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Hazard/Risk Assessment

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

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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, approximately 200 active pharmaceutical ingredients (APIs) over 2016–2019, 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 characterize 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 with measurements for 18 of 20 APIs with comparable predictions and measurements. Seventeen APIs had mean RQs >1, indicating potential risk, while the mean RQ was 2.05 and the 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]), raising the possibility of impacts beyond their RQs. Exposure and risk were also calculated with and without over-the-counter sales, showing that prescriptions explained 70% of PEC magnitude. Likewise, human sales, compared with veterinary, explained 85%. Sales PECs provide an efficient option for ERA, designed to overestimate compared with 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. *Environ Toxicol Chem* 2023;42:2253–2270. © 2023 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

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INTRODUCTION

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 (Sumpter et al., 2022). Pharmaceuticals sold and prescribed for both human and veterinary use have been detected across the range of human-dominated continents in a wide variety of matrices (Wilkinson et al., 2022).

By design, pharmaceuticals are capable of biologically relevant effects at low concentrations, and studies have shown adverse effects in laboratory studies at environmentally relevant levels (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 active pharmaceutical ingredients (APIs) in unpredictable ways (Brown et al., 2014).

Despite this variability, grouping pharmaceuticals by broad organ/system target and mode of action remains a convenient

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and accessible way to generalize effects. Below, we summarize 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 experimental field studies (Kidd et al., 2007) at environmentally relevant concentrations and linked to observed fish sexual disruption in rivers downstream of wastewater-treatment plants (WWTPs; Jobling et al., 1998). However, drawing direct causative links between a given API and an environmental effect remains difficult.

Antidepressants 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 defense; and antidepressants have been shown to affect behavior and reproduction in a range of fish (McDonald, 2017) and aquatic invertebrates (Estévez-Calvar et al., 2017), as well as development in vertebrates (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 other taxa has also been shown (Kovalakova et al., 2020).

Environmental toxicity has also been found in other therapeutically important groups of APIs. Statins, a class of drug widely prescribed to lower blood cholesterol, have shown toxicity to aquatic plants (Brain et al., 2006), invertebrates, and fish (Ribeiro et al., 2015). Analgesics acting via the cyclo-oxygenase pathway, such as paracetamol, diclofenac, and ibuprofen, are toxic to various aquatic species at high concentrations (~1–100 μg/L; Cleuvers, 2004). However, toxicity data available across and within drug groups can be inconsistent and difficult to access, limiting attempts to understand the overall pharmaceutical risk landscape, beyond individual substances.

Environmental risk assessment of pharmaceuticals in Europe

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

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 Committee for Medicinal Products for Human Use [CHMP], 2006). Significant changes to the ERA of chemicals across the European Union are planned, including a movement to a single assessment per substance regardless of manufacturer and application, under the European Green Deal; but at the time of writing relevant legislation has yet to be passed or implemented.

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, whereas later phases use more realistic assumptions. In summary, at Phase 1 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 2 assessment is conducted, comparing toxicity and interactions with the environment, predicted from a panel of standardized laboratory studies, to regulatory thresholds. In addition, 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 1, a log 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 2, these will be further assessed. Persistence screening, based on the European Union technical guidance document (European Commission, 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, whereas 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 is found to be potentially problematic, this is noted in an API's risk assessment; but neither is 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 APIs, including azithromycin, diclofenac, estrone, estradiol, and ethinylestradiol (European Commission, 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 risk quotient (RQ) <1 is generally assumed to be of negligible importance, whereas exceedances indicate a potential issue. However, as with persistence and bioaccumulation, no cost–benefit comparison is conducted because the medical benefit to humanity is judged to outweigh any environmental impact.

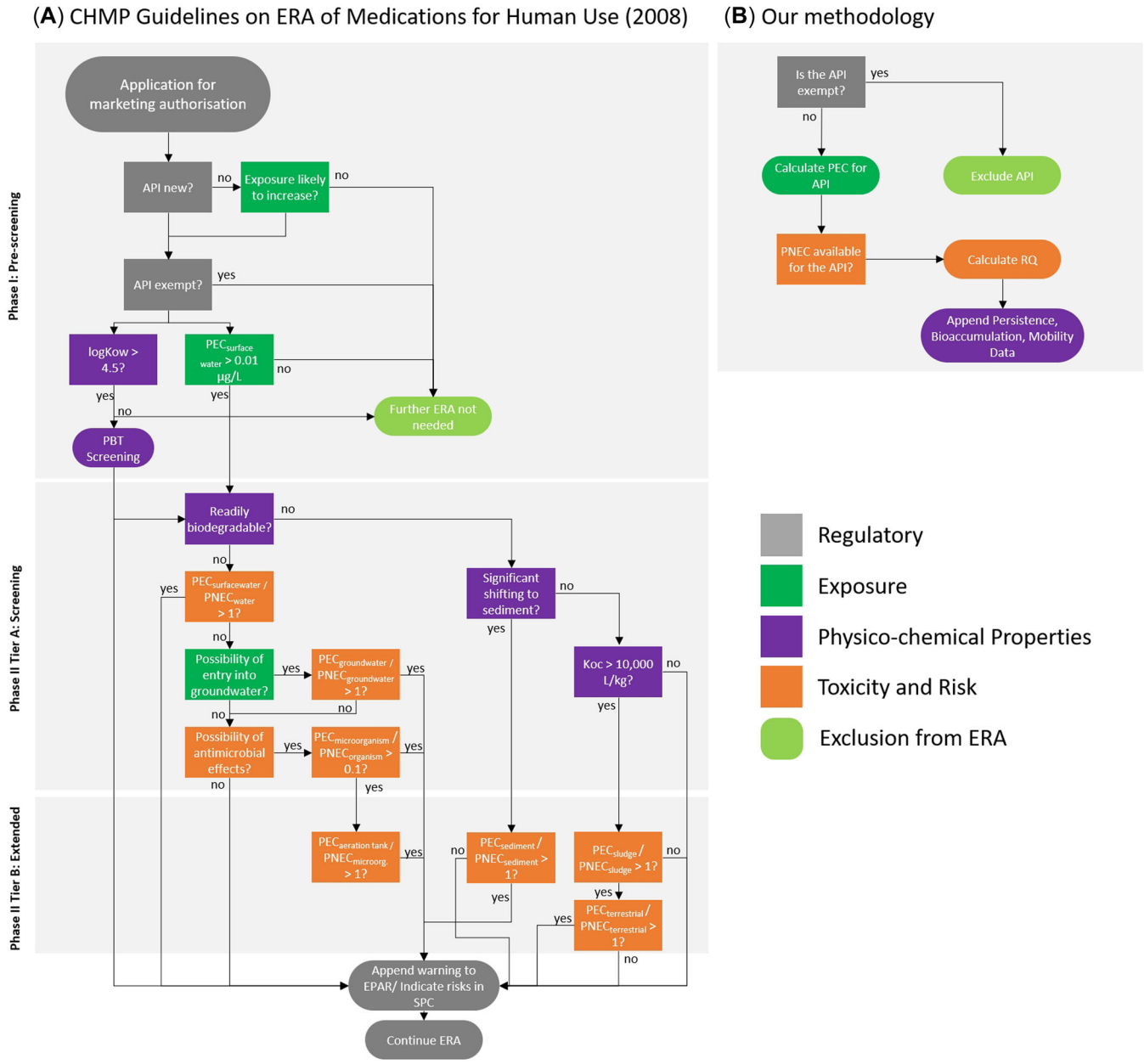

FIGURE 1: Flow diagram of (**A**) full-tiered environmental risk assessment of human medications in the European Union (after European Medicines Agency Committee for Medicinal Products for Human Use, 2006), and (**B**) a condensed adaptation of the protocol applied in the present study. API = active pharmaceutical ingredient; K_{OW} = octanol–water partition coefficient; PEC = predicted effect concentration; PBT = persistent, bioaccumulative, and toxic; ERA = environmental risk assessment; PNEC = predicted-no-effect concentration; K_{OC} = organic–carbon partition coefficient; EPAR = European Public Assessment Report; SPC = Summary of Product Characteristics.

Over the 15 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 authorization 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, whereas 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 are made publicly available, with no ability for researchers to audit the data used in the assessment (Ågerstrand et al., 2014). Meanwhile, the battery of tests used has been criticized as originally designed to assess the toxicity of industrial chemicals to an extremely limited range of species (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 (European Economic Area, 2022), the freshwater species used in standard tests may be insufficient for estimating risk from pharmaceutical pollution. In the technical guidance

document, a default additional assessment factor of 10 is given for extrapolating from freshwater to marine ecosystems (European Commission, 2003).

Across other sides of the multistakeholder table, both the pharmaceutical industry and European nongovernmental organizations have criticized the current state of ERA as too broad, not well equipped to prioritize 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 (Snape & Owen, 2019). In 2018 the EMA released a set of draft guidelines for public consultation that build on the prior guidelines, 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 European Union's plans for pharmaceuticals and its ambitions to reach a toxic-free environment (European Commission, 2021).

In response to this lack of risk assessment 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 (Burns et al., 2018; Grung et al., 2008; Gunnarsson et al., 2019). 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 confidentiality 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 are nominally publicly available (Daughton, 2016) might more properly be called *gray literature*.

Although a wide range of pharmaceutical substances can be easily detected in aquatic ecosystems with modern analytical chemistry, the extensive diversity of pharmaceutical substances and potentially affected ecosystems and the necessarily preemptive 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 measured environmental concentrations (MECs) for 95 APIs in one of the two urban rivers studied in York, UK; while Letsinger and 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 prioritization.

More refined tools that predict environmental concentrations based on an extensive set of hydrological, demographic, and WWTP parameters (see Austin et al., 2022), 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 (Austin et al., 2021), potentially leading to underestimates of emissions even where environmental behavior and fate are well parameterized. Thus, in Norway, where MECs are rare, models of pharmaceutical emissions are crude, but sales data are high-quality and centralized by public authorities, the existing PEC_{SW} (PEC in surface water) prediction equation represents an ideal first-line tool for prediction and prioritization.

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, approximately half of Norway's population lives in Østlandet, in the southeast 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 & 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 approximately 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 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 centralized data collection and relatively well-characterized environment make it an ideal test bed for assessing the effectiveness of sales-based approaches.

Aims

In the present study, we present a top-down method for the ranking of API environmental risk. We build on a data set of 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 MECs for Norway, (2) to calculate the RQ for each API by combining PECs with publicly available environmental toxicity values (PNECs) and make a ranking risk of APIs by RQs, (3) to refine the risk characterization of APIs by inclusion of other chemical properties (persistence, mobility, bioaccumulation),

and (4) to evaluate the added value of additional information sources and their potential effects on the risk characterization.

METHODS

Software and data

All data processing and analyses were conducted in base R 4.2.1 "Shake and Throw" (2022) and RStudio 2022.07.1 Build 554 (2022). Packages used are summarized in the software repository available below.

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

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

The PEC_{SW} equation default variables and parameters are API weight sold per year (grams), 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 specialties website Felleskatalogen (2022), and further PNECs were made available by AstraZeneca (2017) and the European Union Joint Research Centre (Loos et al., 2018). Norwegian MECs (Baz-Lomba et al., 2016; Causanilles et al., 2018; Rodriguez-Mozaz et al., 2020) compiled by the German Environment Agency's Pharmaceuticals in the Environment database were used in validation (Graumnitz & Jungmann, 2021). Then, quantitative structure–activity relationship (QSAR)–predicted properties were taken from OPERA (US Environmental Protection Agency [USEPA], 2018): organic–carbon partition coefficient (log K_{OC}), as a measure of mobility; biodegradation half-life in days, as a measure of persistence; and bioconcentration factor, used to assess the contribution of pollution of the aquatic environment to bioaccumulation.

Predicted "provisional PNECs" from the NORMAN ecotoxicology database (Aalizadeh et al., 2017; NORMAN, 2022; von der Ohe et al., 2011) were also used to characterize the biotic and abiotic properties of APIs where experimental data were not available.

Where necessary, data were 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 the English equivalent. Norwegian API names were also manually matched with English API names.

Calculation of environmental risk

Comparison of PECs and MECs. The PECs were compared with available Norwegian MECs for wastewater influent and effluent samples because 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.

To draw more direct comparisons, PECs for WWTP influent pretreatment ($PEC_{influent}$, Equation 2) were calculated from PEC_{SW} by removing dilution from the equation, representing the fact that the contaminated wastewater has not yet entered the environment. Mathematically, this simply involved removing the dilution factor of 10 from the equation, in effect multiplying PEC_{SW} values by 10.

$$PEC_{influent} = \frac{\text{API sold}}{365 \times \text{Wastewater production} \times \text{Population}} = PEC_{sw} \times 10 \quad (2)$$

PNECs. Toxicity data were obtained in the form of PNECs for 257 substances from the Norwegian pharmaceutical specialties website Felleskatalogen (2022). These PNECs were originally calculated by the Swedish Pharmaceutical Specialities website for FASS (2019b), where full equations and constituent test data were given; however, these data could not easily be converted into a machine-readable format, and hence Felleskatalogen's more accessible but less transparent data set was used. In any case, a full account of the toxicity data's origin is impossible because the studies that produced said data are often not publicly available.

In addition, these data were supplemented with PNECs made publicly available by AstraZeneca (2017) for seven APIs (atenolol, lidocaine, metformin, mepivacaine, naproxen, omeprazole, and tamoxifen) and six PNECs calculated by the European Union's Joint Research Centre (Loos et al., 2018; azithromycin, clarithromycin, diclofenac, erythromycin, estradiol, and ethinylestradiol). Thirty-one APIs had PNECs from more than one source; in six cases these values were inequal. The PNECs calculated by the Joint Research Centre for diclofenac and clarithromycin were more recent (2018) and smaller (640 times and 2.17 times, respectively). In three cases (metformin, naproxen, omeprazole), errors were found in the calculation of Felleskatalogen/Swedish Pharmaceutical Specialties PNECs, and AstraZeneca PNECs were used in their place. Finally, tamoxifen had two valid PNECs (AstraZeneca 0.102 µg/L and Felleskatalogen 0.49 µg/L). In this case, the lowest value, the AstraZeneca PNEC, was used, to maximize conservatism.

RQs. Predicted risks per API per year were calculated as simple RQs (or risk characterization ratios) following the standard ecotoxicological method (Equation 3; EMA CHMP, 2006):

TABLE 1: Total number of active pharmaceutical ingredients with predicted environmental concentrations per year, and substances of which have predicted-no-effect concentrations

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

Predicted-no-effect concentrations (PNECs) are from FASS (2019b), AstraZeneca (2017), and the Joint Research Centre (Loos et al., 2018); QSAR PNECs from NORMAN (2022).
PEC = predicted effect concentration; QSAR = quantitative structure–activity relationship.

$$RQ_{Surface\ water} = \frac{PEC_{Surface\ water}}{PNEC} \quad (3)$$

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

QSAR PNECs. Because access to experimental toxicity data was limited to approximately 25% of APIs, we used modeled PNECs (European Commission, 2003; NORMAN, 2018), referred to in the source literature as *provisional* PNECs, as an alternative for initial screening and prioritization of APIs. These provisional PNECs were calculated by the database authors following standard technical guidance document guidelines for predicted acute toxicity tests across three taxa, with an assessment factor of 1000 applied to the most sensitive species by the database authors (European Commission, 2003; NORMAN, 2018).

Comparing RQs and prioritization. Simple comparisons between RQs 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 the ranking of APIs using various subsets of data.

Data set overview. On average, 820 PECs were calculated per year across the 4-year period, of which approximately 25% also had PNECs available, and 52% had QSAR PNECs (Table 1).

RESULTS

Comparison with MECs

Nineteen APIs had both PECs and WWTP MECs for the 2015–2016 period (Figure 2). The PECs were compared with median MECs for 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 antiepileptic carbamazepine; the antidepressant citalopram; the antihistamine fexofenadine; the local anesthetic lidocaine; and the erectile dysfunction therapy sildenafil. Notably, in no case were both influent and effluent PECs available for the same substance. This is an artifact of the narrow period assessed (2015–2016) and the data quality threshold (i.e., "good") used in the Umwelt Bundesamt database entries.

In 15 cases, $PEC_{influent}$ overestimated compared with 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 1 order of magnitude, whereas no API other than the previously discussed metoprolol was more than 2 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 European Commission rankings (Spearman's $\rho = 0.18$, $p = 0.46$; Table 2). 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.

Characterizing RQs, persistence, mobility, and bioaccumulation

Risk quotients were calculated for 208 substances across the 2016–2019 period. The substances with the 20 highest average RQs over this period are displayed in Table 3, while overall the average RQ of all remaining 188 was 0.24, with a minimum of 6.9E–8 and a maximum of 0.41. Likewise, the persistence classes of the remaining substances were 117 high, 34 moderate, 24 low, and 13 uncertain; the bioaccumulation classes were 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 RQ 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 API 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 among 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 anticancer) APIs abiraterone and fulvestrant feature also in the top 20. Abiraterone, a

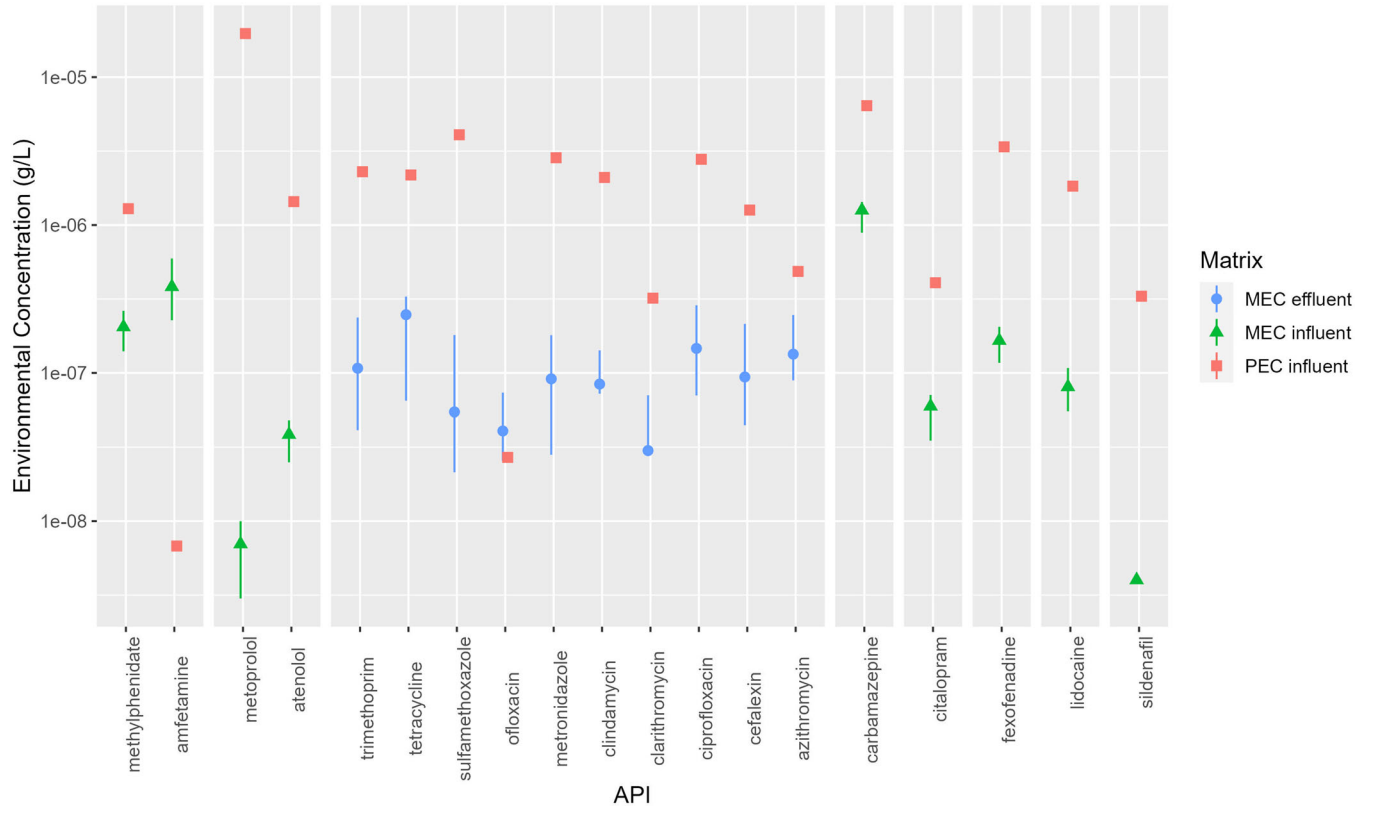

FIGURE 2: Predicted environmental concentrations (PECs; red squares) from 2016, and median measured environmental concentrations for wastewater-treatment plant (WWTP) influent (green triangles) and effluent (blue squares), with minimum and maximum (vertical bars), based on data from the German Environment Agency's Pharmaceuticals in the Environment Database for 2015 and 2016 (Graumnitz & Jungmann, 2021), for 20 active pharmaceutical ingredients, on a log10 scale. Theoretical PECs in WWTPs are obtained by multiplying surface water PECs by 10, canceling out the dilution factor. MEC = measured environmental concentration; API = active pharmaceutical ingredient.

treatment for testicular cancer that acts not only as an inhibitor of the production of androgens (including testosterone), but also as an estrogen agonist, has shown chronic reproductive toxicity to fish at nanogram per liter levels, while fulvestrant, a selective estrogen receptor degrader taken for some breast cancers, affects 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 ERAs include no explicit assessment of toxicity to bacteria, and consequently toxicity is driven by chronic effects to fish, while toxicity data available for amoxicillin were limited to a single study of algal toxicity (Andreozzi et al., 2004).

TABLE 2: Welch's *t* test, Pearson's correlation coefficient, and Spearman's rank correlation coefficient scores between predicted and measured environmental concentrations, observed and provisional predicted-no-effect concentrations, prescription only and total whole sales, and human pharmaceutical sales only and total human and veterinary sales

Test	Compared value	Score/outcome	*p*	*n*
PECs and MECs				
Spearman's rank correlation coefficient	PEC/MEC	0.18	0.46	19
Provisional and experimental PNECs				
Pearson correlation coefficient	PNEC	0.30	0.0073	78
Spearman's rank correlation coefficient	PNEC	0.49	<0.001	78
Prescription and wholesales weights				
Welch's *t* test	PEC	Failed to reject H_0	0.70	42
Spearman's rank correlation coefficient	PEC	0.99	<0.001	42
Spearman's rank correlation coefficient	RQ	0.99	<0.001	42
Human and total weights				
Welch's *t* test	PEC	Failed to reject H_0	0.59	43
Spearman's rank correlation coefficient	PEC	0.99	<0.001	43
Spearman's rank correlation coefficient	RQ	0.99	<0.001	43

p values rounded to 2 s.f.
PEC = predicted effect concentration; MEC = measured environmental concentration; PNEC = predicted-no-effect concentration; RQ = risk quotient; H_0 = null hypothesis.

TABLE 3: Top 20 active pharmaceutical ingredients (of 208) sorted by maximum risk quotient (2016–2019)

API	Type	Highest PEC (µg/L)	Lowest PNEC (µg/L)	Highest RQ	Bioaccumulation	Persistence	Mobility
Levonorgestrel	Sex hormone	2.20×10^{-2}	1.00×10^{-4}	220	Low	High	nM
Ciprofloxacin	Antibacterial	2.80×10^{0}	5.00×10^{-2}	56	Low	High	vM
Abiraterone	Antineoplastic	3.10×10^{-1}	1.30×10^{-2}	24	High	Low	nM
Ethinylestradiol	Sex hormone	6.60×10^{-3}	3.50×10^{-4}	19	High	Low	nM
Diclofenac	Analgesic	6.50×10^{0}	5.00×10^{-1}	13	Low	Moderate	M
Estradiol	Sex hormone	4.80×10^{-2}	4.00×10^{-3}	12	Low	Moderate	nM
Ibuprofen	Analgesic	1.20×1^{2}	1.00×10^{1}	12	Low	Low	vM
Amoxicillin	Antibacterial	8.20×10^{0}	7.80×10^{-1}	11	Low	High	vM
Mycophenolic acid	Immunosuppressant	7.40×10^{0}	6.80×10^{-1}	11	Low	High	M
Paracetamol	Analgesic	8.60×10^{2}	9.20×10^{1}	9.3	Low	Moderate	vM
Chlorhexidine	Antiseptic	6.30×10^{0}	8.40×10^{-1}	7.5	Low	High	NA
Norethisterone	Sex hormone	3.30×10^{-2}	5.00×10^{-3}	6.7	Low	High	nM
Etonogestrel	Sex hormone	1.00×10^{-2}	2.70×10^{-3}	3.8	Low	Moderate	nM
Desogestrel	Sex hormone	9.30×10^{-3}	2.70×10^{-3}	3.5	Low	Moderate	nM
Terbinafine	Antifungal	1.80×10^{0}	5.30×10^{-1}	3.4	High	Low	M
Simvastatin	Statin	6.60×10^{0}	2.00×10^{0}	3.3	Low	Low	NA
Fulvestrant	Antineoplastic	1.60×10^{-2}	5.70×10^{-3}	2.7	Low	Low	NA
Nicotine	Other nervous system	1.40×10^{0}	2.40×10^{0}	0.56	Low	Low	vM
Dronedarone	Cardiac	2.00×10^{0}	4.00×10^{0}	0.49	Low	High	NA
Drospirenone	Sex hormone	1.10×10^{-1}	2.30×10^{-1}	0.47	Low	High	NA

Bioaccumulation hazard statements are translated from Felleskatalogen (2022) and FASS guidelines (2012), where *low* corresponds to a bioconcentration factor (BCF) <500 or log octanol–water distribution ratio (D_{OW}; at pH 7) <4 and *high* to a BCF ≥500 or log D_{OW} (at pH 7) ≥4. Likewise, *high* persistence indicates 50% degradation time (DT50) >120 (Organisation for Economic Co-operation and Development [OECD] test 308 [2002]) or no ready or inherent biodegradation (OECD tests 301 [1992a], 302B [1992b], and 302C [2009]), *moderate* DT50 ≤120 or inherent biodegradation, and *low* DT50 ≤32 or ready biodegradability. Mobility is classified based on OPERA (US Environmental Protection Agency, 2018) quantitative structure–activity relationships (QSARs) of log organic–carbon partition coefficient (log K_{OC}) as either *very mobile* if log K_{OC} <3, *mobile* if log K_{oc} <4, and otherwise *not mobile*. Cells color coded by magnitude of parameter (i.e., red = high risk, mobility, persistance, etc., green = low risk, mobility, persistence, etc. Cells missing data are left white).
API = active pharmaceutical ingredient; PEC = predicted effect concentration; PNEC = predicted-no-effect concentration; RQ = risk quotient; nM = not mobile; M = mobile; vM = very mobile; NA = not available (a QSAR within the applicability domain could not be calculated).

The presence of the analgesic cyclooxygenase inhibitors ibuprofen and diclofenac (nonsteroidal anti-inflammatory drugs [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 micrograms per liter 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 because of 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 laboratory studies, while dronedarone, Norway's principal 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 (Savino & Tanabe, 1989), is likely underestimated because of the inclusion of only strictly medical sales (i.e., nicotine-based smoking cessation aides) in the present study. 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 K_{OC}) were compared (Figure 3) to illustrated patterns of risk across different parameters of interest. Bioaccumulation factors (USEPA, 2018) were omitted from graphs but can be summarized thusly: Only one substance was predicted to bioaccumulate, with a bioaccumulation factor in excess of 8000 (very bioaccumulative), the antineoplastic mitotane. Because no experimental data were 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 anti-Parkinson agent. Of these, desloratadine has been demonstrated to be potentially persistent, but no other comparisons can be drawn.

The QSAR-predicted log K_{OC} values were within applicability domains and calculated for 482 APIs. Three hundred and sixteen substances were classified as very mobile (log K_{OC} <3), 97 as mobile ($4 < \log K_{OC} < 3$), 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; European Commission, 2019),

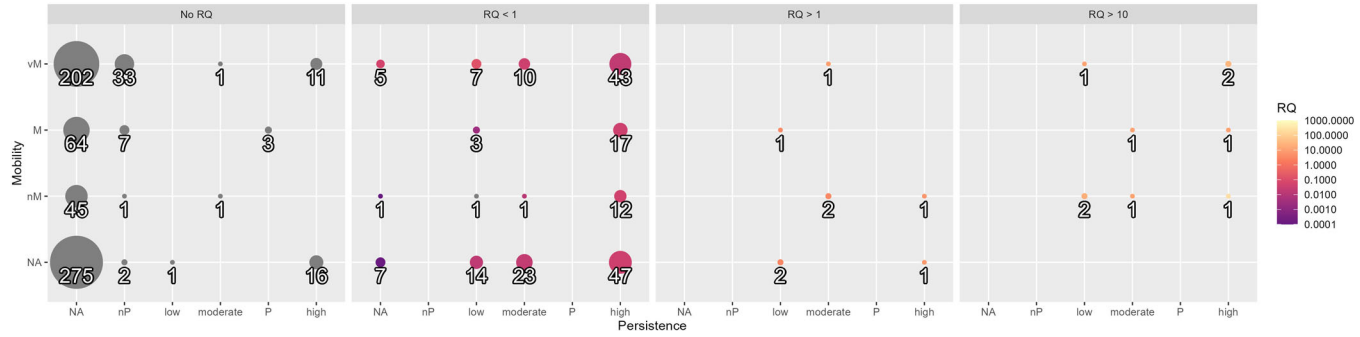

FIGURE 3: Risk quotient (RQ) category (facets), predicted mobility threshold (log organic–carbon partition coefficient, *y*-axis), and combined hazard statements and predictions for persistence (*x*-axis) for 870 active pharmaceutical ingredients (APIs) with varying data availability. Hazard and risk categories containing multiple APIs are combined into a single point of area scaled to the number of APIs; points are also labeled with number of APIs. Points are colored with the mean of the maximum RQs of constituent APIs over the 2016–2019 period. NA = (gray points) data were not available for a given property; nP = nonpersistent; P = persistent; nM = not mobile; M = mobile,; vM = very mobile.

assessment of mobility has been proposed for inclusion in Registration, Evaluation, Authorisation and Restriction of Chemicals assessment (Berger et al., 2018) and has recently undergone public consultation (European Commission, 2022c). Thus, it seems reasonable to assume it will at some point be considered in regulatory ERA of pharmaceuticals.

The predicted mean RQ across the 4 years and experimental PNEC availability across the 20 API types containing the most APIs are summarized 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 seven classes (56 APIs) having 50% or more data. Overall availability of toxicity data in groups containing highest-risk substances, such as antineoplastics, analgesics, and sex hormones, is notably poor. This raises the possibility that overall risk is significantly underestimated because of their omission. However, without knowing how much these substances would drive overall risk, drawing firm conclusions would be premature.

QSAR-predicted toxicity as a supplement to test data

As an alternative to limited available PNECs, QSAR lowest PNECs (provisional 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 (~ 50%), 78 of which also had experimental PNECs, permitting comparisons between results (Figure 4B and C). Correlation between the two data sets was poor (Table 2), with provisional RQs on average 50% higher than standard RQs and low positive correlation between the two values (Pearson's $r = 0.301$, $p = 0.0073$) and rankings (Spearman's $\rho = 0.493$, $p < 0.001$) of RQs (Table 2). 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 with the receptor-driven toxicity (Gunnarsson et al., 2019) of most APIs, especially high-risk sex hormones.

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 OTC 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 whole sales.

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 antiacne drug benzoyl peroxide (21%), the laxative bisacodyl (25%), the antihistamine meclozine (32%), and the antifungal amorolfine (43%). A Welch's *t* test of prescription and total PECs failed to reject the null hypothesis that there was no difference between the groups' means ($p = 0.70$; Table 2).

Calculations of RQs 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 >10%; and RQ overall increased by 19.4 across the nine substances. Prioritizing APIs by RQ gave an extremely similar order both with and without the addition of OTC sales (Spearman's $\rho = 0.99$, $p < 0.01$; Table 2).

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

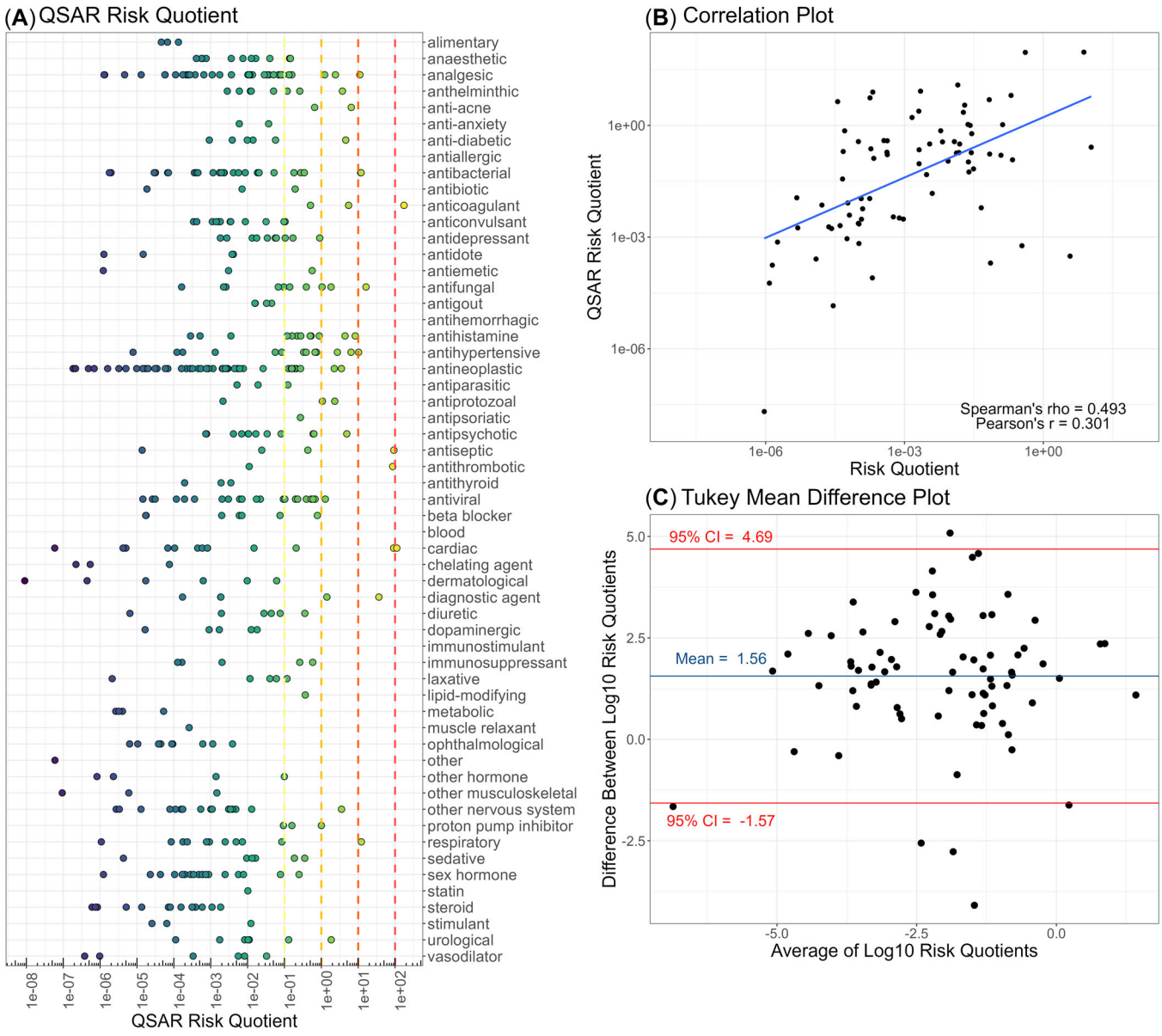

FIGURE 4: (**A**) Risk screening based on NORMAN quantitative structure–activity relationship (QSAR) predicted-no-effect concentrations (NORMAN, 2022) for 428 active pharmaceutical ingredients (APIs) using on 2019 predicted environmental concentrations; (**B**) plotted correlation for 78 APIs between QSAR and experimentally predicted risk quotients (RQs); (**C**) Tukey mean difference (QSAR – experimental) plot of difference between RQs against mean of RQ for 78 APIs.

also known as Solvent Violet 9, is coded as being available OTC.

Of the 43 dual-purpose APIs, on average 84% (94% median) of the 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%). Likewise, a Welch's *t* test failed to reject the null hypothesis that there was no difference between the human-only and total PEC means ($p = 0.59$; Table 2).

Consequent effects on risk could only be calculated for three of these, giving a 94% average (92% median) contribution across the antibiotic amoxicillin (91%), the antiseptic chlorhexidine (99%), and the antifungal miconazole (92%). Again, prioritization based on human data only gave an almost identical order to human and veterinary data (Spearman's $\rho = 0.99$, $p < 0.01$; Table 2).

DISCUSSION

Comparison of PECs 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 with detected levels in WWTP influent and effluent. However, 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 metabolized 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 are 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 (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. First, 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 that the discrepancy observed in our study is probably 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 generalize conclusions from the MECs compared with the entire data set. However, the patterns seen in the present study 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). Also, APIs were ranked by environmental concentration and RQ using measured and predicted values. The generation of significant results was limited by small available sample sizes for comparison, but nevertheless divergences between the two sets of rankings were apparent.

Characterizing risk, persistence, mobility, and bioaccumulation

Predicted API risk, persistence, mobility, and bioaccumulation, summarized across Table 3, Figure 3, and Table 4, were characterized by a general patchiness of data, with experimental or QSAR-based parameters generally available for <50% of APIs.

Where risk could be considered—approximately 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 highest-risk (RQ ≈ 220) of the substances, were sex hormones, characterized largely by progestogenic and estrogenic mode of action and adverse effects on

TABLE 4: Predicted mean risk quotient by the 20 most common active pharmaceutical ingredient types, grouped into bins by 1 order of magnitude

	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%
Anesthetic					0	17	17	100%
Antidiabetic					10	5	15	33%
Alimentary					3	12	15	80%
Urological					3	12	15	80%

Active pharmaceutical ingredients for which no experimental predicted-no-effect concentration was available to calculate risk quotients 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 Joint Research Centre data (AstraZeneca, 2017; FASS, 2019b; Loos et al., 2018); provisional predicted-no-effect concentrations were not considered. Risk quotient intervals are color coded by size (i.e., red = RQ > 100, green = RQ < 0.01).

fish reproduction at low concentrations. Data were, however, poor both within and across categories, 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 antimicrobial resistance (AMR) proposed by Bengtsson-Palme and Larsson (2016) are 3–50 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 single 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 chemicals with unfavorable K_{OC} values will affect the environment.

The use of the lowest-available PNECs notably affected the ranking of APIs. Diclofenac's 640 times smaller 2018 PNEC increased its mean RQ by the same factor and placed it in the top five APIs by RQ. Clarithromycin's RQ was increased approximately twofold, but its average RQ remained low, at a mean of 0.26 across the 4-year period. The use of AstraZeneca's higher PNECs reduced the risk of metformin (mean RQ = 0.21–0.021) and omeprazole (0.0019–0.00081) and moved naproxen out of position 12 of the top 20 highest-RQ substances (mean RQ = 5.95–0.25). Conversely, had AstraZeneca's tamoxifen PNEC been used, its mean RQ would have been 4.8 times higher (0.085–0.41).

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 that 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 characterization using these predicted values, but the general approach may be more applicable as QSARs are refined for various modes of pharmaceutical toxicity.

Effects of inclusion of OTC and veterinary data

On average, 70% of PECs calculated were attributable to prescription medications only (Figure 5). Likewise, 85% of the PEC magnitude was explained by human medications (Figure 6). In both cases, there was no statistically significant difference between the limited and complete data sets. The use of full data sets drove very little change in overall predicted risk, both at the individual API level and in terms of ranking. However, this may be an artifact of the limited toxicity data available because only 25% of APIs had accompanying PNECs.

Limitations and future work

A number of expansions of the work described in our study are foreseen but were beyond the scope of the present study.

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 levels (Sommerschild et al., 2021), meaning it may be possible to efficiently localize 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, because 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 modeling.

Quantification of uncertainty

Uncertainty was difficult to directly quantify in our output data set of RQs because 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 RQs. We aim, in future work, to quantify the contribution of different sources of uncertainty more carefully for a subset of APIs.

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 (e.g., fish feminization and masculinization 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.

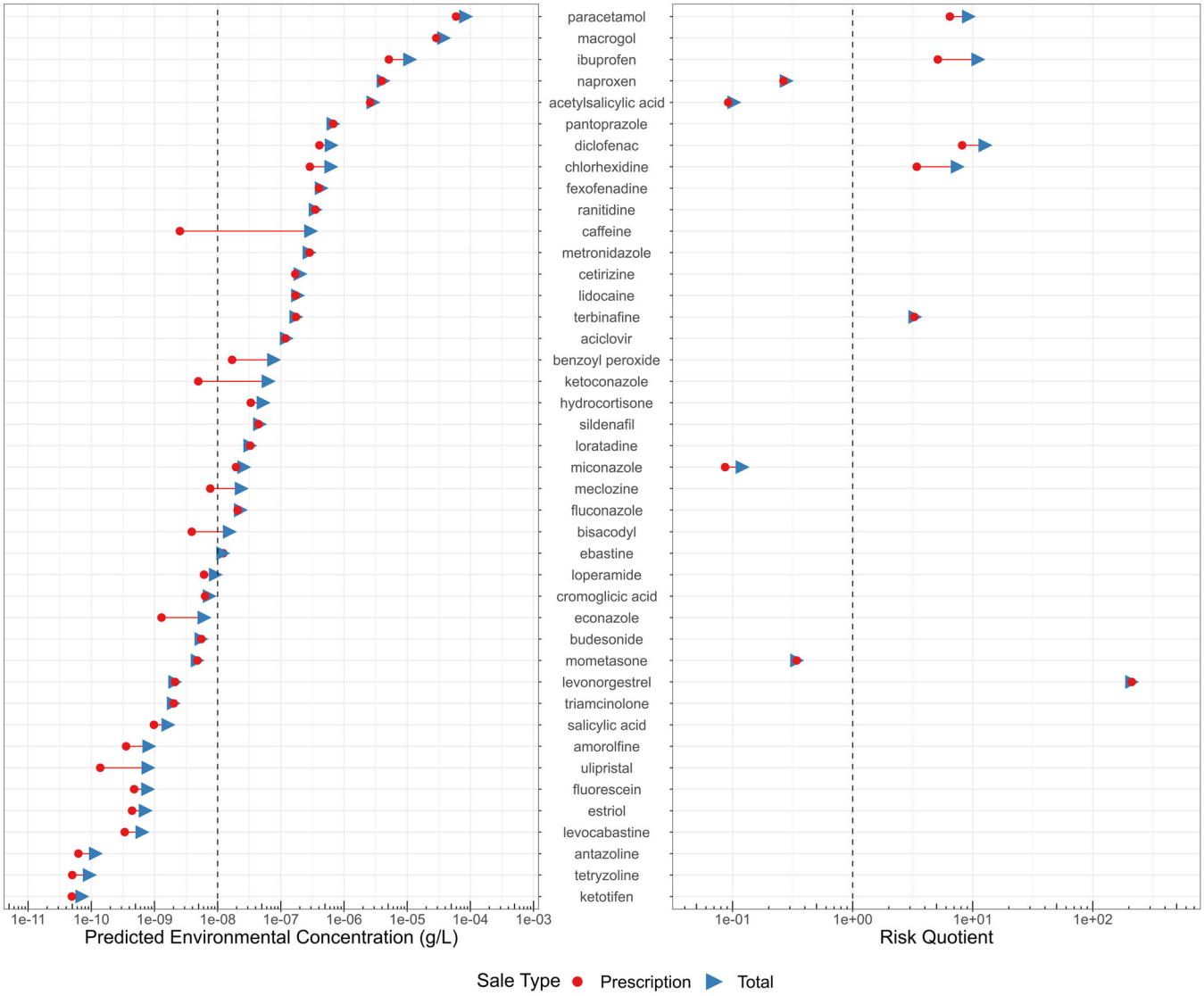

FIGURE 5: Predicted environmental concentrations (PECs) for 42 active pharmaceutical ingredients and risk quotients (RQs) for 10 of these sold both over the counter (OTC) and on prescription, sorted by total PEC. Values for prescription sales alone are shown as red circles and those from prescription and OTC sales (whole sales) as blue arrows. All variables are plotted on log10 scales. The standard regulatory thresholds of PEC > 0.01 µg/L and RQ > 1 are indicated with a dashed line.

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 RQs (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 with the two former, the sum of toxic units is a more scientifically correct approach but also by far the most data-dependent (Organisation for Economic Co-operation and Development, 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 the present study we chose to limit our consideration to the prioritization of single substances.

Relevance to environmental decision-making

Under the terms of the proposed recast Urban Wastewater Treatment Directive, WWTPs in the European Union and European Economic Area (including Norway) above a certain size (10 000 person equivalents) will be legally required to show removal rates of 80% or higher for a panel of 12 substances, including 10 APIs (European Commission, 2022a). Likewise, the European Commission has in its latest update proposed the addition of nine APIs, including ethinylestradiol, diclofenac, estradiol, and ibuprofen (identified as high RQ in Norway), to the Priority Substances List, requiring states to progressively phase out their emission (European Commission, 2022b). Furthermore, the European Union proposed sweeping reform to pharmaceutical legislation, including environmentally relevant subsections, in April 2023 (European Commission, 2023).

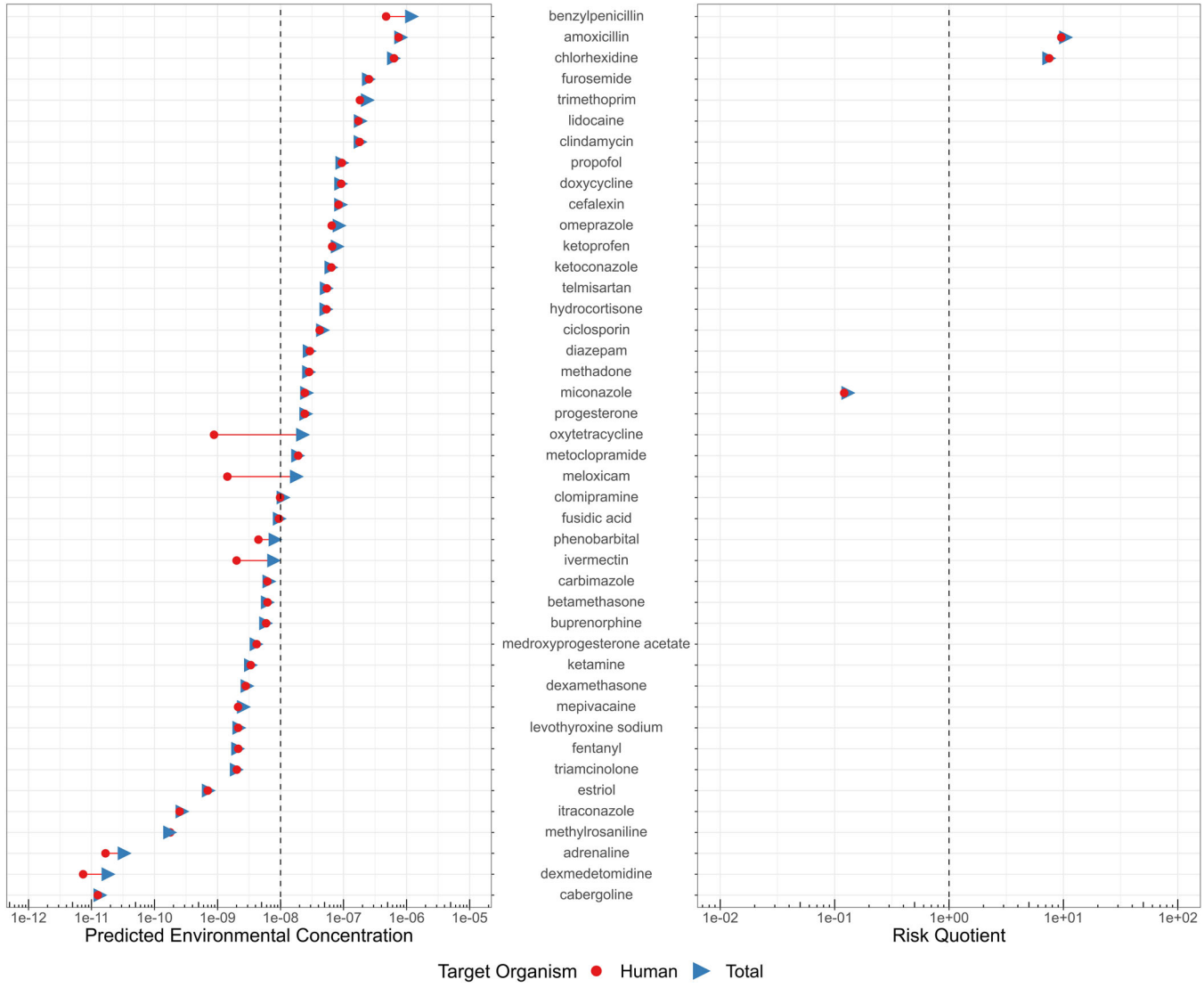

FIGURE 6: Predicted environmental concentrations (PECs) for 43 active pharmaceutical ingredients and risk quotients (RQs) for three of those sold in 2019 for both human and veterinary application, sorted by total PEC. Values for human sales alone are shown as red circles and those from human and veterinary sales as blue arrows. All variables are plotted on log10 scales. The standard thresholds of PEC > 0.01 μg/L and RQ > 1 are indicated with a dashed line.

Against this dynamic legislative backdrop, strong scientific evidence is required for locally and nationally appropriate decision-making. Burns et al. (2017) identified considerable regional variation in prioritization efforts, requiring region-level assessment of environmental concentrations. However, monitoring campaigns in Norway remain relatively limited, meaning that predictive assessments of exposure and risk, such as this, are a valuable tool for ecotoxicological prioritization of pharmaceuticals for future work and mitigation.

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. Many of these substances 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.

Quantitative structure–activity relationship 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 that they may not yet be mature enough to assess the complex, specific receptor-mediated toxicity or modes of action of APIs.

Lastly, we found a relatively small impact of the inclusion of OTC and veterinary sales on risk, compared with the prescription human approach taken in many similar studies. However, this is likely to be skewed by the data scarcity discussed above. Although the exploration of mitigation options was not within the scope of the present study, a few broad areas for future work and investigation present themselves.

Consequently, efforts toward 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 AMR, may also need to be employed. A particular focus on high-risk API categories such as sex hormones may be the most efficient place to start, particularly if optimized experimental testing protocols or validated models can be employed to reduce the cost of testing. Ultimately, a better overall impression of API category toxicity will allow for more environmentally directed use of medicine, with low-RQ substances substituted for those with high RQs, where medically possible.

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 prioritization of APIs and identifying key points where loads of high-risk APIs can be most efficiently intercepted. In addition, these must be paired with continuing environmental compartment monitoring to validate modeled outcomes, determine the behavior of pollutants in aquatic environments, and provide early warning of actual environmental pollution. Desk studies such as our study can be used to select compounds for routine monitoring based on a sampling of those with the highest predicted risk or hazard.

Pharmaceutical pollution remains a somewhat low priority globally and in Norway. Nevertheless, it is important, especially given the probable increase in pharmaceutical demand and consumption in future years, to ensure that data gaps on substance properties and toxicity are filled for those APIs judged most likely to negatively impact the environment. As these gaps are filled, a more considered assessment of the risks of mixtures of pharmaceuticals can begin to be attempted, under a variety of present and future conditions, finally allowing risk assessment to contribute to prevention, rather than cure.

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