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Review

Comprehensive analysis of a widely pharmaceutical, furosemide, and its degradation products in aquatic systems: Occurrence, fate, and ecotoxicity[☆]



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ABSTRACT

Many pharmaceutical compounds end up in the environment due to incomplete removal by wastewater treatment plants (WWTPs). Some compounds are sometimes present in significant concentrations and therefore represent a risk to the aquatic environment. Furosemide is one of the most widely used drugs in the world. Considered as an essential drug by the World Health Organization, this powerful loop diuretic is used extensively to treat hypertension, heart and kidney failure and many other purposes. However, this important consumption also results in a significant release of furosemide in wastewater and in the receiving environment where concentrations of a few hundred ng/L to several thousand have been found in the literature, making furosemide a compound of great concern. Also, during its transport in wastewater systems and WWTPs, furosemide can be degraded by various processes resulting in the production of more than 74 by-products. Furosemide may therefore present a significant risk to ecosystem health due not only to its direct cytotoxic, genotoxic and hepatotoxic effects in animals, but also indirectly through its transformation products, which are poorly characterized. Many articles classify furosemide as a priority pollutant according to its occurrence in the environment, its persistence, its elimination by WWTPs, its toxicity and ecotoxicity. Here, we present a state-of-the-art review of this emerging pollutant of interest, tracking it, from its consumption to its fate in the aquatic environment. Discussion points include the occurrence of furosemide in various matrices, the efficiency of many processes for the degradation of furosemide, the subsequent production of degradation products following these treatments, as well as their toxicity.

1. Introduction

The presence of pharmaceutical compounds in water has been investigated since the 1970s (Hignite and Azarnoff, 1977; Aherne and Briggs, 1989; Ternes, 1998; Stumpf et al., 1999). Since the discovery of clofibrac acid, a drug metabolite, in wastewater treatment plants (WWTPs), the presence of pharmaceutical residues in the aquatic environment has become a significant issue in the field of environmental sciences and is becoming increasingly important due to the growing consumption of drugs (Corvaisier, 2000). These substances cover a very wide range of human and veterinary uses, therefore, there are hundreds of active substances that can be found in different environments (Halling-Sørensen et al., 1998; Heberer, 2002; Kümmerer, 2001; Godoy et al., 2015). Pharmaceutical compounds are created to be biologically active, although they were created for human or domestic animals, their

action also extend to non-targeted populations which is why their occurrence and their persistence in the environment poses a risk to organisms and ecosystems (Kümmerer, 2001; Richardson and Bowron, 2011; Aherne et al., 1990; Isidori et al., 2005).

Pharmaceutical residues may be released into the aquatic environment after their use due to inadequate removal by WWTPs (Boxall et al., 2014) but also during their manufacture by pharmaceutical companies (Kleywegt et al., 2016; Wolf et al., 2012). Moreover, despite some guidelines such as controls on the marketing of pharmaceutical products by institutions as the European Chemical Agency (ECHA) or the US Food and Drug Administration, there are no global regulations limiting their concentrations in effluents (Küster and Adler, 2014). There is no monitoring of the fate of these molecules and the presence of degradation products is not taken into account either. Some of those molecules, sometimes hardly metabolized by humans and excreted in unchanged

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form, are introduced into the environment through wastewater systems (Verlicchi et al., 2016; Daughton and Ruhoy, 2009). Part of these compounds is degraded and is therefore not (or barely) found in the environment, but their degradation products can be identified there and their effects on ecosystems are very poorly documented (Grandcoin et al., 2017; Maculewicz et al., 2022). These compounds are sometimes more toxic than their parent molecules (Świacka et al., 2021). Studying all these compounds seems to be an overly large task, therefore, there is a need to prioritize them. Some well-known medicines are frequently found in prioritization lists such as Ibuprofen, Diclofenac or Paracetamol (Zuccato, 2004a; Riva et al., 2015). Of all these frequently occurring pollutants, furosemide, which is considerably less documented in aquatic media, will be the subject of this review.

Furosemide (4-chloro-N-furfuryl-5-sulphamoylanthranilic acid), has been marketed since 1964 (Stokes and Nunn, 1964) under several brand names, of which the most common are Lasilix, Lasix, Frusemide, Edemid and Furix (DrugBank). Its physico-chemical properties are presented in Table S1. This drug is a powerful diuretic derived from sulphonamides, acting on the kidneys by inhibiting the reabsorption of electrolytes to ultimately increase water loss from the body (DrugBank; RxList. Lasix, 2020; HMDB, 2006; Abbott and Kovacic, 2008). Furosemide is used in humans in cases of cardiac, hepatic or renal insufficiency, high blood pressure and oedema (Abbott and Kovacic, 2008; Chahwakilian and Ferrier-Battner, 2012; Rodriguez-Cillero et al., 2017; van Kraaij et al., 1997; Cheng and Nayar, 2009) and it is also used in children, for diuretic and anti-inflammatory properties (Prandota, 2001). It has anti-epileptic (Haglund and Hochman, 2005) and antioxidant (Lahet et al., 2003) properties but is not used primarily for this purpose. In addition, it is used in the veterinary field to limit the consequences of volume overload in renal and cardiac diseases in dogs, horses and ponies (Abbott and Kovacic, 2008; Hinchcliff and Muir, 1991; Chetboul et al., 2017). Furosemide has also been reported in diverted uses, for example it has been found undeclared in food supplements and also used in sport to help athletes lose weight quickly (Ivanova and Ivanov, 2019). It is also used to mask doping products diluting drug concentrations by increasing the volume of water in the urine but also by lowering the pH, thus modifying the excretion of other doping agents making them less detectable (Hinchcliff and Muir, 1991; Espinosa Bosch et al., 2008; Luiz et al., 2013; Cadwallader et al., 2010; Ventura and Segura, 1996). It is classified, as well as other diuretics, as a masking agent on the WADA Prohibited List (WADA, 2009). Furosemide is the 2nd most frequently detected diuretic in drug screenings (23%) (Cadwallader et al., 2010). It could be used to mix recreational drugs such as MDMA to counteract the secretion of antidiuretic hormones (Schröder et al., 2010a). Furosemide has many applications and is widely distributed across the world. Therefore, it quickly became a pollutant of interest in many countries (Zuccato, 2004a; RxList. Lasix, 2020; Li et al., 2019; Chinnaiyan et al., 2018; Besse and Garric, 2008; Kostich et al., 2014; Christensen et al., 2009a). Therefore, many studies classify it as a priority pollutant based on several parameters. The most common criteria are production or consumption sales data (Riva et al., 2015; Chinnaiyan et al., 2018; de Voogt et al., 2009; Dong et al., 2013; Guo et al., 2015; Mansour et al., 2016; Machado et al., 2017; Ahmed, 2020; Khan et al., 2020). These are easily accessible data which provide direct information on the extent of use of the compound. This information can be used to assess Predicted Environmental Concentrations (PEC) (Besse and Garric, 2008; Kostich et al., 2014). The persistence or stability of the compound is also frequently mentioned (Zuccato, 2004a; de Voogt et al., 2009; Khan et al., 2020; Zuccato et al., 2005; Roos et al., 2012; Daouk et al., 2015; Muñoz et al., 2008). Indeed, a stable compound will not be degraded in the wastewater treatment plants or in the environment and will therefore tend to accumulate in the receiving environment and then determine its occurrence which is the second most listed criteria (Zuccato, 2004a; Chinnaiyan et al., 2018; Kostich et al., 2014; de Voogt et al., 2009; Khan et al., 2020; Roos et al., 2012; Daouk et al., 2015; Gillard et al., 2014). Furosemide is effectively found in many countries and a

large number of studies around Europe, Asia or North America in WWTP effluents, surface water and even in sludge or sediments (see the "occurrence in the environment" section). Some studies consider furosemide as a priority based on its elimination by WWTPs or by its input in wastewater (Kleywegt et al., 2016; Riva et al., 2015; Chinnaiyan et al., 2018; Mansour et al., 2016; Gillard et al., 2014). This ubiquity of furosemide leads many researchers to question its toxicity (de Voogt et al., 2009; Dong et al., 2013; Mansour et al., 2016; Khan et al., 2020; Daouk et al., 2015; Muñoz et al., 2008) and its ecotoxicity (Chinnaiyan et al., 2018; Christensen et al., 2009a; Dong et al., 2013; Guo et al., 2015; Mansour et al., 2016; Roos et al., 2012; Daouk et al., 2015; Muñoz et al., 2008; Gillard et al., 2014), which is the second most cited priority criterion. It is sometimes even classified as preoccupying according to its excretion rate (Riva et al., 2015; Machado et al., 2017). In order to assess the toxicity of furosemide, several studies use tools or indicators combining several parameters. Methods such as the Occurrence, Persistence, Bioaccumulation, Toxicity (OPBT) approach, based on several relevant indicators for the evaluation of the environmental impact, allows to prioritize the molecules (Daouk et al., 2015). The Measured or Predicted Environmental Concentration/Predicted no Effect Concentration (MEC/PNEC or PEC/PNEC) ratio is the most commonly used in ecotoxicology to determine a risk because it is based both on the concentration of a pollutant in the environment and also the sensitivity of the species studied (Chinnaiyan et al., 2018; Besse and Garric, 2008; Roos et al., 2012). The EC5/MC95 (EC5 $\frac{1}{4}$ 5th percentile effect concentration; MC95 $\frac{1}{4}$ 95th percentile measured concentration) (Christensen et al., 2009a), is a probabilistic approach quite similar to PEC/PNEC ratio.

Finally, many pharmacological studies have been carried out on furosemide (Abbott and Kovacic, 2008; Ahmed, 2020; Huang et al., 2016), but quite few on its presence, degradation and impact on the environment. Here, we present a state-of-the-art review of this emerging pollutant of interest, tracking it, from its consumption to its fate in the aquatic environment.

2. Consumption of furosemide

Diuretic compounds are commonly used to treat cardiovascular problems which are one of the main causes of hospitalization in the world (Roger et al., 2011). More than 80% of patients receive a loop diuretic for heart failure but it is also used for oedema disorders or high blood pressure (Buttard, 2016). The incidence of heart failure is growing (Savarese and Lund, 2017) and makes diuretics a highly represented class of drugs in many countries (Table S2). The most commonly prescribed categories for hypertension are thiazide diuretics and loop diuretics (Rimoy et al., 2009; Shalavadi et al., 2018) whereas loop diuretics prevail over the other categories for the treatment of cardiac congestion (Cheng and Nayar, 2009; Buttard, 2016; Boulestreau et al., 2018). Diuretics are extensively used in elderly people (Arrubla et al., 2016) and some studies even mention their overuse (Rodriguez-Cillero et al., 2017; van Kraaij et al., 1997). In France, Buttard (2016) mentions that more than one third of people over 75 years of age are administered diuretics and 70% of the prescriptions are considered inappropriate by this author both in terms of indications and dose administered.

Furosemide is then one of the most widely prescribed diuretics (Ahmed, 2020; Murray et al., 1997; Thapa and Singh, 2019; Osunma-kinde and South Africa; Water Research Commission, 2013; ClinCalc DrugStats Database, 2018; Papageorgiou et al., 2016a; Agence nationale de sécurité du médicament, 2013) and it is also used in the formulation of several products such as co-amilo-fruse or co-amilo-zide (Treadgold, 2012) even if it is not necessarily the best choice over bumetanide and torsemide based on price, bioavailability and hospitalization rates of patients treated (Wargo and Banta, 2009; Di Nicolantonio, 2012). Wargo & Banta (Wargo and Banta, 2009) hypothesized that furosemide is the most widely used because it was the first loop diuretic approved by the US Food and Drug Administration in 1966, and the least toxic for human

(Prandota and Witkowska, 1976). Since 1977, it is considered as an essential medicine by the World Health Organization based on its efficiency, safety and public health importance. The mass of furosemide prescribed or consumed after the 2000s is noteworthy in many European countries (Table S3) and seems to be more significant in more recent years. As furosemide is used for cardiovascular diseases and especially by elderly people, the growing consumption of furosemide is likely linked to the aging of the German, Polish and Italian populations (Vancea and Solé-Casals, 2016) as it is the case for other drugs such as antidepressants (Fratiglioni et al., 1999). Indeed, studies focusing on hospitals, households or care homes have shown that furosemide is among the 20 most consumed drugs in terms of mass in the United-Kingdom and that care homes contribute 67.5% of total mass (Treadgold, 2012). In France, furosemide is significantly consumed (595–1779 mg/day) in several nursing homes for elderly people (Lacorte et al., 2018a). In addition, consumption of furosemide in Germany is much higher by the general public than in hospitals mostly because patients purchase their medication at the pharmacy and consume it in their private residence (Fernandez, 2018a).

3. Occurrence in the environment

In the aquatic environment, furosemide is very widely found and often at high concentrations in wastewater (influent and urban effluents from WWTPs, hospitals, industries ...), in surface waters (rivers, lakes, seas, oceans, estuaries, and deltas) at concentrations ranging from the ng/L level to a few hundred of ng/L and sometimes in groundwater and drinking water (wells, catchments, tap water). It is also found in suspended matter, WWTP sludge and sediments. These matrices are often not considered; therefore, furosemide concentrations may be underestimated. It is also investigated in other matrices such as food in order to estimate the sanitary risk in the case of treated wastewater reuse for crop irrigation.

1 Occurrence in medicalized institutions wastewaters

Medicalized institutions gather a larger number of patients, then, high concentrations of furosemide are expected in their effluents. For example, according to Ort et al. (2010), hospital discharges account for 5.9% of furosemide in total wastewater discharges but are more spatially condensed. Depending on the users of the different institutions (veterinary or human hospital, maternity, oncological institution ...), significant concentrations of furosemide can be found directly at the outlet and even after treatment by the wastewater treatment plants (Fig. 1).

Studies on raw water from medical institutions are less common than on treated wastewater for university hospitals and general hospitals (Fernandez, 2018a; Nielsen et al., 2013; Huber et al., 2016) but for veterinary hospitals, Fernandez (2018a) observed a little higher concentration in the outlets. Furosemide concentrations are around a few hundred ng/L in both sample types, which is relatively low but can be explained by a less important use of furosemide in veterinary medicine. The median concentrations in general hospital influents (7818 ng/L) are a little higher than in the effluents (6295 ng/L) which seems coherent because the effluents are treated. The same applies to university hospitals; median concentration in inlet waters are 4600 ng/L and median concentrations in outlet are 3450 ng/L but mean concentrations are much higher due to very high values of 196000 and 392000 ng/L found in a Norwegian hospital effluent (Thomas et al., 2010). There is a visible difference between general hospitals and university hospitals. In nursing homes, the median concentration is around 3.2 µg/L and the values found by the different authors are quite close. Two relatively high concentrations were found in a maternity hospital and a pediatric hospital (Santos et al., 2013a) which confirms that the use of furosemide in children is also important. Indeed, Prandota (2001) reports its use in premature infants with chronic lung disease, children with nephrotic syndrome, acute or chronic renal failure, congestive heart failure, progressive hydrocephalus. Finally the median concentration of health facilities for human patients is 3915 ng/L. Gillard et al. (2014) found a close value (3207 ng/L) for eight institutions in Belgium (hospitals, neuro-psychiatric units or rest homes). The authors also found important furosemide concentrations up to 57900 ng/L and hypothesized that these concentrations may be related to its heavy use in psychiatric units to counteract the side effects of several psychotropic drugs which have a known anti-diuretic activity (Spigset and Hedenmalm, 1995). While healthcare facilities constitute a major source of high furosemide contamination locally, discharges from individual patients' homes may be less concentrated, but probably more prevalent. Moreover, it was reported that furosemide concentrations found in the effluents of several nursing homes were relatively low, which was attributed to the fact that part of the furosemide was absorbed in the disposable diapers of the incontinent patients in the establishments studied (Lacorte et al., 2018a).

2 Occurrence in WWTPs

The largest number of studies found on the presence of furosemide focus on WWTPs and most of them are conducted in Europe. The highest concentrations of furosemide are found in wastewater influents (Fig. 2).

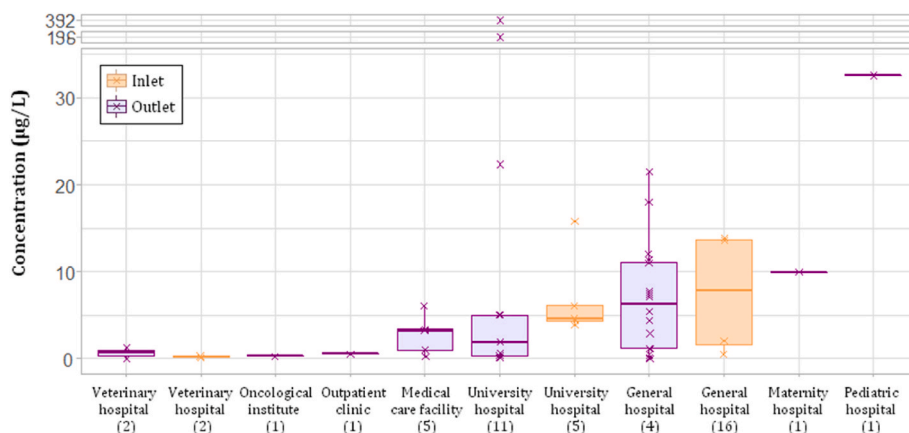


Fig. 1. Furosemide concentration in WWTP effluents and influents (µg/L) of various types of medical institutions. Each x represents a value of furosemide and (number) indicates the number of values per medical institutions. The yellow boxplot shows the concentration in the raw water, the purple boxplot shows the concentration in the wastewater after treatment (Kleywegt et al., 2016; Gillard et al., 2014; Fernandez, 2018a; Nielsen et al., 2013; Huber et al., 2016; Thomas et al., 2010; Oliveira et al., 2015; Lee, 2014; Afsa et al., 2020; Kovalova et al., 2012; Ajo et al., 2018; Gómez-Canela et al., 2019; Mackuřak et al., 2019; Mir-Tutusaus et al., 2017; Nagarnaik et al., 2010; Nelson et al., 2011; Santos et al., 2013a; Verlicchi et al., 2012a; Wahlberg et al., 2011; Yilmaz et al., 2017).

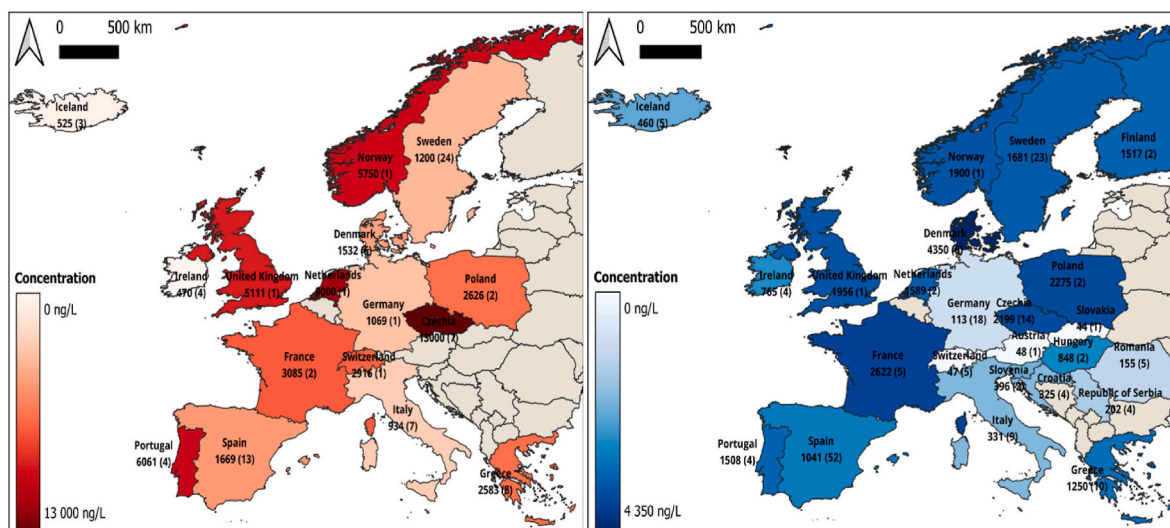


Fig. 2. Furosemide median concentration in municipal, urban, industrial, agricultural or unspecified WWTP influents (left) and effluent (right) (ng/L). The figures have been produced by QGISv3. The gradients on the map represents the range of median concentrations, which also appear under the name of each country. The number of studies per country is indicated in parentheses (Riva et al., 2015); (Huber et al., 2016); (Santos et al., 2013a); (Rozman et al., 2017); (Jacobsen et al., 2004a); (Kjølholt et al., 2003a; Mogensen et al., 2008; Vymazal et al., 2017); (Rodríguez-Navas et al., 2013a); (Feo et al., 2020); (Gros et al., 2012); (Valcárcel et al., 2011); (Gracia-Lor et al., 2012); (López-Serna et al., 2010); (Giebultowicz et al., 2016); (Sandré et al., 2023); (Kot-Wasik et al., 2016); (Kasprzyk-Hordern et al., 2009); (Koronaoui et al., 2023); (Lacey, 2008); (Wahlberg et al., 2011a); (Chen et al., 2016; Møskeland et al., 2006; Schröder et al., 2010a; Papageorgiou et al., 2019; Dasenaki and Thomaidis, 2015; Papageorgiou et al., 2016a; Lacey et al., 2012; Lacey et al., 2008; Verlicchi et al., 2012b; Verlicchi et al., 2013; Verlicchi et al., 2012a; Castiglioni et al., 2018; Jie, 2012; Sousa et al., 2011; Salgado et al., 2010a; Ibáñez et al., 2013a; Gros et al., 2009; Rosal et al., 2010; Ginebreda et al., 2012; Fernandez, 2018a; Pérez et al., 2010; Collado et al., 2014; Teijon et al., 2010; Urtiaga et al., 2013a; Celić et al., 2019; Klammer et al., 2013a; Gros et al., 2017; Kim, 2018a; Falás et al., 2012; Wahlberg, 2010; Golovko et al., 2021; Baresel et al., 2019; Lee et al., 2014; Finckh et al., 2022; Alygizakis et al., 2019a; Al Aukidy et al., 2012; Sousa et al., 2012; Salgado et al., 2011). (Acuña et al., 2015) (Biel-Maeso et al., 2018a; Bueno et al., 2012; Burcea et al., 2020; Campos-Mañas et al., 2017; Díaz-Garduño et al., 2017) (Gómez et al., 2008a) (Jelic et al., 2011) (Martínez Bueno et al., 2007) (Petre et al., 2016) (Petrović et al., 2014) (Prieto-Rodríguez et al., 2012; Prieto-Rodríguez et al., 2013)

In Europe, furosemide median concentration is around 2600 ng/L in WWTP influent with a range of variation between 525 ng/L for Iceland to 13000 ng/L for Czech Republic. Furosemide average concentration is around 4400 ng/L and average concentrations are quite close to the medians, except for Czech Republic, where Rozman et al. (2017) found a maximum concentration reaching 71500 ng/L for Onšov municipality. This result is puzzling given the very low number of inhabitants (230 in 2022), and average age of the population (45.6 years). In this village, furosemide was the pollutant with the highest concentration, ahead of the other commonly-found compounds paracetamol, caffeine and ibuprofen. A much greater number of studies on furosemide is carried out in Spain than other European countries, but the concentrations are below the averages and medians. Compared with the furosemide consumption data shown in Table S3, interestingly, a high concentration of furosemide in the raw water is not necessarily linked to a high consumption, as it is the case for Sweden, for example, but this could be biased by the low number of consumption data.

Outside Europe, a few studies have quantified furosemide in WWTP inlets. In North America, concentrations of 1830 ng/L in Canada (Kleywegt et al., 2016), median concentrations of 3565 ng/L in USA (Lara-Martín et al., 2014; Oliveira et al., 2015) and 436 ng/L in Mexico (Lesser et al., 2018; Estrada-Arriaga et al., 2016) are, thus in the same orders of magnitude as in Europe. In Asia and Africa, furosemide concentrations are globally lower than in Europe, with 170 ng/L, 330 ng/L in Vietnam and Korea respectively (Kuroda et al., 2015; Lee, 2014) and 200 ng/L in Tunisia (Afsa et al., 2020). Despite many studies dealing with pharmaceutical pollutants in China, it should be noted that only one mentioned furosemide. Thus, due to the small amount of data available, it is difficult to conclude on furosemide contamination in these locations.

Globally, several hundred to several thousand ng/L of furosemide were found in untreated wastewater. It has also been found in landfill leaching ponds up to 3840 ng/L (Rodríguez-Navas et al., 2013a) and

fitness center discharges up to 102 ng/L (Schröder et al., 2010a). Fortunately, wastewater treatment processes are sometimes effective in removing furosemide. However, furosemide has been found across Europe in municipal, urban, industrial and agricultural treated wastewater effluents (Fig. 2).

Many more studies have been carried out on WWTP outlets (205) than on inlets (98). These studies allow the evaluation of the treatment efficiency but also the quantification of pollutants transfer/discharge from WWTPs to the environment. In WWTP outlets, the median concentration in Europe is around 1150 ng/L and the average concentration is 1220 ng/L. Median range is from 44 ng/L in Slovakia (Alygizakis et al., 2019a) to 4350 ng/L in Denmark (Huber et al., 2016; Jacobsen et al., 2004a; Matamoros et al., 2009a; UNESCO, 2017). Several concentrations far above 1000 ng/L were found in Denmark (4200 ng/L in Kjølholt et al. (2003a); 4500 ng/L in Jacobsen et al. (2004a); 4600 ng/L in Mogensen et al. (2008); 7200 ng/L in Matamoros et al. (2009a); 1300 ng/L in UNESCO (UNESCO, 2017)) and the highest average concentration reported is in Czech Republic with 4130 ng/L due to two very high concentrations (11000 (Rozman et al., 2017) and 26000 (Vymazal et al., 2017) ng/L). The Czech Republic has the highest concentrations of furosemide found both at WWTPs inlets and outlets.

In North America, a value of 80 ng/L was found by Estrada-Arriaga et al. (2016) in Mexico and a median value of 640 ng/L has been obtained (Lara-Martín et al., 2014; Oliveira et al., 2015; Batt et al., 2008; Meador et al., 2016) in USA. In Asia, furosemide median concentrations of 562, 497 and 3601 ng/L have been found in Japan (Hanamoto et al., 2018; Nakada et al., 2007), Malaysia (Al-Odaini et al., 2010; Al-Odaini et al., 2013) and Korea (Lee, 2014; Kim, 2018a), respectively. This last value is surprisingly high compared to those usually found in treated wastewater. Finally, in Africa, concentrations of 67 ng/L and 1300 ng/L have been found in Tunisia (Afsa et al., 2020) and Uganda (Dalahmeh et al., 2020). In these cases, there are less data available than in Europe, even concerning WWTP outlets to our knowledge, and no data at all

have been published from South America or Oceania to date.

The highest furosemide concentrations in the aquatic environment were found by Kleywegt et al. (2019) in effluents from a pharmaceutical facility in Canada (1200000 ng/L), quite close those found in Denmark by UNESCO (UNESCO, 2017) in WWTP effluents (1300000 ng/L), thus suggesting the proximity of a pharmaceutical facility to the sampling point. Indeed, the river downstream of the pharmaceutical facility in Canada shows very significant furosemide concentrations (3650 ng/L), underlining that this type of facilities contributes significantly to river contamination, raising serious environmental concerns.

Finally, the median concentrations at WWTP outlets are almost three times less concentrated than those at WWTPs inlets, which highlights a substantial overall reduction of furosemide in the aqueous phase by the treatment plants. Another possibility would be a partial transfer of furosemide to solid phases such as sewage sludge (Fig. 3). For instance, Petrovic & Verlicchi (Petrovic and Verlicchi, 2014) have shown that 2% of the furosemide is transferred to the sludge, making it likely that significant levels are present in the sludge of furosemide-laden water, as observed in WWTPs.

According to Fig. 3, furosemide in treated sludge (28 ng/g.dw) is 3 times less concentrated than in raw sludge (80 ng/g.dw), meaning that the different sludge treatments might be relatively efficient for the removal of furosemide. In comparison, Riva et al. (2021) found slightly higher content for Hydrochlorothiazide (36.7 ng/g.dw), the other most used diuretic after furosemide. Different parameters can influence the affinity of furosemide to sludge. However, the furosemide partition coefficient (Table S4) between the dissolved and particulate phases (K_d) suggests that it has a rather good affinity with these matrices.

Stuer-Lauridsen et al. (2000) further showed that the affinity of furosemide with sludge is several orders of magnitude more important than suggested by the partition coefficients; indeed Svahn & Björklund (Svahn and Björklund, 2015) underlined that the sorption mechanisms are effectively too complicated to be estimated from the log p (also log K_{ow} , octanol/water partition coefficient) or log d (pH-dependent partitioning coefficient) of the molecules. The K_d value depends on several parameters, including nature and concentration of organic carbon, and pH which varies during wastewater treatment (between 5 and 9) which could explain why the digested sludge K_d is lower than that of thickened sludge (Jelic et al., 2012).

Moreover, with increasing water stress in some countries, water reuse is becoming an important issue but could be a source of micropollutant contamination, just as sludge spreading and urine use as fertilizer. Sludge spreading and the use of urine as fertilizer could also generate significant contamination. A few studies showed that furosemide can accumulate (weakly) in food crops irrigated by wastewater: Delli Compagni et al. (Delli Compagni et al., 2020) modeled a possible accumulation of furosemide especially in the roots of maize, rice and ryegrass, but also potentially in leaves and seeds by its transfer through the phloem. However, not all plants seem to accumulate. Indeed, Martínez-Piernas et al. (2019) did not detect furosemide in tomatoes while

tomato plants were irrigated with reused water containing 1700 ng/L of furosemide.

3 Occurrence in surface waters

Many studies quantified furosemide in surface water but only a few focus on lakes, seas, oceans, estuaries and deltas. River waters are the most studied for the presence of pharmaceutical compounds and furosemide has been quantified in many locations (Fig. S1). The furosemide median concentration in European rivers is 93 ng/L, with an average concentration of 265 ng/L and a maximum concentration found of 6894 ng/L in Portugal (Palma et al., 2020), which is almost 30 times above average. In non-European countries, the maximum quantified concentration (1235 ng/L) is found in the Hudson River in USA (Cantwell et al., 2018). This relatively high concentration has been explained by the proximity of a WWTP discharge, which contributes strongly to the volume of water present especially during low tides. In other compartments, concentrations are lower in most cases. The few studies which detected furosemide in lakes, estuaries or coastal waters have not reported concentrations over 47 ng/L (Wahlberg et al., 2011a; Matamoros et al., 2012; Togola et al., 2008; Rodríguez-Navas et al., 2013a), except once at 2300 ng/L in coastal waters in Portugal (Almeida et al., 2017). However, this unusual value has not been explained by the authors, nor confirmed by more recent studies.

Generally, furosemide is rarely detected in coastal or oceanic waters (Afsa et al., 2020; Biel-Maeso et al., 2018a; Feo et al., 2020), probably because of the importance of the water volumes involved (dilution effect). Studying the surface water content constitutes the first step toward risk assessment, providing an idea of exposure concentrations of non-target organisms in these environments. In addition, as in the case of sludge, some of the furosemide may be found in the sediment (Fig. 3). The median furosemide content in sediment is 2.7 ng/g.dw. As furosemide has a low polar to apolar surface ratio, it is expected to form more hydrogen interactions with sediments (Bäuerlein et al., 2012). According to the data presented in Fig. 3, in sediments, furosemide is 10 times less concentrated than in treated sludge. This disparity may be due to a significant dilution effect in river water. On the other hand, Björklund et al. (2016) calculated a very high K_d in sediment for furosemide (2517 L/kg). However, the furosemide content in sediment found by these authors is very high (350 ng/g.dw) compared to other values found in the literature (Fig. 3) and could explain this high K_d , which would therefore not be representative of the affinity of furosemide to sediments.

4 Occurrence in ground and drinking waters.

Pharmaceutical residues in groundwater studies investigate the magnitude of the contamination, while analysis of drinking water aims at assessing the risk that residues represent for the population or ecosystems. These environments are rather protected but not totally devoid

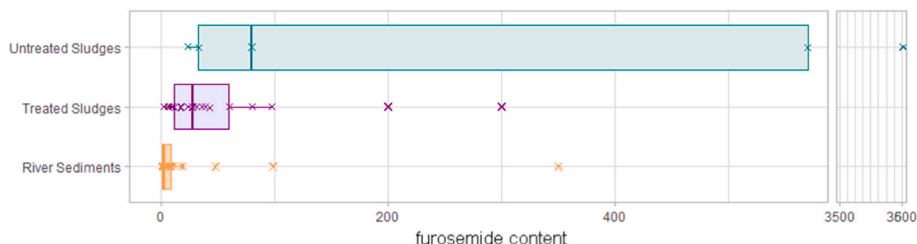


Fig. 3. Furosemide contents in river sediments and WWTP sludge (ng/g dw). Each x represents a value of furosemide. The cyan boxplots represent furosemide concentrations in untreated sludge (no digestion or biological treatments). The magenta boxplot represents the concentrations in the sludge after treatment and the yellow boxplot represents the concentrations in the sediment. Concentrations are given in ng/g of dry content except for Ferrari et al., 2011 which is expressed as ng/g of wet content (Huber et al., 2016; Riva et al., 2021; Björklund et al., 2016; Narumiya et al., 2013; Wahlberg et al., 2011a; Gros et al., 2009; Ginebreda et al., 2012; Salgado et al., 2010a; Ferrari et al., 2011; Ferreira da Silva et al., 2011; Sadutto et al., 2021; Jelić et al., 2009; Rodríguez-Rodríguez et al., 2012).

of furosemide contamination (Table S5). Sources of groundwater contamination include loss from sewage systems, urban runoff by sustainable urban drainage systems which promote the infiltration of runoff water locally (Eriksson et al., 2007), wastewater discharges, industrial discharges or infiltration of river water to the aquifer (Jurado et al., 2012; Sui et al., 2015). Whereas concentrations of a dozen to a few hundred ng/L of furosemide have been found occasionally in France and Spain, it is mostly not even detected in groundwater (Mogensen et al., 2008; Gros et al., 2012; Meffe and de Bustamante, 2014; Vulliet and Cren-Olivé, 2011; Benotti et al., 2006; Valcárcel et al., 2011; Stackelberg et al., 2004), nor in natural river biofilm (Huerta et al., 2016). Furosemide is also rarely detected in drinking water (Wahlberg et al., 2011a; Gracia-Lor et al., 2012; Anderson et al., 2010; Marube et al., 2017; Zuccato et al., 2000; López-Serna et al., 2010), only once reaching 29 ng/L in Poland (Giebułtowicz et al., 2016). Drinking water treatment processes are indeed relatively effective for furosemide (Baken et al., 2018), in particular chlorination, ozonation and UV (Ultra-violet) radiation: the secondary amine or the furan ring in furosemide reacts quickly with chlorine or ozone and it is therefore quickly photodegraded by UV lights (Sandré et al., 2023). However, its degradation can lead to by-products formation (see below) such as 1-acetyl-1-methyl-2-phenylhydrazide (de Jongh et al., 2012).

5 Temporal variation

Temporal variations of furosemide concentrations in the receiving environment have been linked to its use and its elimination efficiency by WWTPs. Delli Compagni et al., (2020) observed lower concentrations of furosemide in summer (≈ 70 ng/L) than in winter (≈ 180 ng/L). As furosemide is well photodegraded, especially in rivers (Hanamoto et al., 2014), the authors hypothesized that the decrease in concentration in summer is due to increased radiation favoring its photolysis. In addition, furosemide degradation is also more important in WWTPs in summer (54%) over winter (8%) (Castiglioni et al., 2006) and in WWTP sludges (8 ng/g.dw in summer, 31 ng/g.dw in winter (Riva et al., 2021) presumably due to a more important biological activity with a warmer temperature. However, one study did not find significant variations in furosemide concentrations between seasons (Kot-Wasik et al., 2016). On the other hand, a higher contribution of furosemide by river to coastal waters was observed in spring (Feo et al., 2020; Moreno-González et al., 2014), which was also the case in a Canadian WWTP effluent with higher concentrations in spring *versus* fall, while undetected in summer (Singh et al., 2015a). In Mexico, two to three times higher concentrations of furosemide were observed in municipal WWTP influent in the dry (514 ng/L) *versus* wet (173 ng/L) season, which could be due to dilution during the rainy season. The authors also noted a better WWTP efficiency during the dry season due to a longer residence time and smaller volumes of wastewaters to be treated (Estrada-Arriaga et al., 2016).

4. Fate of furosemide from its consumption to receiving water

After consumption, furosemide will pass through the human body before being excreted in urine. It will be then transferred to the sewer network and the WWTPs, where it will be eliminated with various efficiency.

1 Metabolization

In adults, most of furosemide (between 69 and 99%) is excreted within the first 4 h after intake regardless of the mode of administration, mainly through urine and marginally through feces (Calesnick et al., 1966; Aranda et al., 1982; Stankiewicz et al., 2015). Furosemide can be metabolized in the liver and the guts by uridine diphosphate glucuronyltransferase but mostly (85%) in the kidneys (Phakdeekitcharoen and Boonyawat, 2012). It is highly bonded to plasma albumin (>90%) which leads to a low-efficiency filtration by the glomerulus (Prandota

and Witkowska, 1976; Phakdeekitcharoen and Boonyawat, 2012; Andreassen and Jakobsen, 2009). Finally, between 11% and 23% of furosemide is excreted in its glucuronide form (Riva et al., 2015; Zuccato et al., 2005; Aranda et al., 1982; Bindschedler et al., 1997; Andreassen et al., 1982; Boles Ponto and Schoenwald, 1990). However, furosemide remains mostly untransformed and an average of 66% (Bindschedler et al., 1997; Andreassen et al., 1982; Zuccato, 2004a) is excreted in unchanged form in adults and 84.5% in children (Aranda et al., 1982). Furosemide can be hydrolyzed to a lesser extent in the human stomach (Andreassen et al., 1982) and in aqueous solutions (Bundgaard et al., 1988). At constant temperature and pH, Bundgaard et al. (1988) describe a first order kinetics, and an improvement of the hydrolysis rate when pH decreases. Furosemide thermal decomposition was studied in the early 2000s (Beyers et al., 2000). However, furosemide only degrades at 218 °C which is far from the environmental conditions.

2 Degradation in WWTPs and advanced process

Furosemide degradation in WWTPs is quite variable. Effective degradation rates around 70% have been found in literature (Matamoros et al., 2009a; Sandré et al., 2023; Kasprzyk-Hordern et al., 2009), owing to more efficient WWTP processes and/or time of sampling: due to the higher temperature in summer, the biodegradation activity is indeed stronger, and furosemide is better degraded. Medium elimination rates 25-40-50-54% were found in conventional mechanical-biological treatment (Castiglioni et al., 2006; Kot-Wasik et al., 2016; Park et al., 2017; Gros et al., 2010). These percentages of removal can be much increased by adding tertiary or quaternary treatments in WWTPs, as shown in Fig. 4.

The degradation of furosemide by innovative processes has been widely studied in more than 35 papers (Fig. 4). The effectiveness of these processes appears very variable, ranging from complete elimination of furosemide to no elimination, or even higher furosemide concentrations following Membrane Bio Reactor (MBR) processes (Nielsen et al., 2013). This phenomenon has been explained by the deconjugation of glucuronidated forms of furosemide, increasing the concentration of quantifiable “native” furosemide (Kovalova et al., 2012; Kosma et al., 2014). Due to their highly variable efficiency, it is difficult to conclude on the performance of MBR (from -14 to 95% elimination of furosemide) and absorption on xylite (from 15 to 100% elimination). The effectiveness of xylite depends on the water residence time within the process, a longer time resulting in a more effective absorption (Rostvall, 2017). The MBR efficiency relies on the upstream processes and the type of membrane used. The lowest removal rates reported for furosemide are obtained with ceramic membranes (Nielsen et al., 2013; Joannis-Cassan et al., 2021). On average, biological treatments (Activated sludge, Anaerobic-Anoxic-Aerobic system (A2O), Peroxidase, Plant, Fugus, Constructed wetland, Chitosan film, MBR) are not much more efficient than physical-chemical treatments (*i.e.*, all the rest): average efficiency of 74% versus 70%, respectively. Filtration techniques such as sand filtration and ultrafiltration are not the most efficient (<50%) although ultrafiltration coupled with Gas-phase Pulsed corona discharge (PCD) shows better performances. On the other hand, reverse osmosis can completely eliminate furosemide due to the membranes that retain even small organic molecules (Eriksson et al., 2007). The majority of the processes found in the literature are oxidation processes. Their efficiency is very variable, and depends on the reactivity of the oxidants involved with furosemide (Sandré et al., 2022). Ozonation processes are among the most efficient due to the quick reaction of ozone with the furan ring and the aniline group of furosemide (Zoumpouli et al., 2021). Photo-Fenton, chlorination, electro-oxidation and peroxydation allow almost complete elimination of furosemide. Peroxidases have also been shown to be very effective (Almaqdi et al., 2019), but the process has not been tested at WWTP scale and may be difficult to implement because it requires high enzyme concentration in high concentrations and the buffering of the pH. On the other hand, UV radiation appears rather



Fig. 4. Removal efficacy of furosemide by different advanced processes (%). Each x represents a value of furosemide removal. The purple boxes represent the techniques for which the removal of furosemide is done by a biological process and the blue boxes represent those for which the process is physicochemical (Machado et al., 2017; Nielsen et al., 2013; Vymazal et al., 2017; Park et al., 2017; Kovalova et al., 2012; Rostvall, 2017; Joannis-Cassan et al., 2021; Sandré et al., 2022; Almaqdi et al., 2019; Badia-Fabregat et al., 2016; Ajo et al., 2018; Jie, 2012; Rosal et al., 2010; Kjølholt et al., 2003a; Ibáñez et al., 2013a; Urriaga et al., 2013a; Klamerth et al., 2013a; Gómez et al., 2008a; Huerta-Fontela et al., 2011; Singh et al., 2015a; Ahmed et al., 2017; Arola et al., 2018; Cruz-Morató et al., 2014; Heidari et al., 2020; Ikonen et al., 2021; Kim et al., 2014; Kovalova et al., 2013; Llorens-Blanch et al., 2015; Machado et al., 2020; Muñoz et al., 2009; Reungoat et al., 2012; Rizzi et al., 2020; Verlicchi et al., 2015; Cuervo Lumbaque et al., 2020).

ineffective. Despite its high sensitivity to photodegradation (Bundgaard et al., 1988), the wastewater matrix must be too complex to allow optimal removal of furosemide. UV-H₂O₂ process on the other hand shows good efficiency because the addition of H₂O₂ results in the formation of reactive oxygen species which will react strongly with furosemide (Miklos et al., 2018). Furosemide elimination by absorption is also interesting. Absorption on xylite, lignite or activated charcoal (in powder or granulated form) shows an efficiency of more than 60%. These techniques have the advantage of trapping the molecules and therefore potentially release less by-products than oxidation methods (Cuthbertson et al., 2019).

3 Natural degradation

Under environmental conditions, furosemide has several degradation pathways. First, furosemide has been known to be photodegradable for a long time: it is sensitive to visible light with fluorescent lamp (Katsura et al., 2015a), sunlight (Starling et al., 2019) and UV radiation (Bundgaard et al., 1988; Moore and Burt, 1981) which will react with the chlorine, furfuryl or sulfamoyl groups (Sandre et al., 2023). Although its photodegradation is unlikely in the wastewater system, it is expected once discharged into the aquatic environment. It has been reported to be biodegraded by environmental bacteria such as *Agrobacterium tumefaciens* and *Arthrobacter ureafaciens* (Laurencé et al., 2014), fungus like *Aspergillus candidus*, *Cunninghamella echinulata* and *Trametes versicolor* (Laurencé et al., 2014; Olvera-Vargas et al., 2016a; Badia-Fabregat et al., 2015; Badia-Fabregat et al., 2016) and anaerobic

microorganisms (Narumiya et al., 2013; Gros et al., 2020), forming several by-products.

5. Degradation by-products of furosemide

During its passage in the human body, in sewage networks, in WWTPs or in the environment, furosemide undergoes several degradation pathways, leading sometimes to its real elimination, but more frequently to the concomitant production of by-products, more or less stable, thus resulting in an apparent furosemide decrease when assessing removal at the WWTPs. These by-products can be formed by various processes, and may remain unidentified if global and sensitive analytical methods such as LC-MS/MS or HRMS are not applied. Furthermore, they may have a significant toxicity, which is currently understudied (poorly taken in account). The structure of several degradation products has been identified in the literature (Table 1). Some of these have been known for a long time and others have been identified only recently with the improvement of screening techniques.

Pathways for the formation of most of these by-products have been proposed (Zoumpouli et al., 2021; Koronaoui et al., 2023; Jakimska et al., 2014a; Peterson, 2013; Shao et al., 2024). As mentioned earlier, the glucuronide form (product 60) is the second most common form of furosemide. It is quite well referenced in the early literature (Aranda et al., 1982; Bindschedler et al., 1997; Andreassen et al., 1982; Mizuma et al., 1998). pH has a strong influence on its stability, it is more stable at pH < 6, while more basic pH leads to a rearrangement into a β -glucuronide. However, both forms ultimately hydrolyze into furosemide (Hammarlund-Udenaes and Benet, 1989). The half-life of furosemide glucuronide in aqueous medium at physiological pH is 5.3 h (Yang et al., 2006). Like furosemide, its glucuronide form is photodegraded but 20 times faster (Sekikawa et al., 1995). The chlorine atom can be substituted by a hydroxyl group by photodegradation leading to the product 59. Three major pathways for the formation of saluamine (32), the glucuronide form (60) and the Glutathione S-conjugate form (57) have been described (Peterson, 2013). Furfural (61), another degradation product, has been long known. Furfural is a small, highly soluble molecule that is also produced naturally by plants such as corn (Yue et al., 2022) and is rapidly biodegraded (Mandalika et al., 2014). Saluamine is the most referenced degradation product of furosemide and has been identified as a metabolite in humans (Andreassen et al., 1982; Hammarlund-Udenaes and Benet, 1989). It can be obtained by several processes: Electro-Fenton (Laurencé et al., 2011), acid catalyzed hydrolysis (Beyers et al., 2000), photodegradation (Katsura et al., 2015a; Koronaoui et al., 2023; Jakimska et al., 2014a; Della Greca et al., 2004a) and biodegradation (Laurencé et al., 2014; Olvera-Vargas et al., 2016a). It was also found after incubation in sediments spiked with furosemide (Li et al., 2014a).

The pyridinium of furosemide (51) has been identified as a degradation product much more recently. Initially produced by electrochemistry (Laurencé et al., 2011), it was first obtained by microsomal incubations of furosemide (Chen and Burka, 2007), by furosemide bioconversion by two fungi, *Aspergillus candidus* and *Cunninghamella echinulata* (Laurencé et al., 2014; Olvera-Vargas et al., 2016a) and finally found in furosemide treated-patients urine (Laurencé et al., 2019), therefore qualifying it as a human metabolite.

The gamma-ketocarboxylic acid (product 49) has been identified on several occasions as well (Peterson, 2013; Bukkitgar and Shetti, 2016; Williams et al., 2007a). According to the reaction pathway proposed by Olvera-Vargas et al. (2016a), this product would be an intermediate preceding the formation of the pyridinium of furosemide (51) or the formation of the hydroxyketone product 48, which can be hydrolyzed to saluamine (32). The hydroxyketone (48) has also been repeatedly identified as an anodic oxidation (Olvera-Vargas et al., 2016a), metabolism (Williams et al., 2007a) or biotransformation product (Peterson, 2013).

Most of the degradation products structures are proposed following

NMR or mass spectrometry analysis but the absence of analytical standards makes it challenging to ascertain their authenticity. Some products have been obtained by the same processes in several other studies, which reinforces their probability to be genuine, such as ozonation products 13 and 40 (Zoumpouli et al., 2021; Tsilikidis et al., 2015) and product 58, a dimer from photodegradation of furosemide was observed (Della Greca et al., 2004a; Isidori et al., 2006a). Product 2 seems to be the most frequently found both as a photodegradation product (Sandre et al., 2023; Katsura et al., 2015a; Jakimska et al., 2014a; Yagi et al., 1991) and as a degradation product of furosemide glucuronide (Mizuma et al., 1998). On the other hand, several products were described only once in the literature. It may be due to their very low concentration, or because they are intermediates of transformation and disappear quickly (Sandre et al., 2023; Tsilikidis et al., 2015; Aalizadeh et al., 2019). These structures are mostly similar to furosemide, Saluamine (32) or pyridinium of furosemide (51), with variations in hydroxyl or sulfhydryl groups, chlorine substitutions, furan cycles opening or rearrangements (Laurencé et al., 2014; Koronaoui et al., 2023; Jakimska et al., 2014a; Shao et al., 2024). The prevalence of a degradation product depends on the media conditions. For example, saluamine (32) and product 2 were detected in several matrices (Jakimska et al., 2014a), whereas product 34 was only found in treated wastewater and could therefore be a result of water treatment processes. Saluamine is one of the least well documented degradation products. Saluamine (32) has rarely been searched for, and, to our knowledge, only two studies quantify it in WWTP effluents, with concentrations of 48 ng/L and 470 ng/L (Sandre et al., 2023; Koronaoui et al., 2023). We also recently quantified pyridinium of furosemide (51) in WWTP effluent over 200 ng/L. The presence of these two compounds has been verified unambiguously using analytical standards, which is not the case for the remaining by-products. Furthermore, Koronaoui et al. (2023) performed a non-target analysis on WWTP samples and showed the presence of products 14 (\approx 350 ng/L), 13 (\approx 25 ng/L), 23 (\approx 330 ng/L), 34 (320 ng/L) in the influents, and 13 (\approx 25 ng/L), 10 (\approx 220 ng/L), 34 (208 ng/L) in the effluents.

6. Toxicity and ecotoxicity of furosemide and its degradation products

1 Health hazard of furosemide

As a medication, the toxicity of furosemide on humans has been widely reviewed. In short, numerous adverse effects have been reported such as dehydration in the most common case (23%) and hydrolytic disturbance (21%) (Peterson, 2013).

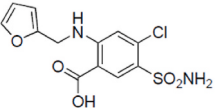
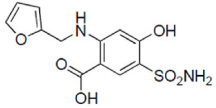
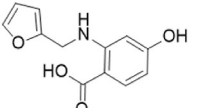
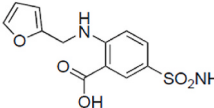
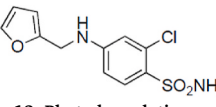
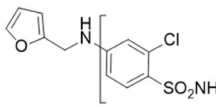
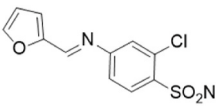
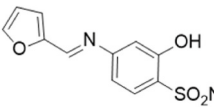
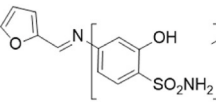
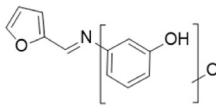
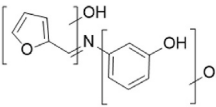
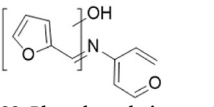
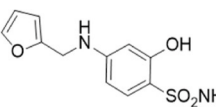
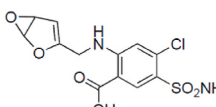
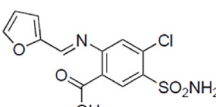
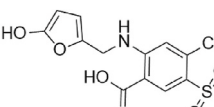
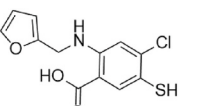
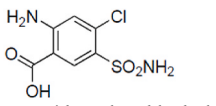
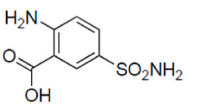
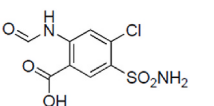
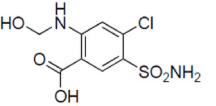
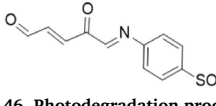
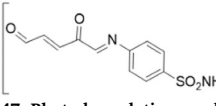
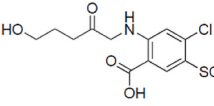
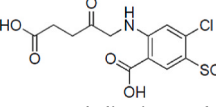
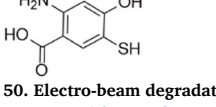
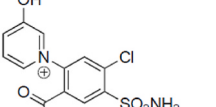
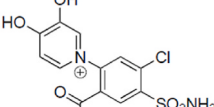
2 Environmental toxicity of furosemide

The impact of furosemide in the environment and aquatic fauna has been less investigated than in humans, but a few studies aim to assess the risk of pharmaceutical compounds. Risk calculations are based on ratios between Measured Environmental Concentrations (MECs) or Predicted Environmental Concentrations (PECs) and Predicted No-Effect Concentrations (PNECs). PNECs are determined from the Effect Concentrations (ECs) obtained experimentally on different classes of organisms or estimated using different models such as ECOSAR (Table 2).

The bacterium *Aliivibrio fischeri* seems to be the most sensitive to furosemide followed by the green algae *Selenastrum capricornutum*. Among invertebrates, the crustacean *Daphnia magna* appears as the most sensitive organism. In comparison, the EC50s obtained in the fish cell lines appear to be quite high. However, these results cannot be extrapolated to toxicological relevance in whole organisms and ecosystems because these *in vitro* tests do not take into account systemic effects of the molecule, neither organ/tissue specific effects nor possible detoxification processes.

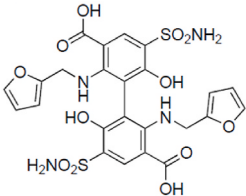
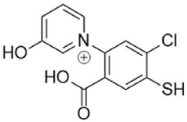
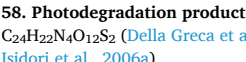
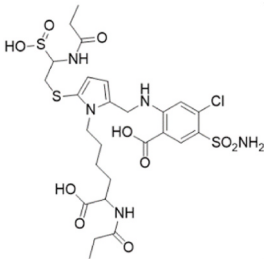
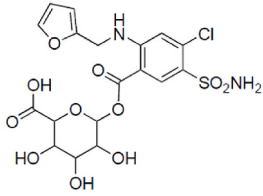


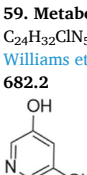
It should be noted that the data summarized in Table 2 for lethality, immobilization or growth inhibition are obtained in acute exposure (*i.e.*,

Table 1
Degradation products of furosemide.

 <p>1. Furosemide C₁₂H₁₁ClN₂O₅S 330.7</p>	 <p>2. Photodegradation product C₁₂H₁₂N₂O₆S (Sandré et al., 2023; Katsura et al., 2015a; Koronaiou et al., 2023; Jakimska et al., 2014a; Mizuma et al., 1998; Yagi et al., 1991; Brienza et al., 2019) 312.3</p>	 <p>10. Photodegradation product C₁₂H₁₁NO₄ (Koronaiou et al., 2023) 233.1</p>	 <p>11. Photodegradation product C₁₂H₁₂N₂O₅S (Shao et al., 2024; Jakimska et al., 2014a) 296.3</p>
 <p>13. Photodegradation product C₁₁H₁₁ClN₂O₃S (Koronaiou et al., 2023; Vargas et al., 1998) 286.0</p>	 <p>14. Photodegradation product C₁₁H₁₁ClN₂O₄S (Koronaiou et al., 2023) 302.0</p>	 <p>15. Photodegradation product C₁₁H₉ClN₂O₃S (Koronaiou et al., 2023) 284.0</p>	 <p>16. Photodegradation product C₁₁H₁₀N₂O₄S (Koronaiou et al., 2023) 266.0</p>
 <p>18. Photodegradation product C₁₁H₁₀N₂O₅S (Koronaiou et al., 2023) 282.0</p>	 <p>19. Photodegradation product C₁₁H₉NO₃ (Koronaiou et al., 2023) 203.1</p>	 <p>20. Photodegradation product C₁₁H₉NO₄ (Koronaiou et al., 2023) 219.1</p>	 <p>22. Photodegradation product C₁₀H₉NO₃ (Koronaiou et al., 2023) 191.1</p>
 <p>23. Photodegradation product C₁₁H₁₂N₂O₄S (Koronaiou et al., 2023) 268.0</p>	 <p>28. Metabolization, anodic oxidation product C₁₂H₁₁ClN₂O₆S (Laurencé et al., 2011; Mitchell et al., 1976) 346.7</p>	 <p>29. Anodic oxidation, photodegradation product C₁₂H₉ClN₂O₅S (Koronaiou et al., 2023; Shao et al., 2024; Laurencé et al., 2011; Bukkitgar and Shetti, 2016; Lumbaqué et al., 2021) 328.7</p>	 <p>30. Electro-beam degradation product C₁₂H₁₁ClN₂O₆S (Shao et al., 2024) 346.0</p>
 <p>31. Electro-beam degradation product C₁₂H₁₀ClNO₃S (Shao et al., 2024) 283.0</p>	 <p>32. Acid catalyzed hydrolysis, Electro-Fenton, metabolization, photodegradation product C₇H₇ClN₂O₄S (Beyers et al., 2000; Almaqdi et al., 2019; Laurencé et al., 2014; Koronaiou et al., 2023; Peterson, 2013; Laurencé et al., 2011; Brienza et al., 2019; Jakimska et al., 2014a; Lumbaqué et al., 2021; Della-Flora et al., 2021; Carda-Broch et al., 2000; Williams et al., 2007a; Baranowska et al., 2010; Li et al., 2014a; Katsura et al., 2015a; Olvera-Vargas et al., 2016a) 250.7</p>	 <p>34. Photodegradation product C₇H₈N₂O₄S (Koronaiou et al., 2023; Jakimska et al., 2014a) 216.2</p>	 <p>40. Ozonation product C₈H₇ClN₂O₅S (Zoumpouli et al., 2021; Tsilikidis et al., 2015) 278.7</p>
 <p>42. Chlorination product C₈H₉ClN₂O₅S (Sandré et al., 2023) 280.7</p>	 <p>46. Photodegradation product C₁₁H₁₀N₂O₄S (Koronaiou et al., 2023) 266.0</p>	 <p>47. Photodegradation product C₁₁H₁₀N₂O₅S (Koronaiou et al., 2023) 282.0</p>	 <p>48. Anodic oxidation, Ozonation, Biotransformation, Metabolization product C₁₂H₁₁ClN₂O₆S (Zoumpouli et al., 2021; Peterson, 2013; Williams et al., 2007a; Olvera-Vargas et al., 2016a) 346.7</p>
 <p>49. Metabolization product C₁₂H₁₃ClN₂O₇S (Peterson, 2013) 350.7</p>	 <p>50. Electro-beam degradation product C₇H₇NO₃S (Shao et al., 2024) 185.0</p>	 <p>51. Chemical, enzymatic oxidation,</p>	 <p>52. Bioconversion product^a</p>

(continued on next page)

Table 1 (continued)

Bukkitgar and Shetti, 2016; Williams et al., 2007a) 364.8	 58. Photodegradation product $C_{24}H_{22}N_4O_{12}S_2$ (Della Greca et al., 2004a; Isidori et al., 2006a) 622.6	bioconversion, photodegradation product $C_{12}H_{10}ClN_2O_5S$ (Laurencé et al., 2014; Peterson, 2013; Laurencé et al., 2011; Chen and Burka, 2007; Laurencé et al., 2019) 329.7	$C_{12}H_{10}ClN_2O_6S$ (Laurencé et al., 2014; Shao et al., 2024) 345.7
 56. Electro-beam degradation product $C_{12}H_9ClNO_3S$ (Shao et al., 2024) 282.0	 59. Metabolization product $C_{24}H_{32}ClN_5O_{10}S_3$ (Peterson, 2013; Williams et al., 2007a) 682.2	 59. Metabolization product $C_{24}H_{32}ClN_5O_{10}S_3$ (Peterson, 2013; Williams et al., 2007a) 682.2	 60. Metabolization product $C_{18}H_{19}ClN_2O_{11}S$ (Peterson, 2013; Mizuma et al., 1998; Williams et al., 2007a) 506.9
 61. Anodic oxidation, photodegradation product $C_5H_4O_2$ (Laurencé et al., 2014; Carda-Broch et al., 2000) 96.1	 66. Electro-beam degradation product $C_5H_5NO_2$ (Shao et al., 2024) 113.0	 67. Electro-beam degradation product $C_5H_5NO_2$ (Shao et al., 2024) 113.0	

Structure have been drawn by ChemDraw15. Name, structure, and molecular masse are listed under each product.

^a The position of the hydroxyl group can vary on the pyridin ring.

short duration exposure). Chronic exposures (*i.e.*, long term exposure) would be more representative of environmental conditions. For chronic exposures, Isidori et al. (2006a) indeed obtained much lower EC50s for *Brachionus calyciflorus* (2.5 mg/L) and *Ceriodaphnia dubia* (2.3 mg/L) versus 100 mg/L and 84.1 mg/L in acute exposure, respectively. Riva et al. (2019) and Mendoza et al. (2015) set a PNEC of 45.15 µg/L and 1.56 µg/L based on the ECs of algal, crustacean and fish toxicity tests. These PNECs are then used to determine the Risk Quotient (RQ) or Hazard Quotient (HQ) by calculating the ratio MEC/PNEC. When this ratio is greater than 1, it is considered that there is a risk for the environment. Papageorgiou et al. (2016a) have assessed furosemide RQ and, according to European Guidelines (EMEA, 2006), it presents a high toxicological risk for invertebrates and moderate risk for fish. As a result, risk assessments may underestimate its impact. Moreover, most of the time, ECs are based on the lethality of compounds to organisms, which is not a very sensitive parameter. For example, based on those lethality values, furosemide was considered as not problematic for aquatic environments (Lacey, 2008; Carlsson et al., 2006). However, an increasing number of studies reported that analysis of organism behavior, which integrates many physiological processes, is environmentally more relevant to anticipate impacts on survival, as behavioral toxicity can be observed at concentrations 10 to 100 times lower than lethal concentrations (Sandré et al., 2022; Legradi et al., 2018). Thus, furosemide, at the concentrations mentioned above, may well have a negative impact on aquatic organisms' survival.

Other markers may be also relevant to study. For example, genotoxic and cytotoxic effects of furosemide were shown on *Danio rerio* (Rocco et al., 2010) and in rodent hepatocytes (Mondal et al., 2012) along with an irreversible binding to hepatocyte were found (Williams et al., 2007a). Hepatotoxicity was associated with depletion of GSH (reduced form of glutathione) and protein thiols at high concentrations (Peterson, 2013; Fent et al., 2006) noted an estrogenic activity *in vitro* experiments. This endocrine disruption potential could have negative impacts not only at the individual level but also at the population level, endangering its survival. Despite some information on toxicity, to our knowledge

there is no information on furosemide accumulation in biota.

3 Toxicity of furosemide degradation products

The toxicity of furfural (product 61) has been well studied because it is used to produce furfuryl alcohol which is extensively used in various industrial process (Grosse et al., 2017). Furfural exposure in humans occurs through the lungs or skin and provokes irritations (Flek and Sedivec, 1978). Furfural is rapidly metabolized by enteric bacteria under both aerobic and anaerobic conditions and 83–88% is excreted in urine in 72 h (Boopathy et al., 1993). In the environment, furfural presents a higher toxicity than furosemide with an LC50 of 29 mg/L for 24 h exposure and 13 mg/L for 72 h exposure in *Daphnia magna*. For fish, LC50 after 96 h exposure is 10.5 mg/L for *Poecilia reticulata* and 32 mg/L for *Pimephales promelas* which is also lower than furosemide for different fish species. Chronic exposure of fishes to furfural leads to growth retardation, morphological abnormalities, and lethargy (Reed and Kwok, 2014). There is little data concerning the other degradation products of furosemide. Saluamine (32) is only referenced as a degradation product of furosemide and is therefore much less studied. Only one study investigated its toxicity, which showed that it induces changes in some body parameters in mouse models such as increased alanine and aspartate aminotransferases, increased creatinine, reduced blood glucose, liver and kidney congestion (Al-Omar et al., 2009). We recently showed that pyridinium of furosemide (51) leads to the development of characteristic biomarkers of Parkinson's disease in mice and generates oxidative stress and inhibition of the mitochondrial respiratory chain (Laurencé et al., 2019). Furthermore, Olvera-Vargas et al. (2016a) noted an EC50 of 34.4 mg/L and an EC20 of 18.9 mg/L in *Aliivibrio fischeri* for 15 min exposure, which is lower than the EC20 of 72.3 mg/L they obtained for furosemide in the same conditions. Collectively, these results suggest that pyridinium of furosemide (51) is also more toxic than furosemide. A study conducted on the photodegradation product 58 showed that its EC50 values were lower than for furosemide for *Brachionus calyciflorus* (1.04 mg/L) and *Ceriodaphnia dubia* (0.57 mg/L)

Table 2

EC (Lethality, Immobilization or growth inhibition) value for several organisms exposed to furosemide.

	Species	Duration	EC (mg/L)
Bacteria	<i>Aliivibrio fischeri</i>	EC10 15 min (Di Nica et al., 2017)	7.5
		EC20 15 min (Olvera-Vargas et al., 2016a)	72.3
		EC50 15 min (Di Nica et al., 2017)	33.2
		EC50 30 min (Isidori et al., 2006a)	> 200
Green algae	<i>Desmodesmus subspicatus</i> <i>Pseudokirchneriella subcapitata</i>	EC50 72H (Guo, 2015)	322.2
		EC50 72H (Christensen et al., 2009a)	142
		ECOSAR (Kuzmanović et al., 2015)	19.8
Zooplankton	<i>Brachionus calyciflorus</i>	EC50 24H (Isidori et al., 2006a)	> 100
Crustacean	<i>Artemia salina</i>	EC50 24H (Diaz-Sosa et al., 2020)	273.0
		EC50 48H (Diaz-Sosa et al., 2020)	225.1
	<i>Daphnia magna</i>	ECOSAR (Kuzmanović et al., 2015)	560
		EC50 24H (Isidori et al., 2006a)	60.6
		EC50 48H (Christensen et al., 2009a)	239.0
	<i>Thamnocephalus platyurus</i> <i>Ceriodaphnia dubia</i>	EC50 24H (Isidori et al., 2006a)	70.6
		EC50 48H (Isidori et al., 2006a)	84.1
Cnidarian	<i>Hydra vulgaris</i>	Acute tox. (Pascocoe et al., 2003)	> 1
Teleosts	<i>Pimephales promelas</i> <i>Cyprinodon variegatus</i> <i>Cyprinus orfus</i>	ECOSAR (Kuzmanović et al., 2015)	521
		EC50 96H (Christensen et al., 2009a)	497
		EC50 (Hanisch et al., 2002)	> 500
Cell line	<i>Oncorhynchus mykiss</i> <i>Poeciliopsis lucida hepatoma</i>	EC50 24H (Christensen et al., 2009a)	1131
		EC50 24H (Christensen et al., 2009a)	2576

EC = Effect Concentration.

reflecting a higher toxicity (Isidori et al., 2006a), as well as mutagenic activity at concentrations between 6.25 and 100 mg/L. The hydroxyketone product 48 with an EC20 of 37.42 mg/L in *Aliivibrio fischeri* for 15 min exposure (Olvera-Vargas et al., 2016a) and a metabolite corresponding to product 28 are also more toxic than furosemide, the latter causing hepatic necrosis in rats, mice and hamsters after intraperitoneal injections (Mitchell et al., 1976).

Assessing the toxicity of all by-products is a challenging task, given their considerable number. Some studies therefore tend to predict their acute or chronic toxicity using an *in-silico* methodology such as that provided by the ECOSAR software. Thus, the toxicity of some thirty products derived from the photodegradation of furosemide was evaluated (Koronaoui et al., 2023; Shao et al., 2024). These studies quickly highlighted the possibly high acute (products 15, 18, 19, 20, 22, 31, 46 and 56) or chronic (products 11, 14, 15, 16, 18, 19, 20, 22, 23, 29, 30, 31, 46, 47, 50, 51, 56, 66 and 67) toxicity of furosemide by-products in fish, daphnia and/or algae and the hypothesis that imine formation, decarboxylation, desulfurization and the presence of chlorine, lead to more toxic by-products (Koronaoui et al., 2023). Concerning chlorination products, many of these remain unknown, with regard to the specific analysis and complex chemistry of halogenated compounds. The assessment of their toxicity is thus a major challenge, and the few

publications, yet showing the carcinogenic, cytotoxic, genotoxic activities as well as adverse modification on benthic and fish communities structures of some known by-products (Cuthbertson et al., 2019; Prasse et al., 2015), insufficiently reflect the toxicity of the majority of the unknown by-products. In the case of furosemide, out of the 74 by-products identified (see Table 1 and Table S6), only one comes from chlorination (product 42 (Sandré et al., 2023)). This reduced number of chlorination by-products is in accordance with previous findings (Koronaoui et al., 2023), which indicated that dechlorination is one of the major processes forming most of furosemide by-products. While *in silico* models prove useful in predicting the toxicity of various substances, their capacity remains limited in the face of the intrinsic complexity of living systems, particularly due to challenges in integrating crucial parameters such as exposure time, organism sensitivity, and contaminant bioavailability. For a more complete evaluation of the environmental impact, mixtures should also be taken into account. Indeed, interactions between molecules can lead to synergistic or antagonistic effects (cocktail effects) and are quite complex. Because furosemide is a medication, it is frequently in interaction with other compounds such as benzalkonium chloride or spironolactone. However, there is very few data about the ecotoxicity of the mixture or about the interactions between furosemide and its degradation products. To the best of our knowledge, only one study presents toxicity data of mixtures of 30 compounds including furosemide, resulting in a 30% decrease in liver cell (HEK293) proliferation (Pomati et al., 2006).

7. Conclusion

Given the wide consumption of medicines, increasing demographical urban pressure and population aging, the chemical and ecotoxicological assessment of pharmaceuticals and their metabolites constitutes major challenges. Improving our understanding of drugs follow-up to and in the environment in the framework of water resources protection against these new pollutants is crucial. Furosemide is a good example of contaminants of emerging concern as a widely prescribed loop diuretic for the elderly, but also for younger adults and children, and in veterinary medicine, for almost 60 years. It is one of the most sold drugs in the world and considered essential by the World Health Organization. Many studies classify it as a priority pollutant based on its production, sale or consumption, its occurrence in the environment, its persistence in freshwater, its removal in WWTP or input in wastewater, its excretion rate and its toxicity or ecotoxicity. Indeed, a significant consumption of furosemide in medical institutions or by individuals has been noted, in particular in European countries. Furosemide can be metabolized or degraded in WWTPs with an average removal of over 50%. However, new processes or processes used for other purposes are being studied to obtain a better degradation of furosemide. Among the most efficient processes (>90%) are absorption processes on chitosan and on activated carbon, followed by oxidation processes such as ozonation, chlorination, electro-oxidation, photo-Fenton and reverse osmosis. The elimination of furosemide by fungi (*Trametes versicolor*) also seems promising. However, furosemide, like many other anthropogenic compounds including pharmaceuticals, still remains in treated WWTP effluents and significant concentrations can be discharged in the receiving water. Moreover, furosemide is degraded into several by-products, list of which is growing as progress is made in the development of highly sensitive analytical technologies enabling the detection of contaminants - including by-products - in the ng/L range. The best known is the glucuronide conjugate, but it is not of great concern because it is rapidly degraded. On the other hand, saluamine, pyridinium of furosemide, furfural, and certain products resulting from metabolization or photodegradation present a higher toxicity than the parent molecule. There are also new or simply little studied degradation products for which information on their toxicity is needed.

Furosemide is highly concentrated at sources such as hospitals and WWTP influents but also after treatment of these effluents for which

most studies are conducted in Europe. Furosemide is also found in WWTP sludges. Consequently, furosemide and its degradation products end up in the receiving environment. In river water, furosemide is found at a few hundred ng/L and has been observed in groundwater. It has also been reported in sediment. It is important to analyze the solid phases as well as the aqueous phase when evaluating the extent of furosemide contamination, as significant concentrations of this substance are present in both. By doing so, a more comprehensive understanding of the contamination can be obtained. Therefore, furosemide is widely present in the environment and could be a problem due to its occurrence and persistence in water. Although its acute toxicity is moderate, its chronic toxicity has been shown to be more important. Furosemide has hepatotoxic effects in rodents, cytotoxic and genotoxic effects in fish, and an estrogenic activity has also been demonstrated *in vitro*. In addition, its degradation products are more toxic for those of which we have information. Three of its degradation products are rather preoccupying, as the limited information available suggests that they have a more important acute toxicity than furosemide, affecting physiological parameters, growth and mitochondrial respiration. Furthermore, this could be also the case for some of the other identified degradation products, for which standards do not even exist, and for those remaining to be discovered to date. Unfortunately, there is a gap of knowledge about their fate in the environment. It is then absolutely necessary to continue the chemical, toxicological and ecotoxicological characterizations of these pollutants, and in a wider scope, those of pharmaceuticals and their degradation products. Non-targeted analytical chemistry approaches are a powerful tool to find new degradation products. Adverse outcome pathway (AOP) studies could be interesting approaches to understand the mechanisms of action of these new pollutants and multi-model approaches in ecotoxicology could lead to a better understanding of their off-target effects and the environmental risk for ecosystems.

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CRediT authorship contribution statement

Fidji Sandré: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. **Régis Moilleron:** Writing – review & editing. **Christophe Morin:** Writing – review & editing. **Laure Garrigue-Antar:** Conceptualization, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envpol.2024.123799>.

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