	18	22	82%
antipsychotic					6	14	20	70%
cardiac				2	1	17	20	85%
antidepressant				1	4	15	20	75%
diagnostic agent					6	11	17	65%
antifungal			1	1	4	11	17	65%
anaesthetic					0	17	17	100%
anti-diabetic					10	5	15	33%
alimentary					3	12	15	80%
urological					3	12	15	80%

Paper III: Probabilistic risk calculation for chemical mixtures: environmental risk of pharmaceuticals under future scenarios