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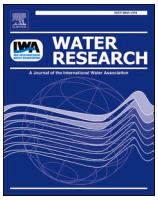

Occurrence, hazard, and risk of psychopharmaceuticals and illicit drugs in European surface waters

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ABSTRACT

This study aimed to provide insights into the risk posed by psychopharmaceuticals and illicit drugs in European surface waters, and to identify current knowledge gaps hampering this risk assessment. First, the availability and quality of data on the concentrations of psychopharmaceuticals and illicit drugs in surface waters (*occurrence*) and on the toxicity to aquatic organisms (*hazard*) were reviewed. If both occurrence and ecotoxicity data were available, risk quotients (*risk*) were calculated. Where abundant ecotoxicity data were available, a species sensitivity distribution (*SSD*) was constructed, from which the hazardous concentration for 5% of the species (HC_5) was derived, allowing to derive integrated multi-species risks. A total of 702 compounds were categorised as psychopharmaceuticals and illicit drugs based on a combination of all 502 anatomical therapeutic class (*ATC*) 'N' pharmaceuticals and a list of illicit drugs according to the Dutch Opium Act. Of these, 343 (49%) returned occurrence data, while only 105 (15%) returned ecotoxicity data. Moreover, many ecotoxicity tests used irrelevant endpoints for neurologically active compounds, such as mortality, which may underestimate the hazard of psychopharmaceuticals. Due to data limitations, risks could only be assessed for 87 (12%) compounds, with 23 (3.3%) compounds indicating a potential risk, and several highly prescribed drugs returned neither occurrence nor ecotoxicity data. Primary bottlenecks in risk calculation included the lack of ecotoxicity data, a lack of diversity of test species and ecotoxicological end points, and large disparities between well studied and understudied compounds for both occurrence and toxicity data. This study identified which compounds merit concern, as well as the many compounds that lack the data for any calculation of risk, driving research priorities. Despite the large knowledge gaps, we concluded that the presence of a substantial part (26%) of data-rich psychopharmaceuticals in surface waters present an ecological risk for aquatic non-target organisms.

1. Introduction

Psychoactive pharmaceuticals (psychopharmaceuticals) are a class of pharmaceuticals primarily used to treat mental disorders and illnesses, as well as other conditions relating to the nervous system, such as analgesics (painkillers) and anaesthetics. These psychopharmaceuticals are vital for our modern society, and their use has been steeply increasing around the world due to a multitude of factors, such as growing number of psychopharmaceutical-based treatments, growing global access to psychopharmaceuticals, growing global population, an ageing population in several regions, loss of social stigma, and increased availability of mental health treatment (European Medicines Agency, 2021; Gao et al., 2013; Massey et al., 2018; Read et al., 2014; World Health Organization, 2011).

Psychopharmaceuticals often alter the neurochemistry of the brain, by changing the concentrations and uptake of neurotransmitters such as serotonin and dopamine and/or by agonising or antagonising specific receptors (Jozwiak-Bebenista and Nowak, 2014; Wrobel, 2007). However, their activity is not limited to the brain, such as in the case of analgesics which work on the nervous system (Ghanem et al., 2016; Graham and Scott, 2005; Jozwiak-Bebenista and Nowak, 2014). In 1976, the WHO created The anatomical therapeutic chemical (ATC) classification system, a systematic approach to classify pharmaceuticals into therapeutic groupings based on the organ or biological system on

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which they act, as well as on their pharmacological and chemical properties, otherwise known as the mechanism of action (MOA). The ATC system distinguishes 14 categories in which psychopharmaceuticals are classified, with ATC—N standing for nervous system (WHO Collaborating Centre for Drug Statistics Methodology, 2018). Of the over 4000 pharmaceuticals administered worldwide, 502 belong to the ATC—N class (Wishart et al., 2018). In addition to psychopharmaceuticals, illicit drugs such as stimulants, dissociatives, hallucinogenics, illicit opioids and cannabinoids can have strong effects on the nervous system as well, having a similar MOA as psychopharmaceuticals. Yet, studies on illicit drugs tend to consider these in isolation (e.g. Deng et al., 2020; Huizer et al., 2021; Li et al., 2016; Thomas et al., 2012), even though some illicit compounds are screened as candidates for therapeutic uses (e.g. ketamine, cannabis, MDMA, Aan Het Rot et al., 2012; Ebbert et al., 2018; Krystal et al., 2019; Mathew et al., 2008; Sessa, 2017). Hence, it makes sense to jointly assess the presence, hazard, and risks of psychopharmaceuticals and illicit drugs in the aquatic environment.

Increased use has led to the widespread occurrence of psychopharmaceuticals and their transformation products in the aquatic environment (aus der Beek et al., 2016). Pharmaceuticals have been reported in the aquatic environment since the 1960s (Stumm-Zollinger and Fair, 1965), but specific concern for psychopharmaceuticals was only raised in the late 1990s (Daughton and Ternes, 1999; Halling-Sørensen et al., 1998). Consequently, there has been a significant increase in the amount of data on the occurrence of psychopharmaceuticals and their transformation products in surface waters, attributed also to advancements in analytical techniques such as LC—HRMS (Heberer, 2002; Luo et al., 2014; Ort et al., 2014; Richardson, 2007), which can detect pharmaceuticals in the ng to pg/l range (e.g. Zrnčić et al., 2014).

Wastewater treatment plants (WWTPs) are a major source of psychopharmaceutical and illicit drug residues entering the environment, to such a point that wastewater has become a frequently studied medium to reveal drug use trends in the connected populations (Deng et al., 2020; Huizer et al., 2021; Ort et al., 2014; ter Laak et al., 2010; van Nuijs et al., 2011). Currently, up to 60–70% of the consumed pharmaceuticals, illicit drugs and the respective transformation products are not removed by WWTPs and end up in surface waters, depending on the physico-chemical properties of the compounds and the setup of the WWTP. Once in the aquatic environment, the fate and persistence of psychopharmaceuticals can vary considerably between the different compounds, with some degrading very quickly, which are therefore not being detected in the environment, while some others have reported half-lives ($t_{1/2}$) that can exceed one year. For example, carbamazepine has a $t_{1/2}$ of 2400–10,000 h, while paracetamol has a $t_{1/2}$ of 40–350 h (Andreozzi et al., 2003; Yamamoto et al., 2009; Zou et al., 2015). This is, however, an understudied field (Bu et al., 2016), emphasising the need to further study the fate of (psycho)pharmaceuticals in the aquatic environment.

Whether or not the presence of psychopharmaceuticals and illicit drugs in the aquatic environment leads to adverse effects on non-target species typically depends on their sensitivity to these compounds. Since the neural and nervous architecture of humans is shared across many different organisms that deviated in evolutionarily terms eons ago (Edsinger and Dölen, 2018; Weiger, 1997), psychopharmaceuticals and illicit drugs designed to interact with the human nervous system may also successfully interact with the nervous system of non-target organisms, with potential negative ecological impacts (Claessens et al., 2013; Schwarz et al., 2021; Wang et al., 2021). For example, antidepressants can affect predatory behaviour in bass, impacts tissue metabolic capacities, and may compromise the adaptive responses in trout when accumulated through gills or through the food chain (Best et al., 2014; Bisesi et al., 2016, 2014). Adverse effects of illicit drugs have also been observed, but are considerably less studied than the effects of conventional pharmaceuticals (Mohan et al., 2021). Outside the aquatic environment, acute effects of psychopharmaceuticals such as changes in physiology and foraging behaviour have been reported for birds (Bean et al., 2014), which are susceptible to exposure through the food chain (Bean et al., 2018; Lazarus et al., 2015), as well as through direct exposure to sewage sludge (Bean et al., 2014). Beyond ecological effects, there is also concern about human safety (Kümmerer, 2010), because of the presence of psychopharmaceuticals in drinking water (Baken et al., 2018; Houtman et al., 2014), and in vegetables grown using recycled water (Fu et al., 2019; Goldstein et al., 2014; Kim et al., 2017; Paltiel et al., 2016). Both psychopharmaceuticals and illicit drugs have the potential to disrupt so-called 'infochemicals', which are compounds used for intra-species communications (e.g., navigation, predator avoidance, mating behaviour, etc.), since psychopharmaceuticals can mimic natural infochemicals in structure (Van Donk et al., 2016; Vera-Chang et al., 2018). Therefore, endpoints that derive from neurological and infochemical interactions are more sensitive than the classical endpoints (i.e., mortality, growth, and reproduction), and are likely to be of high ecological relevance for compounds that produce these effects. Despite the increasing amount of pharmaceuticals, psychopharmaceuticals, and illicit drugs present in the environment, the number of studies on their occurrence, hazards, and risks has been relatively stagnant when compared to other drivers of ecological changes, such as habitat loss and climate change (Bernhardt et al., 2017). In addition, the focus is often on the same few psychopharmaceuticals and illicit drugs (e.g., carbamazepine, paracetamol, fluoxetine) rather than on the newer or more used compounds such as escitalopram (Elsevier B.V., 2020a, 2020b). It is therefore of utmost importance to determine the contribution of psychopharmaceuticals and illicit drugs to the presently ongoing degradation of environmental quality by assessing the environmental risk posed by these chemicals, and to put such risks into context by using metrics such as prescription data.

Ecological risk assessments are used to determine which compounds merit concern by weighing the concentrations in the environment (occurrence) and the effect concentrations (hazard) to produce risk quotients (RQs), which informs of the likelihood of effects occurring in the environment. Under this system, an RQ of 1 or higher means that the concentration of a compound in the environment has surpassed the minimum concentration to expect ecotoxic effects. Averaging the calculated RQs for all species for which ecotoxicity data are available provides a median risk for a specific compound (species-level risk). Alternatively, when sufficient ecotoxicity data are available, Species Sensitivity Distributions (SSDs) can be generated, which integrate all available ecotoxicity data, allowing the derivation of the Hazardous Concentration for 5% of the species (HC_5), which is then entered into the RQ calculations instead of the species-specific effect concentrations. Hence, this method can be considered as an integrated M. species risk assessment (Posthuma et al., 2001). However, SSDs require extensive ecotoxicity data to be considered robust, and multiple taxonomic groups to be considered more representative of natural communities (Wheeler et al., 2002; European Commission, 2018). Therefore, deriving an SSD may only be feasible for a limited number of data-rich compounds.

Despite the rise in the use of psychopharmaceuticals and illicit drugs, scientific attention to the presence in the environment, ecotoxicological hazards, and environmental risks of these compounds is still rather limited. Currently, reliable environmental risk assessments are hampered by a limited insight into the availability of data on the occurrence in the aquatic environment and the hazard to non-target organisms. Therefore, the aim of the present study was to review the data on occurrence and ecotoxicological hazard of psychopharmaceuticals and illicit drugs in European surface waters, paying attention to the accompanying uncertainties and knowledge gaps. To this end we provided an ecological risk assessment of psychopharmaceuticals and illicit drugs in European surface waters by weighing their occurrence and hazard. We contextualised these risks using (Dutch) prescription data.

2: Methods

2.1: Selection and classification of psychopharmaceuticals and illicit drugs

We based our selection of psychopharmaceuticals on the ATC—N list of 502 chemicals (WHO Collaborating Centre for Drug Statistics Methodology, 2018). Illicit drugs, such as stimulants, dissociatives, hallucinogenics, illicit opioids and cannabinoids, were added to this list by using the Opium Act of the Netherlands, containing 282 illicit compounds. Illicit and recreational drugs such as caffeine, nicotine, cocaine, THC, and amphetamines were merged to make a '*Stimulants & Illicits*' class, since the ATC categories of these select compounds (e.g., cocaine as an anaesthetic) were deemed inappropriate. Since the ATC—N list also includes compounds that are used as illicit drugs (e.g., opioids), duplicates were removed. The resulting list totalled to 702 compounds (Tables 1, S1). CAS numbers were obtained from DrugBank and PubChem (Kim et al., 2021; Wishart et al., 2018).

2.2. Occurrence data retrieval, filtering, and confidence score

To retrieve data on the occurrence of psychopharmaceuticals and illicit drugs in surface waters, the EU's IPCHEM monitoring platform (European Commission, 2021) was used, which contains 18 environmental occurrence databases. Four of these databases contained psychopharmaceuticals and illicit drugs, and data were extracted in July 2021 (Table S2). These four databases were the German UBA "Pharmaceuticals in the Environment" database (Eike et al., 2019), the NORMAN Network database (NORMAN—Network of reference laboratories, 2021), the French Naïades Database (Naïades, 2020), and the EU WATERBASE database (EEA, 2021). In addition, we were given access to two Dutch databases that were not represented in IPCHEM. These were the WKP (Rijkswaterstaat, 2021) and the RIWA databases ("RIWA-Rijn," 2021). To maximise the amount of data collected, the top 50 most prescribed drugs in the Netherlands from 2015 to 2020 (Zorginstituut Nederland, 2021) that did not have data in the aforementioned databases were manually searched for in literature by using the search terms '"*<Drug name>*", *environmental, environment, occurrence, detection, detected, surface water*' in Google Scholar in June 2021.

Occurrence data were filtered for European surface waters only (Table S3), removing values for other water matrices, such as sewage effluent, groundwater, etc. False positives, such as nitrophenol being confused with phenol by search engines, were also removed. If the database flagged any data as 'questionable', these data were not used. Outliers that were unusual or unrealistically high values (e.g., 1×10^{11} mg/l) were either verified when the original source agreed with the database, corrected when the source disagreed with the database or else deleted if the original source was unavailable. Upon merging the data from the six databases, any duplicates were removed by inspecting sources, monitoring locations, monitoring location codes, and dates. For all data below the limit of detection (<LOD), the 90th percentile was calculated for all <LOD data per compound (Weltje and Sumpter, 2017), which helped to provide enough data to calculate the risk for compounds for which all data were <LOD.

Table 1
Numbers of ATC—N psychopharmaceuticals and illicit drugs.

Type (Source)	Number of Compounds
ATC—N (DrugBank)	502
N01 - Anaesthetics	43
N02 - Analgesics	75
N03 – Anti-Epileptics	40
N04 - Anti-Parkinson's	34
N05 – Psycholeptics	166
N06 - Psychoanaleptics	104
N07 - Other	41
Illicit Drugs (NL Opium Act)	282
Total (Duplicates Removed)	702

An occurrence data confidence score was created as an indication of the amount and range of environmental occurrence data per compound. Since not all compounds have the same quantity and diversity of occurrence data, this will serve as an indication of data quantity and diversity. It should be noted that the occurrence confidence score was made before the LOD adjustments, meaning that values below or above the LOD are treated equally in the confidence assessment. The total score was calculated from 3 sub-scores: the number of entries (measurement frequency), countries (spatial distribution), and years (temporal distribution):

$$Occurence\ Score = \frac{\#\ Entries}{57} \times \frac{\#\ Countries}{12} \times \frac{\#\ Years}{2}$$

Equation 1: Occurrence data scoring system, with #Entries ≤ 57, #Countries ≤ 12, and #Years ≤ 2. These numbers are the median values for each of those categories (see Tables S5 and S7). I.e., the median number of entries was 57, the median number of countries was 12, and the median number of years was 2.

2.3 Ecotoxicity data retrieval, filtering, and confidence score

Ecotoxicity data were extracted from the US EPA ECOTOX Knowledgebase (EPA, 2013) and the German UBA ETOX database (Umweltbundesamt, 2008) in July 2021. In all cases, both compound names and CAS numbers were used as search criteria. In addition, the top 50 most prescribed drugs in the Netherlands in the years 2015 to 2020 (Zorginstituut Nederland, 2021) that did not have data in the aforementioned databases were manually searched for in literature by using the search terms '"*<Drug Name>*", *ecotoxicity, ecotoxicology*' in Google Scholar in June 2021.

Ecotoxicity studies with no results, no stated endpoint, or irrelevant endpoints (i.e., bioaccumulation factors) were removed. To maximise the usable data, values recorded as below or above lowest or highest test concentration were adjusted to the lowest or highest test concentration, respectively (e.g., <1 μg became 1 μg, and >1 μg became 1 μg). Outliers that were unusual or unrealistic were either verified when the original source agreed with the database, corrected when the source disagreed with the database or else deleted if the original source was unavailable.

For studies that reported multiple endpoints per compound, only the most sensitive relevant endpoint was used to avoid cases for which studies with multiple endpoints held a greater weight than studies with a single endpoint. The ecotoxicity data included many different measures of toxicity, including ECx (Effective Concentration), LCx (Lethal Concentration), LOEC (Lowest Observed Effect Concentration), NOEC (No Observed Effect Concentration) and MATC (Maximum Acceptable Toxicant Concentration). To maximise the amount of usable data, these were extrapolated to either acute EC50 values (Effective Concentration for 50% of the exposed organisms) or to chronic NOEC values (No Observed Effect Concentration), following the methods for extrapolation described by Posthuma (2019). To this end, the first step was to categorise datapoints as either "chronic" or "acute", following the criteria of ECETOC (1993, Table S4), with acute and sub-chronic ecotoxicity data being merged as "acute" (Table S4). Secondly, all measures of toxicity were put into two categories, NOEC or EC50, based on the original measure of toxicity (See Posthuma et al., 2019). These two steps yielded four categories of data: acute NOEC, chronic NOEC, acute EC50 and chronic EC50. Acute NOEC values were multiplied by 1/3 to give chronic NOEC values, and chronic EC50 values were multiplied by 3 to give acute EC50 values. This resulted in two final data categories: the (extrapolated) chronic NOEC (denoted as cNOEC) and the (extrapolated) acute EC50 (denoted as aEC50) ecotoxicity data, which were then used for all further analyses in the study.

If enough ecotoxicity data were available, SSDs were generated to derive HC_5 values, allowing for an integrated multispecies measure of the hazard of that specific compound. To avoid that lacking ecotoxicity

data hampered our analysis, SSDs were constructed based on a minimum number of 5 data points using the US EPA "SSD Generator" (EPA, 2016). Different SSDs were produced for cNOEC and aEC50 values. aHC_5 (acute) and cHC_5 (chronic HC_5) values, defined as the hazardous concentration for 5% of species, were derived from the SSD plots of the respective compounds.

In order to assess the quantity and diversity of the ecotoxicity data per compound, we assigned a confidence score to each compound's cHC_5, aHC_5, cNOEC, and aEC50 values based on the TG27 criteria (European Commission, 2018). For each compound we scored the number of datapoints (out of a maximum of 10) and for taxa (out of a maximum of 8). These were then multiplied to create an ecotoxicity data score between 0 and 1 (Equation 2).

$$Ecotoxicity\ Score = \frac{\#\ Entries}{10^*} \times \frac{\#\ Taxa}{8^*}$$

Equation 2: Ecotoxicity data scoring system, with #Entries ≤ 10 and #Taxa ≤ 8

**Based on TG27 criteria*

2.4 Ecological risk assessment and confidence scores

By weighing the occurrence and ecotoxicity data, the ecological risk for each compound was assessed. Two-dimensional matrices of risk quotients (RQs) were created where each occurrence value was divided by each aEC50, cNOEC, aHC_5, or cHC_5 value per compound Consequently, each compound could have up to four associated RQ matrices. To compare the effect of including the 90th percentile of the <LOD data (see 2.2), risk matrices were also made without the <LOD data.

$$RQ = \frac{Concentration\ in\ the\ Environment}{Effect\ Concentration}$$

Equation 3: Calculation of Risk Quotients (RQs), where effect concentration can be aEC50, cNOEC, aHC_5*, or* cHC_5 *values.*

The calculated RQs were then plotted in a logarithmic boxplot, and the percentage of RQ > 1 was determined, indicating a potential risk. A risk confidence score was calculated for each type of the four risk analysis using the following formula:

$$Risk\ Score = Occurence\ Score \times Ecotoxicity\ Score$$

Equation 4: Calculation of risk confidence score.

All confidence scores were simplified into 5 categories (Table 2). Ecotoxicity data uses an adjusted lower boundary due to the nature of the scoring system described in 2.3. All numerical confidence scores can be found in the supplementary information (Table S9).

2.5 Statistical analyses

Pearson correlations were performed to assess relations between (Dutch) prescription data (Zorginstituut Nederland, 2021) and other variables, namely occurrence, occurrence data quantity (I.e. raw number of entries per compound), occurrence data confidence, ecotoxicity, ecotoxicity data quantity, ecotoxicity data confidence, and risk. A second series of Pearson correlations were performed to assess relations between risk (both cNOEC and aEC50) and these same variables. These correlations were log-transformed and performed using native Excel functions, with formulae embedded in Table S10. T-tests were performed on the cumulative data for occurrence, cNOEC and aEC50 data per compound class to test for significance between compound classes using native Excel Functions (Table S11).

Table 2
Simplified scoring system for all confidence scores.

Confidence Score Category	Description	Range (Ecotox)	Range (Occurrence/ Risk)
VH	Very High	>0.75	>0.75
H	High	0.5 - <0.75	0.5 - <0.75
M	Medium	0.1 - <0.5	0.1 - <0.5
L	Low	0.015 - <0.1	0.01 - <0.1
VL	Very Low	<0.015	<0.01

3: Results and discussion

3.1 Data availability for the selected compounds

For 343 out of 702 (49%) of compounds, occurrence data were reported in European surface waters, but for 194 (28% of the total, or 57% of the number of compounds with occurrence data), the concentration in the environment was below the LOD, leaving 149 compounds (21%) with at least one occurrence datapoint above the LOD. Only for 105 psychopharmaceuticals (15%) ecotoxicity data were available, immediately highlighting that ecotoxicity data were even less available than occurrence data. Only for 87 (12%) compounds both occurrence and ecotoxicity data were available, allowing for a risk assessment. An overview of occurrence, ecotoxicity and risk data can be found in Tables S5, S6 and S7, respectively. The NORMAN database provided most of the occurrence data in this study (Table 3), because it includes both literature studies and monitoring data. We noticed that there is a lack of parity between the multi-national occurrence databases, most notably the UBA, NORMAN and WATERBASE databases, which contain outdated references to each other. WATERBASE, RIWA, WKP, and NAÏADES returned relatively low amounts of data, likely because these are general monitoring databases, which focus on other contaminants. This highlights the low priority of psychopharmaceuticals compared to legacy contaminants such as solvents and persistent organic pollutants. The occurrence literature search did not return any additional results for the countries included in this study (Table S3). Considering that the EPA and UBA databases are both collections of current ecotoxicity literature, there was a large lack of parity between the two ecotoxicity databases, with the EPA database being far larger than the UBA database. Moreover, additional ecotoxicity data were found during the present literature search.

3.2 Occurrence of psychopharmaceuticals and illicit drugs in european surface waters

Over half of all psychopharmaceuticals and illicit drugs did not return occurrence data (Fig. 1). Of the 343 (49%) psychopharmaceuticals occurrence data was available, only 52 (7%) compounds had the highest possible occurrence data confidence, while for almost all others (278, 40%) the confidence was medium or lower (Table S5). For 340 compounds the concentration was below the LOD, and so the 90th percentile procedure was used for those datapoints (Fig. 1). Lithium presented by far the highest median concentration (0.016 mg/l), likely due to its natural occurrence as a mineral. In addition, common solvents such as diethyl ether, trichloroethylene, and phenol, were also present in high median concentrations due to uses in other applications such as industrial solvents. Common analgesics such as paracetamol, salicylamide, salicylic acid, aspirin, and ibuprofen, as well as carbamazepine, were also present in high concentrations (Fig. S5).

The low number of data entries per compound contributed most to the generally low occurrence confidence when compared to the number of countries and years. This indicates that there is a large disparity between well studied and understudied compounds in terms of raw data, with five compounds (caffeine, carbamazepine, chloroform, trichloroethylene, and ibuprofen) out of 702 compounds accounting for over 50% of all occurrence data (Table S5), with caffeine alone accounting for almost 20% of positive detection data. Importantly, occurrence data were missing for common and highly prescribed compounds such as betahistine, pyridostigmine, and distigmine (Tables S5, S8). For the illicit compounds, 127 out of 199 did not return any occurrence data, which were often obscure 'new psychoactive substances', or

Table 3
Summary of databases used, including geographic location, timespan, data type, positive (>LOD) and negative (<LOD) detections.

Database	Location	Years	Data Type	#Compounds After Cleaning/Filtering (Positive Detection)	#Compounds After Cleaning/Filtering (Negative Detection)
UBA 'Pharmaceuticals in the Environment'	DE + Worldwide	1997–2016	Occurrence (Literature)	82	74
NORMAN	**Europe	2000–2016	Occurrence (Literature + Monitoring)	121	330
WATERBASE	EU + EEA	1987–2019	Occurrence (Monitoring)	7	18
Naïades	FR	2015–2020	Occurrence (Monitoring)	17	20
RIWA	NL	2015–2020	Occurrence (Monitoring)	22	22
WKP	NL	1989–2019	Occurrence (Monitoring)	25	30
Occurrence Literature*	**Europe	2012–2019	Occurrence (Literature)	0	–
EPA ECOTOX	–	1939–2021	Ecotoxicity	94	–
UBA ETOX	–	1964–2017	Ecotoxicity	20	–
Ecotoxicity Literature*	–	2008–2020	Ecotoxicity	8	–

* Only top 50 most prescribed drugs based on yearly average DDD in the Netherlands were searched for in literature.
** See table S3 for countries and regions incorporated.

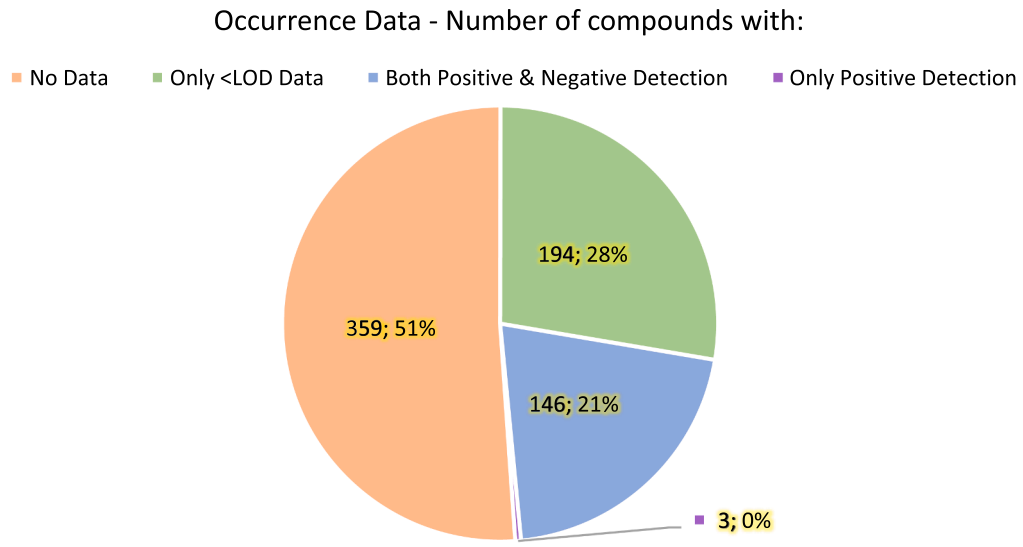

Fig. 1. Breakdown of the occurrence data showing the number of compounds that did not return data, only returned <LOD data, returned both <LOD and positive data, and only returned positive data.

'smartdrugs' (Table S5, Castiglioni et al., 2021; Weinstein et al., 2017). Other compounds without data included discontinued psychopharmaceuticals, such as hexapropymate, metamizole, and iproniazid.

Mean occurrence concentration, occurrence data quantity, and occurrence data confidence all showed a positive relation to Dutch prescription data (Conc.: $r = 0.207$, $p = 0.015$, Quant.: $r = 0.234$, $p = 0.006$, Conf.: $r = 0.299$, $p < 0.001$, Table S10). That is to say, the more a compound is prescribed, the higher its concentration in the environment, the higher the amount of data available, and the better its confidence score (data variety).

When considering the different drug classes (Table 4), Stimulants/Illicits were present in the highest median concentration (8.70×10^{-5} mg/l), which can be solely attributed to the data dominance of caffeine (Table S5). The lowest median concentration (3.90×10^{-6} mg/l) was presented by the 'other' class. However, the highest and lowest median concentration per class differed only a factor of 26, whereas the difference within the Psycholeptics group, for example, was a factor of over 10,000. The T-tests showed that the median concentrations differed significantly between classes, except for the 'other' class and all other classes (Table S11). The range in the median concentrations within classes were much wider, partly attributed to a small number of compounds present in high concentrations, e.g., Lithium in the Psycholeptics class, paracetamol in the analgesics class, and carbamazepine in the antiepileptics class. This indicates that pharmaceutical class is generally not the governing property for environmental occurrence, and other properties such as persistence and prescription may better predict the concentrations in the environment.

Table 4
Mean concentration, median concentration, standard deviation (S.D.), and median occurrence confidence per compound class. Median confidence is reported as low (L) or medium (M). Concentrations include values calculated from <LOD data as described in 2.2.

Class	Mean Conc. (mg/l)	Median Conc. (mg/l)	S.D.	Median Confidence
Anaesthetic	5.63×10^{-3}	6.00×10^{-5}	8.82×10^{-2}	M
Analgesic	2.12×10^{-1}	2.50×10^{-5}	9.93	L
Antiepileptic	1.21×10^{-2}	6.10×10^{-5}	7.12×10^{-1}	M
Anti-Parkinson's	7.53×10^{-6}	5.00×10^{-6}	1.01×10^{-5}	L
Psycholeptics	3.23×10^{-1}	5.40×10^{-5}	3.08	L
Psychoanaleptics	2.89×10^{-5}	5.90×10^{-6}	1.06×10^{-4}	L
Other	6.63×10^{-3}	3.90×10^{-6}	7.94×10^{-2}	L
Stimulants/Illicits	1.92×10^{-4}	8.70×10^{-5}	7.45×10^{-4}	L

To maximise the amount of occurrence data, we utilised all data below the LOD by taking the 90th percentile of the collective LODs per compound as described by Weltje and Sumpter (2017). While this method allows the evaluation of risks for compounds that otherwise would have lacked any occurrence data (see 3.4), it may, however, overestimate the occurrence for these compounds. Therefore, we also included occurrence values for compounds using positive detections only to compare the method (Table S5). The median of medians for dataset using the <LOD method was 4.85×10^{-6} mg/l, while the median of medians for the dataset not using the method was 5.63×10^{-6} mg/l, a 16% difference. However, by including the <LOD data, for 21 additional compounds the risk could be calculated (Table S7), giving merit to the method of Weltje and Sumpter (2017).

3.3 Aquatic ecotoxicity of psychopharmaceuticals and illicit drugs

105 (15%) psychopharmaceuticals returned ecotoxicity data, with none of the compounds achieving the requirements for a maximal ecotoxicity data confidence score. While there are numerous compounds that appear to be quite toxic, the top 10 most toxic compounds all had a low or very low data confidence, leaving the hazard assessment quite ambiguous (Table S6). Compounds with very high data confidence included carbamazepine, chloroform, paracetamol, ibuprofen, fluoxetine, phenol, and trichloroethylene. Carbamazepine demonstrated the highest toxicity of all compounds and with a very high data score (cNOEC = 0.01 mg/l, S6). For both the cNOEC and the aEC50 datasets, the TG27 requires higher plants as one of the species groups to be included to provide an ecosystem-wide approach, which were lacking for all compounds. Yet, even without higher plants as a mandatory category, no compound would have achieved the maximum confidence score for either cNOEC or aEC50 (Table S6). Only 10 compounds achieved a high or very high data confidence, with over half of all compounds having a low or very low confidence (Table S6). As for the occurrence data, only a few compounds (phenol, trichloroethylene, carbamazepine & chloroform) accounted for over 50% of all ecotoxicity data, with phenol accounting for 25%. Therefore, ecotoxicity data were also characterised by a large disparity between well studied and understudied compounds. Most of the raw ecotoxicity data (61%) were extrapolated into an aEC50, which was because older studies tended to report acute results rather than chronic.

Considering inter-class differences in ecotoxicity (Table 5), there was no clear indication as to which compound class was more toxic. For example, according to the cNOEC data, Stimulants/Illicits were the most toxic (0.08 mg/l), while anaesthetics were the least toxic (6.3 mg/l). However, according to the aEC50 data, both of these two classes exhibited a very similar toxicity (47 and 42 mg/l respectively). The T-tests showed that there were only a few statistical differences in toxicity between compound classes, with the exception for differences between anaesthetics and Psychoanaleptics for both datasets, which is likely due to the high cNOEC values for the antidepressants in the Psychoanaleptics class (Table S11). Aside from the notable exception of anaesthetics and Psychoanaleptics, the broad lack of significant differences in ecotoxicity between compound groups could be related to the low confidence scores of all compound classes (Table 5), making it difficult to draw firm conclusions as to which class is most toxic. Indeed, the top 5 most toxic Psychoanaleptics had a low or very low confidence, while 3 out of 5 of the most toxic anaesthetics had a high or higher data confidence, which could indicate that poor data quality explains why the T-tests showed a significant difference between these two classes. Like for the occurrence data, the intra-class differences were much larger than the inter-class differences, as reflected by the large standard deviations. This highlights that each compound needs to be assessed independently, and groupings such as therapeutic class obviously do not reflect species-specific nor compound-specific sensitivities.

For only 11 out of 702 compounds enough data were available to generate SSDs based on the non-stringent criteria used here (i.e., a minimum of five species), with none reaching the TG27 requirements of 10 diverse species. There was a lack of test species diversity, as fish, crustaceans, and algae accounted for almost 75% of all test species and data for invertebrates, insects, molluscs, plants, worms and amphibians are largely lacking (Fig. 2). This clearly calls for more extensive and more diverse ecotoxicity data. To combat this lack in ecotoxicity diversity and data, for all psychopharmaceuticals in use ecotoxicity data should be generated that follow the protocol in TG27. While it may seem counter-intuitive to include higher plants as test species for psychoactive compounds, we argue that this creates a level playing field between species and chemical classes. In addition, psychopharmaceuticals may exert ecotoxic effects on higher plants that we simply do not know about due to a total lack of data, which was the case in the past for herbicide effects on animals (Perkins et al., 2000; Tsui and Chu, 2003). Including such data would help to obtain a better estimation of the hazard of psychopharmaceuticals by means of an SSD, aiding a reliable estimation of the risk on a M. species level. We do, however, acknowledge that testing many different species may be unfeasible, which calls for prioritisation. An additional and alternative approach could be to run more *in silico* tests since there have been strides to move away from animal testing in recent years (Scholz et al., 2013). As such, *in silico* methods, like QSARs (Schüürmann et al., 2007), have been improving in recent years with the use of machine learning (Lovrić et al., 2021; Wu et al., 2021). Another *in vitro* alternative is cellular bioassays (Fent, 2007; Lammer et al., 2009), although there are concerns over the ecological relevance of such bioassays (Schirmer, 2006). While it is beyond the scope of this study to go into detail about *in silico/in vitro* to *in vivo* extrapolation, it is an interesting topic for future research (Bell et al., 2018).

Unlike for occurrence data, for which there is a validated procedure for dealing <LOD data (Weltje and Sumpter, 2017), such a procedure is lacking for hazard data. Following our pragmatic approach to adjust ecotoxicity data recorded as below or above the lowest or highest test concentration to the lowest or highest test concentration, we might respectively under- or over-estimate ecotoxicity. Exact effect concentrations were not established in only a small number (6%) of the datapoints used in this study. However, our approach still maximises the number of ecotoxicity data which is relevant given the lack of data.

Only 13% of the ecotoxicity data considered behavioural end points (Fig. 2). Since psychopharmaceuticals are designed to influence behaviour, and behavioural effects occur by definition at lower concentrations than survival, toxicity may be underestimated when using

Table 5
Median ecotoxicity (mg/l), standard deviation (S.D.), and ecotoxicity data confidence score per compound class for both ecotoxicity datasets.

Class	Median cNOEC (mg/l)	cNOEC S.D.	cNOEC Conf.	Median aEC50 (mg/l)	aEC50 S.D.	aEC50 Conf.
Anaesthetic	6.3	211	M	42	951	L
Analgesic	1.0	153	L	102.3	5,173,023	L
Antiepileptic	0.047	274	L	56.4	426	L
Anti-Parkinson's	0.891	–	L	58.6	307	L
Psycholeptics	2.943	83	L	65.5	2249	L
Psychoanaleptics	0.056	146	L	1.7	327	M
Other	0.013	6	L	0.242	84	L
Stimulants/Illicits	0.085	257	L	47.4	1154	L

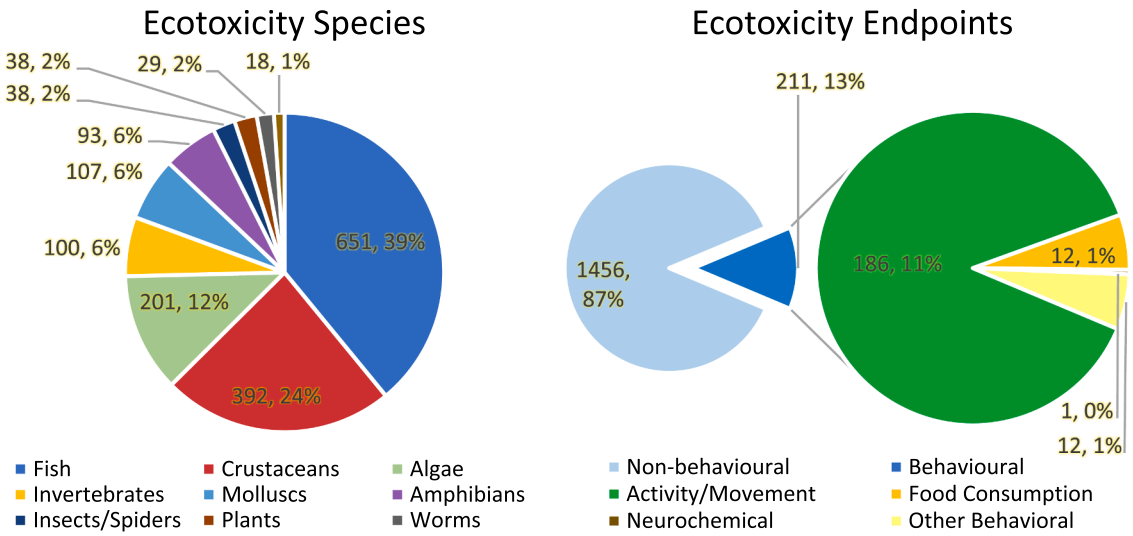

Fig. 2. Proportion of taxa within the ecotoxicity data (a) and breakdown of the studied ecotoxicity endpoints (b) showing the proportion of non-behavioural to behavioural endpoints, and the breakdown of behavioural endpoints.

only non-behavioural endpoints.

3.4: Risks of psychopharmaceuticals in european surface waters

Only for 87 out of 702 (12%) compounds enough occurrence and ecotoxicity data were available to calculate indicative environmental risks, for which the chronic results are visualised in Figs. 3 and 4, where data above an RQ of 1 (red line) are indicative of risk (Table S7). Table 6 shows the 20 out of 87 compounds that demonstrated a potential risk based on the% of RQs above 1 from the cNOEC analyses, while an additional 3 compounds indicated a potential risk based on the aEC50 results (Table S7) resulting in 23 compounds carrying a potential (at least 1 RQ>1) risk. The five riskiest compounds in this analysis were risperidone, carbamazepine, paracetamol, cocaine, and ibuprofen, for which at least 10% of the RQs above 1. In addition, the cHC_5 results showed that fluoxetine also carried a high risk (35%, Fig. 4, Table 6). However, only for carbamazepine, paracetamol, fluoxetine, and ibuprofen the confidence of this risk assessment was high or very high.

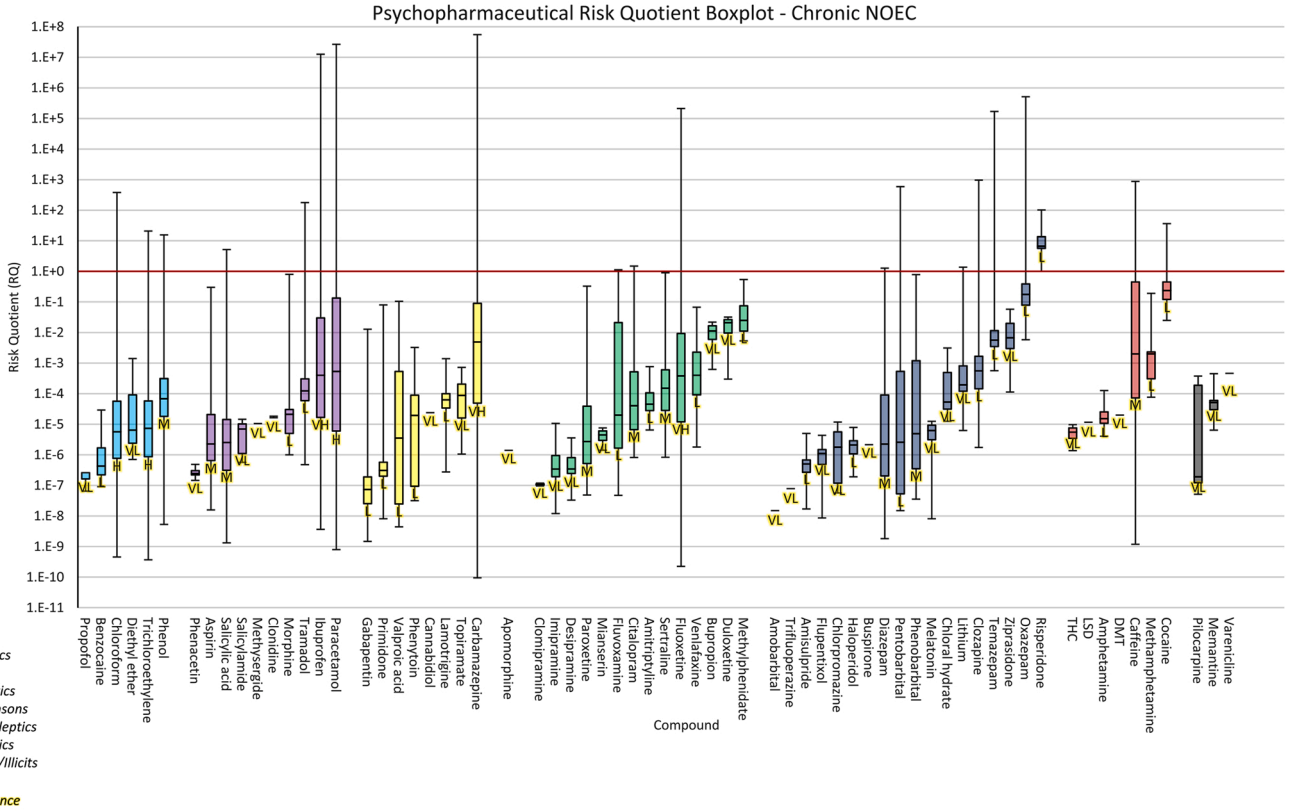

Fig. 3. Risk quotient boxplot based on occurrence and (extrapolated) chronic NOEC ecotoxicity data. Whiskers represent upper and lower quartiles, while the box represents middle upper and middle lower. The central line indicates the median value. Compounds have been grouped and colour-coded based on therapeutic class. Confidence level is indicated in the floating text by each box. (LV=Very Low, *L*=Low, *M*=Medium, *H*=High, VH=Very High).

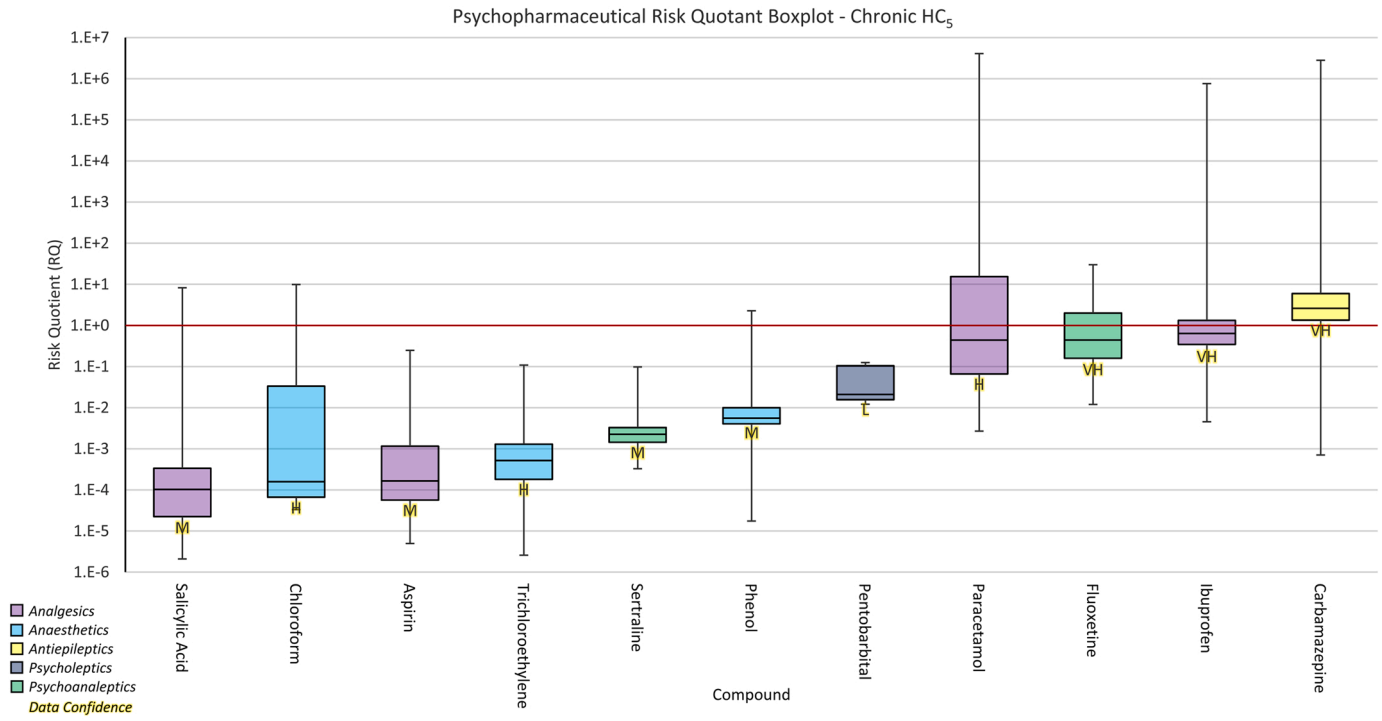

Figure 4: Risk quotient boxplot based on occurrence and cHC₅ values calculated from (extrapolated) chronic NOEC ecotoxicity data. Whiskers represent upper and lower quartiles, while the box represents middle upper and middle lower. The central line indicates the median value. Compounds have been colour-coded based on therapeutic class. Confidence level is indicated in the floating text by each box (LV=Very Low, L=Low, M=Medium, H=High, VH=Very High).

Fig. 4. Risk quotient boxplot based on occurrence and cHC_5 values calculated from (extrapolated) chronic NOEC ecotoxicity data. Whiskers represent upper and lower quartiles, while the box represents middle upper and middle lower. The central line indicates the median value. Compounds have been colour-coded based on therapeutic class. Confidence level is indicated in the floating text by each box (LV=Very Low, *L*=Low, *M*=Medium, *H*=High, VH=Very High).

Table 6
Compounds that demonstrated a potential risk based on the cNOEC dataset, along with confidence. Where applicable, the cHC_5 results are also included, as are the whole drug classes for reference.

Drug/Class	cNOEC Risk (Mean)	cNOEC Risk (Median)	cNOEC Risk (%)	cHC_5Risk (Mean)	c HC_5 Risk (Median)	cHC_5 Risk (%)	Data Confidence
Anaesthetics	$\mathbf{1.38 \times 10^{+1}}$	$\mathbf{6.04 \times 10^{-6}}$	**0.22%**	–	–	–	**M**
Chloroform	$7.57 \times 10^{+1}$	5.68×10^{-6}	0.25%	1.99	1.59×10^{-4}	1.85%	**H**
Phenol	3.12	6.80×10^{-5}	0.14%	4.59×10^{-1}	5.53×10^{-3}	0.23%	**M**
Trichloroethylene	4.18	7.36×10^{-6}	0.18%	2.21×10^{-2}	5.19×10^{-4}	0.00%	**H**
Analgesics	$\mathbf{7.85 \times 10^{+5}}$	$\mathbf{1.38 \times 10^{-5}}$	**6.69%**	–	–	–	**L**
Ibuprofen	$2.52 \times 10^{+6}$	4.00×10^{-4}	6.53%	$1.52 \times 10^{+5}$	6.35×10^{-1}	33.35%	VH
Paracetamol	$5.33 \times 10^{+6}$	5.30×10^{-4}	16.92%	$8.16 \times 10^{+5}$	4.41×10^{-1}	40.22%	H
Salicylic acid	1.03	2.52×10^{-6}	0.18%	1.65	1.03×10^{-4}	0.74%	M
Tramadol	$3.57 \times 10^{+1}$	1.23×10^{-4}	0.09%	–	–	–	L
Psycholeptics	$\mathbf{7.60 \times 10^{+3}}$	$\mathbf{3.76 \times 10^{-6}}$	**4.79%**	–	–	–	**VL**
Diazepam	2.55×10^{-1}	2.26×10^{-6}	0.11%	–	–	–	M
Oxazepam	$1.03 \times 10^{+5}$	1.75×10^{-1}	9.20%	–	–	–	L
Pentobarbital	$1.18 \times 10^{+2}$	2.57×10^{-6}	4.00%	5.58×10^{-2}	2.09×10^{-2}	0.00%	L
Temazepam	$3.39 \times 10^{+4}$	5.65×10^{-3}	1.42%	–	–	–	L
Clozapine	$1.92 \times 10^{+2}$	5.59×10^{-4}	7.71%	–	–	–	L
Risperidone	$2.58 \times 10^{+1}$	6.67	100.0%	–	–	–	L
Lithium	2.75×10^{-1}	1.95×10^{-4}	0.07%	–	–	–	VL
Psychoanaleptics	$\mathbf{3.05 \times 10^{+3}}$	$\mathbf{4.29 \times 10^{-5}}$	**2.16%**	–	–	–	**L**
Citalopram	3.00×10^{-1}	4.03×10^{-5}	0.71%	–	–	–	M
Fluoxetine	$4.27 \times 10^{+4}$	3.80×10^{-4}	3.40%	6.51	4.41×10^{-1}	35.57%	VH
Fluvoxamine	2.30×10^{-1}	1.98×10^{-5}	1.39%	–	–	–	L
Antiepileptics	$\mathbf{1.39 \times 10^{+6}}$	$\mathbf{2.16 \times 10^{-5}}$	**9.65%**	–	–	–	**L**
Carbamazepine	$1.11 \times 10^{+7}$	4.90×10^{-3}	9.74%	$5.60 \times 10^{+5}$	2.61	85.37%	VH
Stimulants/Illicits	$\mathbf{2.62 \times 10^{+1}}$	$\mathbf{1.99 \times 10^{-5}}$	**16.46%**				**L**
Caffeine	$1.76 \times 10^{+2}$	2.00×10^{-3}	16.48%	–	–	–	M
Cocaine	7.45	2.35×10^{-1}	10.17%	–	–	–	L
Anti-Parkinson's	$\mathbf{1.40 \times 10^{-6}}$	$\mathbf{1.40 \times 10^{-6}}$	**0.00%**	–	–	–	**VL**
Other	$\mathbf{2.32 \times 10^{-4}}$	$\mathbf{5.13 \times 10^{-5}}$	**0.00%**	–	–	–	**VL**

Carbamazepine stands out as the only compound in any analysis to have both a median risk above one, and very high confidence (Fig. 4). Moreover, for many of the compounds for which a risk could be assessed (56 out of 87 compounds) the confidence scores were below 1% (Table S9), and thus are labelled as having very low confidence.

For only 11 out of 702 compounds sufficient ecotoxicity data were

available to generate SSDs and, therefore, to calculate integrated multi species risks. However, none of these SSDs met the TG 27 criteria, so these results should be interpreted with caution (Figs. 4, S7b, Table S7). Comparing the results of Figs. 3 and 4 reveals that the risk for compounds based on the cHC_5 are higher than those based on the individual ecotoxicity data (see e.g., carbamazepine). Since SSDs provide an estimation of a multi-species hazard that is closer to being ecosystem wide, and therefore provide a more robust estimation of the actual hazard, our results indicate that ecosystems are indeed vulnerable to psychopharmaceuticals.

The most prescribed compounds are also the most well studied, e.g., carbamazepine, paracetamol, ibuprofen, and fluoxetine collectively accounted for 23% of the ecotoxicity data and 28% of the occurrence data. When comparing the Dutch prescription data in defined daily doses to the calculated risks, the compounds that carry the highest risk are often also the most used and prescribed (Table S8). Nonetheless, Pearson correlations (Table S10) did not indicate that prescription correlated to risk.

The amount of occurrence data positively correlated with a higher observed risk (cNOEC: $r = 0.656$, $p < 0.001$, aEC50: $r = 0.659$, $p < 0.001$), as did the amount of cNOEC data ($r = 0.590$, $p < 0.001$), and aEC50 data ($r = 0.556$, $p < 0.001$). Confidence in both ecotoxicity datasets also correlate to risk (cNOEC: $r = 0.487$, $p = 0.001$, aEC50: $r = 0.460$, $p = 0.006$) (Table S10). Hence, the better a compound is studied, the higher the resulting calculated risk. This is worrisome, since this may indicate that many poorly studied compounds may carry hidden risks and that more research is needed into the occurrence and hazards of psychopharmaceuticals to elucidate if these hidden risks are present.

In contrast to the general observations discussed above, not for all commonly prescribed compounds reliable data were available (Fig. 5). Evaluating the data plotted in Fig. 5 in more detail reveals that risperidone (37th most prescribed in NL, Table S8) demonstrated the highest median risk of all compounds, but with a confidence on the cusp of 'low' and 'very low' (Table S9) and therefore its calculated risk cannot be considered reliable. Similarly, risk could not be calculated for betahistine (7th most prescribed in NL, Table S8) due to a lack of both ecotoxicity and occurrence data. For the sedative tramadol, numerous occurrence data entries were obtained, resulting in a maximum occurrence data score, yet only one ecotoxicity datapoint was found. Even for the most prescribed psychopharmaceutical, paroxetine, the risk was calculated with only a medium confidence, owing to a lack of ecotoxicity data. Since illicit drugs do not have prescription data, we were not able to perform a similar comparison. However, it is notable that some illicit stimulants demonstrated some risk, e.g., cocaine (Table 6). The stimulants group, which consists of many illicit and recreational drugs (caffeine, nicotine, etc.), included multiple compounds with very high occurrence confidence, but low or no ecotoxicity confidence (Table S9).

The present study differs from other risk assessments, in that we did not include additional assessment factors. This was done because we did not intend to derive environmental quality standards, but rather aimed to calculate the risk of adverse effects on non-target organisms based on measured concentrations of psychopharmaceuticals in European surface waters and measured effect concentrations. This approach, therefore, leads to a data-driven quantification of the risks of psychopharmaceuticals in surface waters, which is less stringent than other assessments that do incorporate these assessment factors.

3.5 General discussion

The present study demonstrated that for psychopharmaceuticals, inter-class differences were smaller than intra-class differences, emphasising that each psychopharmaceutical should be assessed individually and that making assumptions based on related drugs ('cross reading') could be problematic in a regulatory setting. When considering the chemical structures of psychopharmaceuticals of a certain class, there can be very major differences. The SSRI class of

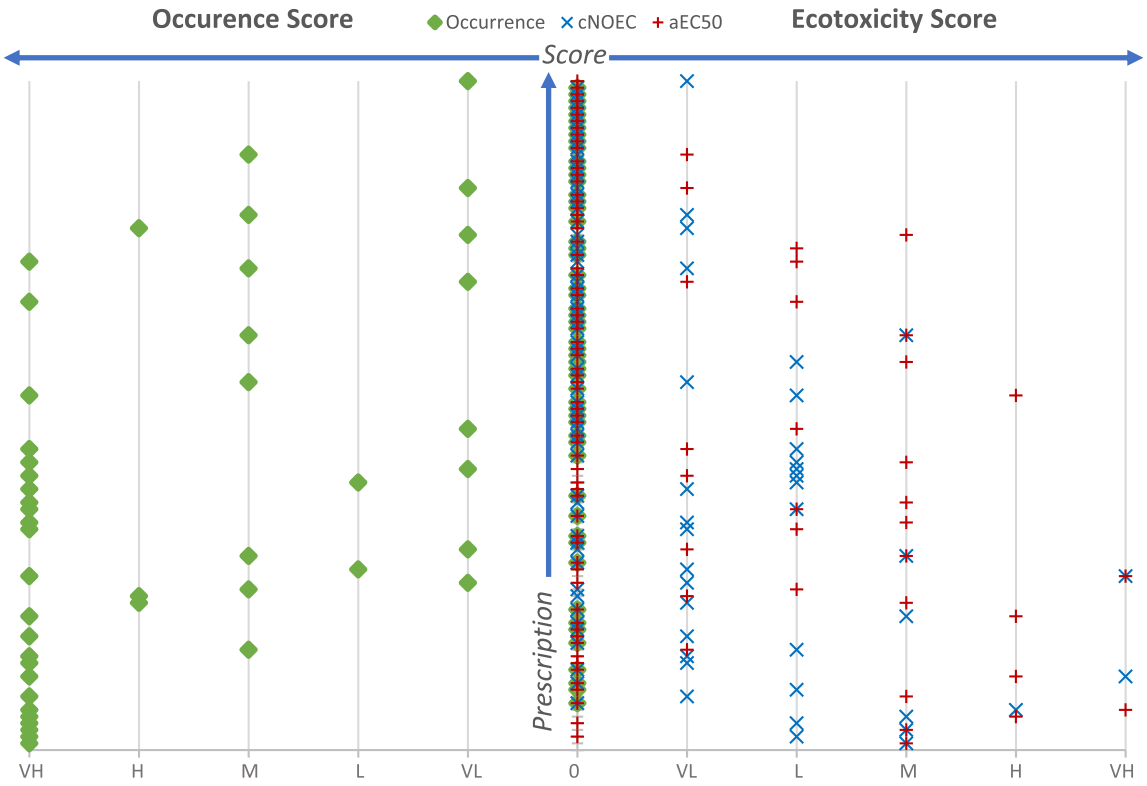

Fig. 5. Scatter plot showing the distributions of ecotoxicity (right) and occurrence (Left) data scores vs (Dutch) prescription rank (Centre Axis) for the top 100 prescribed psychopharmaceuticals. Both cNOEC and aEC50 are shown on the ecotoxicity side (Right).

antidepressants highlights this very well (See Table 1 in Silva et al., 2012), since compounds within this class have a high degree of variability in chemical structure, even though this group has a common pharmacological MOA. As an alternative to class categorization, groupings based on chemical structure may therefore be further explored.

We found that only for 15% of the psychopharmaceuticals ecotoxicity data were available. This appears to be about 19% for human pharmaceuticals in general (Gunnarsson et al., 2019), indicating that the lack of data is not just limited to psychopharmaceuticals. As highlighted by Gunnarsson et al. (2019), this stems from mandatory ecotoxicity testing during clinical trials only starting in 2006 in the EU and not at all in the US, indicating that data are missing for legacy (prior to 2006) pharmaceuticals. Comparing psychopharmaceuticals in general to other anthropogenic compounds revealed that they have lower cumulative chronic NOECs than other industrial chemicals, but higher when compared to biocides, pesticides and general pharmaceuticals. This was still the case when common solvents were removed from the psychopharmaceutical series (Fig. 6, van Dijk et al., 2021). This outcome likely stems from the fact that biocides and pesticides are designed to be toxic, and as Gunnarson (2019) points out, pharmaceuticals that disrupt the endocrine system tend to be the most toxic. In addition, as shown in Fig. 2, the ecotoxicity data in this study was lacking behavioural endpoints, which may suggest that the cumulative NOECs presented in Fig. 6 may be lower with better ecotoxcity data. Nonetheless, in the EU, psychopharmaceuticals, along with pharmaceuticals, are regulated by the European Medicines Agency (EMA), and the EU Pharmaceutical legislation does not provide environmental protection goals, unlike legislation for industrial chemicals. Greater regulatory harmonisation of (psycho)pharmaceuticals with other industrially produced compounds can help to alleviate both the lack of data presented in the current study, as well as the risk through a more coherent regulatory framework. Indeed, the need for a 'one substance – one assessment' approach, proposes an assessment that does not differentiate between use class, but rather on the individual chemical (van Dijk et al., 2021).

A 2022 study on pharmaceutical occurrence in global rivers yielded somewhat comparable results to the occurrence data presented here (Wilkinson et al., 2022). Interestingly, the concentrations of most compounds werehigher in the global rivers than in European surface waters (median concentrations of e.g. paracetamol were 296 vs 148 ng/l in the present study, gabapentin 272 vs 200 ng/l, caffeine 500 vs 98 ng/l, nicotine 128 vs 40 ng/l), with the notable exeption of carbamazepine, which showed higher concentrations in the present study (29 vs 73 ng/l). This, however, is in line with the study of Wilkinson et al. (2022), since they noted that anticonvulsant concentrations vary heavily depending geographic region.

A 2014 risk assessment of pharmaceuticals in French waters using a PNEC-based risk assessment found paracetamol, ibuprofen, oxazepam and carbamazepine to present a "likely" risk (Bouissou-Schurtz et al., 2014). This broadly agrees with the results presented here (Table 6, Figs. 3 and 4), although Bouissou-Schurtz et al. (2014) considered a much smaller geographical area and only seven psychopharmaceuticals. It is interesting to note that Bouissou-Schurtz et al. (2014) identified five pharmaceuticals to pose a risk, four of which being psychopharmaceuticals. In contrast, a case study of two WWTPs in Italy found that the three psychopharmacuticals included in the study (propyphenazone, carbamazepine and diazepam) were less of a risk than other pharmacuetical groups, such as antibiotics (Al Aukidy et al., 2012). A review on the risks of antidepressants to fish yielded comparable results as those shown by the cHC_5 results of the present study (Fig. 3). Gould et al. (2021) reported a median RQ of 0.41 for Fluoxetine, compared to 0.44 in the present study. Sertraline differered by a factor of 10 (0.01 vs 0.001 in the present study). The most notable difference was for Venlafaxine, for which Gould et al. (2021) reported a median RQ of 0.66, the highest in the study, while we reported 3.1×10^{-4}. However, we did not create an SSD for venlafaxine due to inssuficient ecotoxicity data, and Gould et al. (2021) only perform risk assesments for fish, which may account for the differences observed between the two studies. Nonetheless, the present study, along with some of the aformentioned studies, indeed reports risks for some psychopharmacueticals in the aquatic environment.

Beyond surface waters, risks have also been reported for psychopharmaceuticals in terrestrial environments, namley soils that have been treated with sewage sludge (Aydın et al., 2022; Camotti Bastos et al., 2020; Martín et al., 2012; Mejías et al., 2021). Such studies tend to

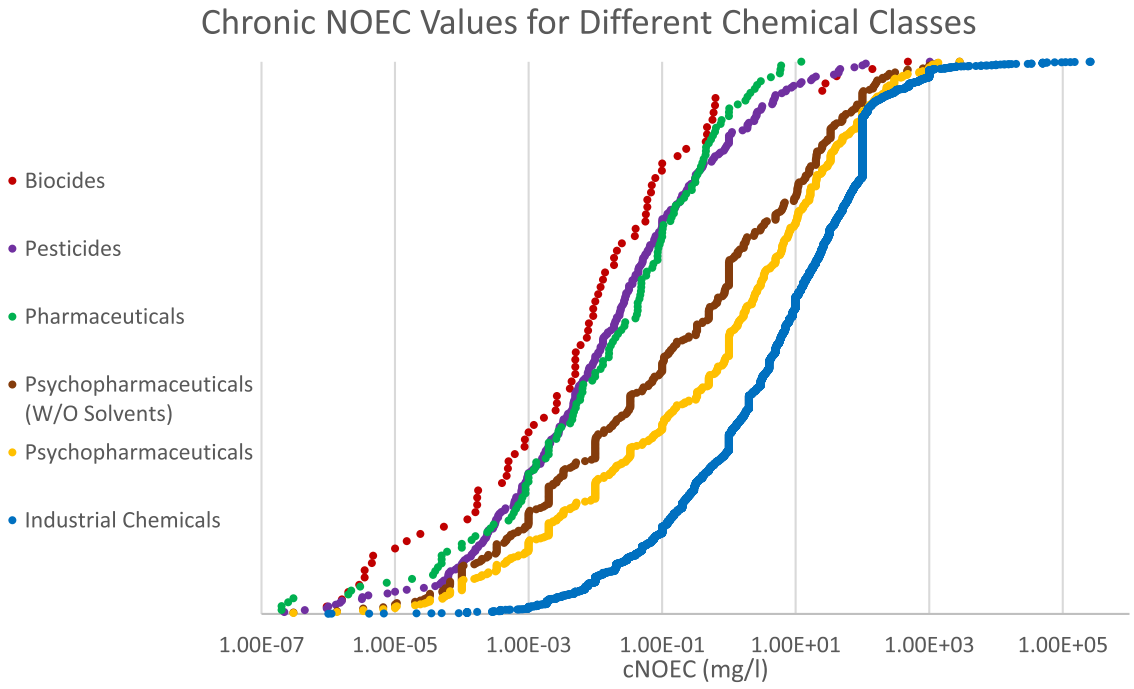

Fig. 6. Comparison of cNOEC values for various groups of anthropogenic compound classes. Psychopharmaceutical and Psychopharmaceutical)(W/O) series are from the present study, other series were taken from Gunnarsson et al., 2019; Gustavsson et al., 2017; van Dijk et al., 2021. Note that assessment factors were not included in this plot.

focus on other pharmacueticals, such as antibiotics and endocrine disruptors, since these have a higher risk than psychopharmacuticals. Soil-based studies also show that the risk posed by psychopharmaceuticals appears to be less than those presented in the current study, which may indicate that the aquatic environment is the more sensitive ecosystem. However, carbamazepine, sertraline, ibuprofen, and fluoxetine have demonstrated risks in soils in some studies (Martín et al., 2012; Mejías et al., 2021) which demonstrate that wastewater effluent is not the only source of environmental psychopharmaceutical risk, and that our arguments for more data also extends to other ecosystems.

3.6 Study limitations and future research

This study did not focus on specific locations or situations, though site specific risk assessment can be of relevance, since prescription, consumption, and removal of psychopharmaceuticals may depend on local factors. Temporal variation can also be relevant, as prescriptions can vary depending on the time of the year (Heald et al., 2021; Winkler et al., 2019). Furthermore, population densities in different WWTP catchment areas, WWTP removal efficiencies, and drought conditions (Sjerps et al., 2017) influence occurrence. Events such as natural disasters and the COVID-19 pandemic can influence prescription and consumption patterns of psychopharmaceuticals (Andalo, 2020; Boehnke et al., 2021; Palmer and Seoudi, 2021; Robinson, 2021; Usher et al., 2012). Despite using European occurrence data, we only used prescription data from the Netherlands, as finding prescription data from all European countries was not feasible. Yet, this does mean that conclusions based on prescription data may not be fully generalisable. As such, as a follow up and refinement of the present study, site specific risk assessments may also investigate local cases, such as a single nation or region, accounting for specific and temporal differences. We also could not verify every datapoint (both ecotoxicity and occurrence) due to the large amount of data points, and only focused verification efforts on outliers.

We defined psychopharmaceuticals as the ATC—N class plus illicit drugs according to the Dutch Opium Act. The ATC system gives an ATC code to a compound based on its uses in past and present treatments but overlooks a drug's MOA when that MOA is not specifically employed in a medical treatment. For example, the muscle relaxant phenprobamate is in the ATC-M class (Muscular system), and has no ATC—N number associated to it, yet it has displayed sedative effects (Demir et al., 2015). Other examples include illicit compounds that are being screened for various therapeutic uses (Aan Het Rot et al., 2012; Mathew et al., 2008; Sessa, 2017). Therefore, many of the non-ATC—N pharmaceuticals can in principle exert relevant MOAs, which may affect relevant behavioural endpoints. However, due to the infeasibility of checking all compounds for these MOAs, these were not included. This also lends itself in favour of a 'one substance – one assessment' style approach, where non-psychopharmaceuticals (in the strict sense) should be screened for behavioural ecotoxicological endpoints alongside pharmaceuticals. In addition, this will need to be performed not only for new chemicals, but also for (highly used) legacy chemicals. However, we do acknowledge that this is a costly recommendation, and thus could be supplemented with other types of ecotoxicity testing, as discussed in 3.3.

Transformation products can be found in higher concentrations than parent compounds in the environment (Buser et al., 1999; Langford and Thomas, 2011; Zhang et al., 2008), and are generally more mobile and harder to remove by WWTPs (Rivera-Utrilla et al., 2013). The toxicity of transformation products is of concern, since many transformation products may still be biologically active, and thus exert a specific toxicity above baseline toxicity through a viable MOA (Celiz et al., 2009; Escher and Fenner, 2011; Neuwoehner et al., 2009). The lack of quantitative occurrence data on transformation products is often a practical issue since detection by techniques such as LCMS requires standards for these transformation products. In the case of transformation products, these standards are often more expensive compared to the parent compound, or might not exist at all as an analytical standard and therefore must be synthesised *de novo* at large financial costs (Hernández et al., 2011; Wong and MacLeod, 2009). The lack of availability, or the large investments involved, often deter researchers from detecting transformation products, unless the study is specifically focussed on transformation products for reasons such as calculating consumption of illicit drugs (Ort et al., 2014; Thomas et al., 2012), or utilises parent: metabolite ratios to predict metabolite concentrations (de Jongh et al., 2012; ter Laak et al., 2014). The transformation product challenge also extends to ecotoxicity data, even more so, since ecotoxicity experiments require higher volumes. Hence, transformation products are often overlooked in both pharmaceutical occurrence and ecotoxicity studies (Celiz et al., 2009; Charuaud et al., 2019; Cleuvers, 2003; Fram and Belitz, 2011; Frédéric and Yves, 2014; Kar and Roy, 2012; Mompelat et al., 2009; Vestel et al., 2016).

This study did not incorporate mixture toxicity into the hazard assessment. For psychopharmaceutical mixture toxicity only a limited number of studies are available. For example, additive mixture effects have been demonstrated for SSRIs (Christensen et al., 2007), and for a mixture of carbamazepine and ibuprofen (Cleuvers, 2004). These mixture toxicity experiments represent realistic scenarios, since the compounds present in these mixtures have indeed been demonstrated to be jointly present in surface water samples, as listed in the data bases used in this study (Patrolecco et al., 2013). Moreover, in the occurrence databases (Table 3) many other examples of jointly present psychopharmaceuticals can be found. This should thus be considered in future, more focused, risk assessments. Future studies should also screen for transformation products in environmental monitoring and investigate their ecotoxicological impact, alongside other parent drugs and transformation products in mixture toxicity tests. Focus should be given to compounds that are highly used, present a risk, or have low data confidence, as defined in the present study.

4. Conclusions

Our findings revealed a lack of both occurrence and ecotoxicity data, hampering a reliable environmental risk assessment of most psychopharmaceuticals, with ecotoxicity data being the scarcest. Moreover, the limited data were also not spread uniformly, with a handful of well researched compounds dominating both occurrence and ecotoxicity data. Non-behavioural endpoints and only a few test species were dominating the ecotoxicity data. Thus, many compounds may present a risk that cannot be estimated due to missing or skewed data. This is alarming, since we showed that better studied compounds carried higher risks.

We found that the most prescribed compounds in the Netherlands were the most studied and occurred most frequently. However, many of the highly prescribed psychopharmaceuticals still lack proper data. Common illicit drugs also demonstrated risks, and generally provided good occurrence data, but lacked ecotoxicity data. Furthermore, intra-class differences were larger than inter-class differences, emphasising that therapeutic grouping may not be an appropriate way to categorise compounds and that each compound should rather be individually assessed for risk

Despite the presently identified large knowledge gaps, we conclude that the presence of a substantial part of data-rich psychopharmaceuticals in surface waters present an ecological risk for aquatic non-target organisms.

Author contribution

Charlie J. E. Davey – Designed and performed study, wrote the manuscript

Michiel H. S. Kraak – Contributed to study design and manuscript

Antonia Praetorius – Contributed to study design and manuscript

Thomas L. *ter Laak – Contributed to study design and manuscript*

Annemarie P. van Wezel – Contributed to study design and manuscript

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.watres.2022.118878.

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