Diclofenac

in the Baltic Sea

Baltic Marine Environment
Protection Commission

Hazardous substances

BSEP n°170

Diclofenac in the Baltic Sea
– Sources, transport routes and trends

This report was written to support the update of the HELCOM Baltic Sea Action Plan (BSAP). The BSAP is a programme to restore good ecological status of the Baltic marine environment by 2021 and was adopted in 2007 by all the HELCOM Contracting Parties. The study addresses the thematic area "Hazardous substances".

It provides background information that is relevant in the process of evaluating the efficiency of currently implemented measures, and for suggesting additional measures, needed to achieve good environmental status in the Baltic Sea.

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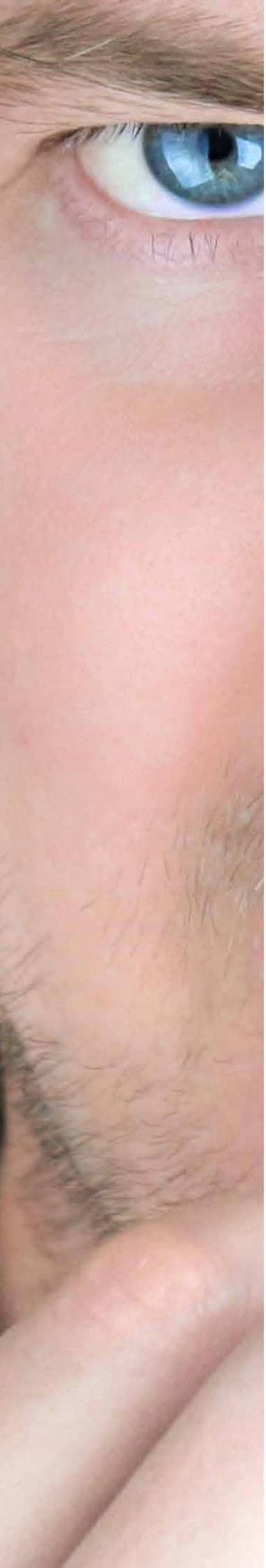
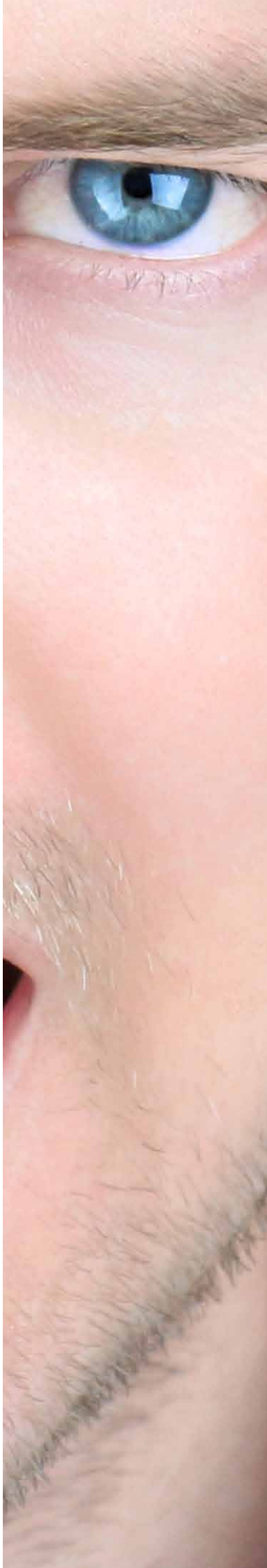


Content



Background

Diclofenac (2-(2,6-dichloranilino)phenylacetic acid) is an active pharmaceutical ingredient invented by a Swiss pharmaceutical company in 1973 (Lonappan et al., 2016). It is a non-steroidal anti-inflammatory drug (NSAID) used both in human and veterinary medicine. It is sold under various names (Lonappan et al., 2016; Vieno and Sillanpää, 2014) e.g. as shown in Table 1.

Acoflam	Dicloabac	Dolgit-Diclo
Algosenac	Diclo-denk	Eese
Almiral	Diclodoc	Effekton
Ana-Flex	Diclofenac-Asteria	Jutafenac
Anthraxiton	Diclofenaco Normon	Monoflam
Antiflam	Diclofenac-Ratiopharm	Motifene Dual
Arcanafenac	Diclofenbeta	Rewodina
Arthrex	Diclomex	Sigafenac
Arthrife	Diclowal	Volini
Arthotec	Dicuno	Voltaren
Diclabeta	Difen	Voltaren Emulgel
Didac	Diklotab	Votalin

Table 1. *Examples of medicinal products containing the active pharmaceutical ingredient diclofenac*

Diclofenac is infamous for its higher human cardiovascular risk compared to other NSAIDs (McGettigan and Henry, 2013; Schmidt et al., 2018) and the severe environmental consequences observed in e.g. India, Pakistan and Nepal where vulture populations have declined after feeding on carcasses of cattle treated with high doses of diclofenac (Oaks et al., 2004). Consequently, veterinary use of diclofenac is banned in India, Pakistan, Nepal and Bangladesh (Lonappan et al., 2016).

Photo: Artinun Prekmoung/Mostphotos

Diclofenac is also one of the most commonly measured and detected pharmaceuticals reported worldwide in WWTPs and environmental matrices (aus der Beek et al., 2016; UBA, 2019). A large share of the measurements are made in the EU, and most of the EU measurements in surface waters are from Germany (aus der Beek et al., 2016; UBA, 2019). Annual average Environmental Quality Standards (AA-EQS) for diclofenac in freshwater and marine waters have been proposed and updated several times since 2011, when the German UBA drafted the first EQS dossier. The threshold was originally 100 ng/L (freshwater) and 10 ng/L (marine), in a revised proposal from 2017 this EQS was set to 50 ng/L and 5ng/L in fresh and marine waters, respectively (UBA, 2017). An updated version of the EQS dossier is underway; the final EQS of diclofenac will be settled only when and if diclofenac is made a priority substance under the EU Water Framework Directive.

Globally, surface water concentrations are commonly below 100 ng/L, but levels in the low µg/L range are occasionally reported (Vieno and Sillanpää, 2014). In Pakistan, diclofenac concentrations of 8500 ng/L have been observed in waters receiving untreated wastewater and industrial effluents (reviewed by (Vieno and Sillanpää, 2014)). Diclofenac was included in the first Watch List under the Water Framework Directive in 2013, and has consequently been monitored in many waterbodies throughout Europe. The data gathered during the first Watch List monitoring (Loos et al., 2018) and other data sources during 2006 – 2016 show that diclofenac was quantified in 73% of all samples of surface water, and the median concentration was between 40 and 69 ng/L, depending on how concentrations reported as below the quantification limit were treated in the statistical analysis (UBA, 2017).

In Europe, model predictions have indicated that the proportion of European river length where concentrations exceed the first proposed annual average AA-EQS of 100 ng/L for inland surface water is ca 3% (EC, 2012), however in Germany the frequency of exceedance was predicted to be >10% (Johnson et al., 2013). This number is similar to the result of a Swedish screening study in 2012-2013 where 3% of inland water samples had diclofenac concentrations >100 ng/L, and in 30% of all samples, concentrations were in the range of 10-50 ng/L (Törneman et al., 2014). A compilation made by HELCOM of riverine concentrations in the Baltic Sea catchment show that mean concentrations in several countries are close to or exceeding the more recently proposed 50 ng/L threshold (Denmark 76 – 102, Estonia 61, Finland 23, Germany 170, Latvia 8.4 (max), Lithuania <10, Poland 94, Sweden 28-880 ng/L) (HELCOM, 2018).

Observations of diclofenac in marine waters are scarce. Diclofenac has been detected in several locations in the Baltic Sea, both in coastal and open waters (UNESCO HELCOM, 2017). Due to the short half-life of diclofenac in the environment (see p. 6), highest marine concentrations are expected in coastal areas. The highest diclofenac concentration in the Baltic Sea, reported in the first HELCOM data call, was 54 ng/L (in Germany) (UNESCO HELCOM, 2017), in the second data call (with data from 2014 – 2017) the highest reported concentration of diclofenac was 15.6 ng/L; the highest marine concentrations are observed in the southwest Baltic Sea (HELCOM, 2018). Examples of median observed concentrations of diclofenac in coastal sea water from scientific studies are 9.2 ng/L in the Baltic Sea (Germany 2009) and 4.6 ng/L in the Aegean Sea and Dardanelles (Greece and Turkey 2010 and 2011) (Nödler et al., 2014). More recently, concentrations in seawater in the range 1.4 – 16.3 ng/L have been reported from south of Greece (Alygizakis et al., 2016).

Due to the short half-life of diclofenac in the environment, highest concentrations are expected in coastal areas.

Photo: Hans Christiansson/Mostphotos

The status of diclofenac contamination in the Baltic Sea is uncertain (Figure 1). Diclofenac is a pre-core indicator tested by Helcom (HELCOM, 2018). The status assessment for this test-indicator is based on the more recently suggested threshold AA-EQS of 0.05 µg/L = 5 ng/L in marine waters. The threshold in biota is 1 µg/kg = 1 ng/g ww, corresponding to 0.007 µg/L = 7 ng/L (UBA, 2017). The Helcom assessment of diclofenac in water indicates that levels exceed the AA-EQS in several coastal locations, but not in open water. However, the detection limits of the methods used are in most cases exceeding the AA-EQS, making the assessment uncertain. Measurements in biota are scarce. Diclofenac has been detected in blood and urine in Swedish otters in levels of 0.16 – 0.82 ng/g ww and 0.052 – 0.23 ng/g ww, respectively (Roos et al., 2017). Human therapeutic plasma concentrations, for comparison, range from 420 ng/ml = 420 000 ng/L to >2000 000 ng/L. Fish exposed to water concentrations of about 82 000 ng/L water in a laboratory experiment had plasma concentrations of diclofenac of about 370 000 ng/L = 370 ng/ml ≈ 370 ng/g ww, whereas fish exposed to just 1600 ng/L had plasma concentrations of just below 10 000 ng/L = 10 ng/ml ≈ 10 ng/g ww (Cuklev et al., 2011). Thus, fish exposed to diclofenac in concentrations ca 1000 times higher than commonly measured in freshwater, had plasma concentrations of diclofenac in the low range of human therapeutic plasma concentrations, and ca 1000 times higher than plasma concentrations in the Swedish otters. Diclofenac has been analyzed but not detected in fish and bivalves along the Swedish coast (LOQ 10 ng/g) (Ek et al., 2019; Fick et al., 2014), in bivalves in Latvian freshwater (Ikkere et al., 2018) and in bivalves in the Gulf of Gdansk (Caban et al., 2016).

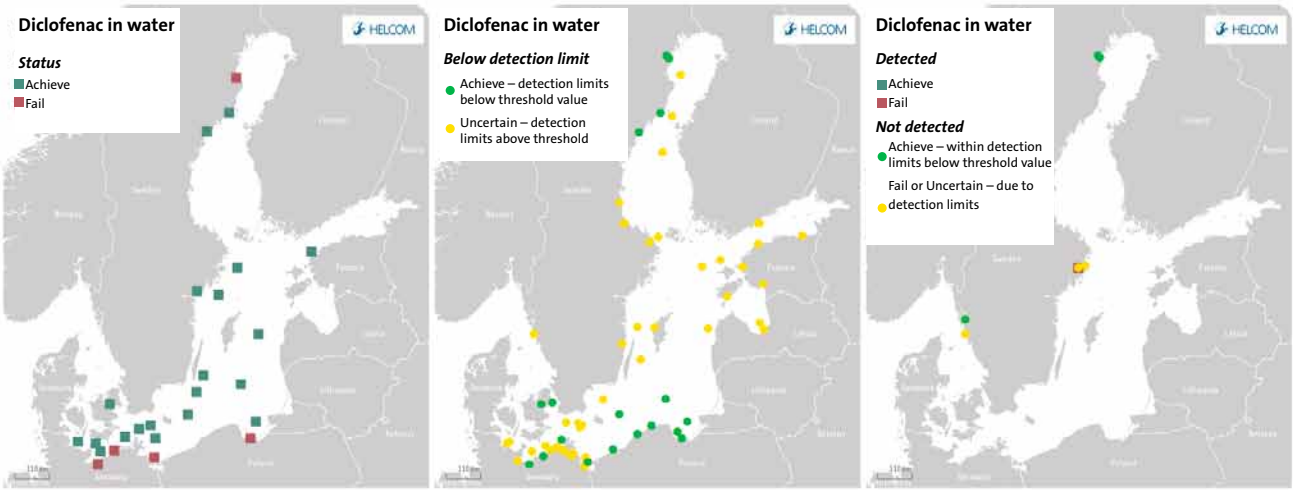


Figure 1. *HELCOM Status assessment for diclofenac. From web-page (as viewed 161019) http://stateofthebalticsea.helcom.fi/pressures-and-their-status/hazardous-substances/#1530549884208-3b50f876-b3c0*

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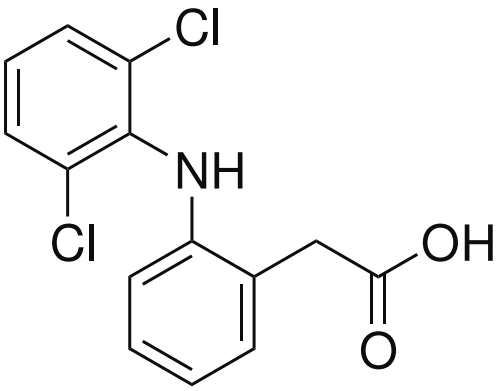


Figure 2. *Molecular structure of diclofenac.*

Diclofenac (Figure 2) is a weak acid with a pKa of 4.15, and is largely dissociated at environmentally relevant pH (median pH in European rivers is 7.8, but lower in Scandinavia, median in Sweden is 7.0) (UBA, 2017). The fraction of ionic and uncharged form depends on pH and therefore the bioaccumulation potential varies with pH. Only the uncharged form partitions passively over biological membranes. Log KOW of the neutral species is 4.51, however log D (i.e. the distribution coefficient which indicates the apparent partition coefficient accounting for both ionic and neutral species) is ca 2.25 at pH 6 and decreases to 0.75 at pH 8 (Avdeef et al., 1998). For unknown reasons, the bioconcentration factor (BCF) of diclofenac appears to be concentration dependent (lower at higher concentrations) as reported in some studies referred to in the 2017-version of the diclofenac EQS dossier (UBA, 2017). Potential explanations are that diclofenac affect the gills and thereby the gill-uptake, and alternatively that higher concentrations of diclofenac might induce metabolism of the substance resulting in more efficient elimination (UBA, 2017) or complete saturation of tissues by diclofenac at the highest concentrations (Schwaiger et al., 2004). The whole body BCF was estimated from BCFs measured for individual organs to 147 at a water concentration of 0.007 µg/L (i.e. QSbiota) (UBA, 2017). The whole body BCF measured in mussels exposed to 1 µg/L was 180 (UBA, 2017). These values are above the trigger value for an assessment of secondary poisoning (i.e. BCF>100) in These values are above the trigger value for an assessment of secondary poisoning (i.e. BCF>100) in the

Diclofenac is not likely to bioaccumulate in aquatic food webs.

Photo: Mysak/Mostphotos

Photo: Anna Jaeger/IGB Berlin

Both laboratory experiments and field studies indicate that diclofenac is susceptible to photodegradation and biodegradation.

guidance for derivation of EQSs (Guidance Document No: 27 Technical Guidance For Deriving Environmental Quality Standards), but considerably lower than the threshold set in most contexts to define a bioaccumulative substance (e.g. REACH B-criteria is BCF > 2000). From a scientific perspective, a chemical with BCF < 5000 and log KOW < 5 shows a lack of potential to biomagnify in water-respiring organisms, and hence likely pose little risk to appear in high concentrations in top predators due to aquatic food chain bioaccumulation (Gobas et al., 2009).

Diclofenac is water soluble with only moderate removal efficiencies in WWTPs. The variability is however large, the removal efficiency has been estimated to be on average 36% in conventional activated sludge treatment and nearly 50% in membrane bioreactors (Vieno and Sillanpää, 2014). Other estimates of removal efficiencies in conventional WWTPs are 25 – 43% with a mean removal of 34% (Kehrein et al., 2015) and in another study the removal efficiency was 10-20% (Falås et al., 2012). In rivers, observed attenuation (disappearance from water column) of diclofenac was about 15-60% along a 6-12 kilometer stretch downstream of a WWTP (Li et al., 2016). A high susceptibility to photolysis in laboratory experiments and in the environment is generally observed (Buser et al., 1998; Kunkel and Radke, 2012), but also biodegradability has been reported. Radke and Mayer found half-lives of diclofenac to vary between 9 and 29 days in bottle experiments using river sediment and water, whereas no dissipation was observed in incubations with sediment from a small creek in Sweden (Radke and Maier, 2014). In another study based on the same type of experiments, following the OECD 308 guideline, half-lives of 25 ±9 days (average, stdev) for diclofenac were observed (Coll et al., n.d.). In both studies, experiments were carried out in darkness, excluding photolysis. In flume mesocosms, that are used to better simulate environmental conditions, diclofenac dissipated within one day. The faster dissipation in the flume experiments may at least partly be explained by that they were carried out in daylight, thus including some photolysis (Posselt et al., 2020). Degradation in the environment depends on several environmental factors including shading, nutrient conditions, turbidity, exchange between surface water and the hyporheic zone (Kunkel and Radke, 2012), bacterial community in the sediment (Coll et al., n.d.; Posselt et al., 2020) and attenuation is therefore not easily predicted (Li et al., 2016).

Sources and pathways to the Baltic Sea

Diclofenac may enter the environment from facilities of pharmaceutical companies (R&D, manufacturing), after use as human or veterinary medicine, or by disposal of excess/expired medicine in sewers or landfills (Lonappan et al., 2016). Maximum concentrations of diclofenac observed in the environment often occur downstream WWTPs in urban areas, and although studies of surface water concentrations of pharmaceuticals rarely report emission sources (as these are not assessed), urban wastewater appears to be the dominant emission pathway globally (aus der Beek et al., 2016). The main source of diclofenac in the Baltic Sea aquatic environment is most likely emissions due to human use followed by excretion and transport in wastewater through municipal WWTPs and subsequent emissions via effluents as discussed in the following sections.

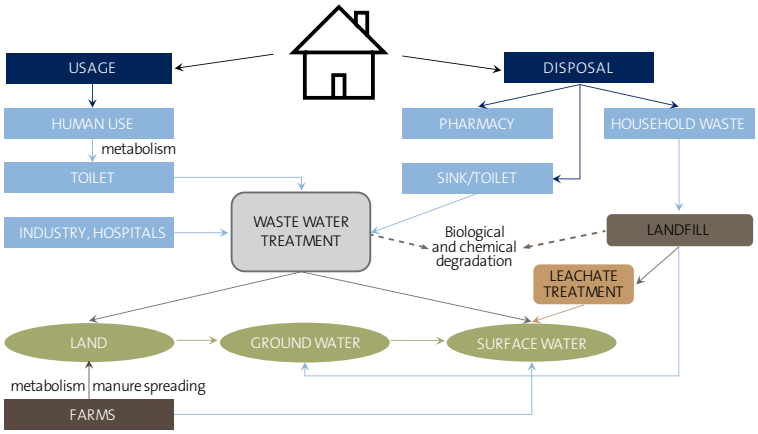


Figure 3. *Main sources and pathways of pharmaceuticals to the environment, from (UNESCO HELCOM, 2017).*

Diclofenac may be emitted to the environment in several stages of the manufacturing process. In the Baltic Sea region this is however likely a minor source.

Photo:Dotshock/Mostphotos

Emissions from production

Emissions from production sites is a potential source of diclofenac in the Baltic Sea environment. There are pharmaceutical manufacturing plants in the Baltic Sea countries, but information about emissions are not available (UNESCO HELCOM, 2017). Although research and development within the pharma industry is mostly performed in developed countries, the manufacturing of active pharmaceutical ingredients (APIs) takes place mostly in non-European countries (BIO Intelligence Service, 2013). Tracking production sites of pharmaceuticals is complex. The API can be purchased by pharmaceutical companies from several subcontractors, as there is a need to secure the availability of the substance (Therese Ringbom, Swedish Medical Products Agency, personal communication). The API manufacturers that have applied for certificates for diclofenac (which is not mandatory, however facilitates business) from the European Directorate for the quality of medicines and health care (EDQM, https://extranet.edqm.eu/publications/Recherches_CEP.shtml, site accessed 2019-08-30) are located in Italy, Taiwan, Spain, China and India.

Diclofenac may also be emitted during later stages of the manufacturing process, e.g. production of the medical products from active substances and packaging. In Sweden, for example, there are 166 manufacturers and importers of pharmaceuticals (Therese Ringbom, Swedish Medical Products Agency, personal communication), to what extent emissions occur in the Baltic Sea region from these stages of the product life cycle is however unknown.

Emissions due to incorrect disposal

A widely discussed source of pharmaceuticals in the environment is improper disposal of unused medicines. The fate of unused medicines is variable depending on country (with different regulations, recommendations, take-back systems, awareness in the population, level of connection to municipal sewage systems), type of residents (town, countryside), formulation (liquid or not), type of pharmaceutical (used at home or in hospitals) etc. A systematic review of studies assessing this issue found that worldwide, disposal in the household garbage seems to be the most common method (Kusturica et al., 2016). Disposal into the sewage is also common, in particular for liquid dosage forms (Kusturica et al., 2016). There are however large differences between and within countries. The systematic review study included results of interview studies from three HELCOM countries published between 2007 and 2009: Lithuania, Sweden and Germany (Table 2). Whereas town residents in Lithuania mainly dispose of unused medicines in the rubbish bin, 50% of countryside residents burn unused drugs with other household waste (backyard burning). In Sweden, the majority of unused medicines are either stored in the homes or returned to pharmacies, and not disposed of in the toilet or sink. The Swedish take-back system dates back to 1971, which contributes to its well-functioning. In Germany, 10% of the interviewed persons state that they always flush down liquid medication, but otherwise returning to pharmacy and the rubbish bin are the main disposal methods, and in addition disposal at recycling centers (Kusturica et al., 2016).

Photo: Gopixa/Mostphotos

The fate of unused medicines varies between different countries.

METHOD OF DISPOSAL OF UNUSED PHARAMACEUTICAL							
		Return to pharmacy	**Rubbish bin**	**Store medicines in home**	**Flush down**		**Backyard burning**
Sweden		43%	3%	55%			
	town	3%	89%		8%		2%
Lithuania	suburb		87%		6%		13%
	countryside		50%				50%
		Return to pharmacy	**Rubbish bin**		**Flush down soild**	**Flush down liquid**	
	always	29%	7%		1%	10%	
	usually	11%	9%		2%	8%	
Germany	sometimes	15%	14%		7%	13%	
	rarely	11%	13%		6%	12%	
	never	34%	57%		84%	57%	

Table 2. *Method of disposal of unused pharmaceuticals. Summary of interview results from studies reviewed in (Kusturica et al., 2016). Percent of respondents.*

Photo: LightRoom/Mostphotos

Information on how much diclofenac that is incorrectly disposed of in HELCOM countries is not available.

More recent information on incorrect disposal of pharmaceuticals is available in the UNESCO/HELCOM Pharmaceuticals report from 2017 (UNESCO HELCOM, 2017). This report demonstrates that the approach taken to handle pharmaceutical waste differs between the HELCOM Contracting Parties. Estonia and Finland both classify pharmaceuticals as hazardous waste and report amounts of pharmaceuticals collected. Sweden defines only certain pharmaceuticals as hazardous waste, however producers are responsible for arranging take-back of all other pharmaceuticals and destruction. These three countries also provide some numbers of amounts collected, however comparing these numbers is not straightforward. The amount of pharmaceuticals returned to pharmacies per inhabitant appears higher in Sweden compared to Finland (ca 80 and 30 g/person and year, respectively, including weight of packaging). Finland estimates that the amounts of pharmaceuticals in general disposed incorrectly as solid waste and via sewers are similar, however considerably lower than the amounts properly collected. Russia reports that most pharmaceuticals end up in landfills and municipal sewage systems. Germany reports that pharmaceutical waste is handled at local level, and that the most common disposal methods are household rubbish bins, collection at local recycling centers with responsibilities for hazardous waste and returning to pharmacies (UNESCO HELCOM, 2017).

Information on how much diclofenac that is incorrectly disposed of in the Helcom countries is hence not available. As disposal of pharmaceuticals in the toilet or sink is more common for liquid medicines, this may not be a common practice for diclofenac, which is sold mainly as creams, pills and suppositories. A case study from St Petersburg Russia indicated that the major part of sold diclofenac is distributed via pills (HELCOM, 2018). It is however notable that a comparatively low fraction of diclofenac is excreted from the human body in unchanged form or as easily hydrolysable conjugates (see section on excretion below), making even small amounts of diclofenac flushed down the drain correspond to a large amount of ingested diclofenac. It is also conceivable that diclofenac

is often stored in homes (as common in Sweden for pharmaceuticals in general (Persson et al., 2009)) as this is, in several countries, an over the counter painkiller that people may take now and then, in addition to as part of a treatment schedule. A study from the UK showed that 80% of people consume all painkillers they buy (Bound and Voulvoulis, 2005).

Various studies indicate that incorrect disposal of pharmaceuticals in rubbish bins is a common practice. This may not be a problem if the municipal trash is incinerated. Diclofenac degrades at less than 200 °C (Giordano et al., 2003). The Industrial Emission Directive (2010/75/EU) Article 50 requires temperatures of the gas in waste incineration plants to reach at least 850 °C for 2 seconds.

If waste that contains pharmaceuticals is landfilled, these substances may be released via landfill leachate. In Sweden and Germany, less than 1% of the municipal waste is landfilled. In Lithuania however, 33% of the waste is landfilled according to Eurostat (Eurostat, 2019). Poland is the EU-member in HELCOM with the largest fraction of municipal waste landfilled (42%), and in addition the largest absolute amount due to the large population (see Figure 4). Diclofenac has been found in the ng/L to µg/L range in landfill leachates in e.g. Asia (Qi et al., 2018) and landfill leachates have been recognized as sources of groundwater contamination of many chemicals. Diclofenac, however, which is one of the most commonly analyzed pharmaceutical, has a low detection rate (1%) in groundwater according to a recent assessment of monitoring data from European countries (Lapworth et al., 2018). It can also be noted that the EU defines technical requirements for waste and landfills in Directive 1999/31/EC to prevent emissions to the environment. In a Swedish study, pharmaceuticals were analyzed in landfill leachates from two sites and although levels of ibuprofen (420 and 780 ng/L) were in the same range as in WWTP effluents, diclofenac concentrations in leachates (10 and 20 ng/L) were ca 10 – 100 times lower than concentrations measured in WWTP effluents in the same region (Wärnersson and Larsson, 2007). Considering that the volume of landfill leachate is very small compared to the volume of WWTP effluents, this source can be considered negligible.

Photo: OpticOptic/Mostphotos

Incorrect disposal of pharmaceuticals in rubbish bins is a common practice.

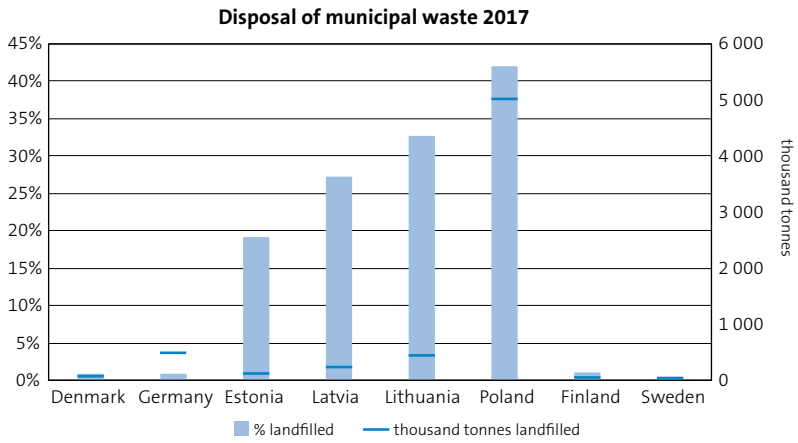
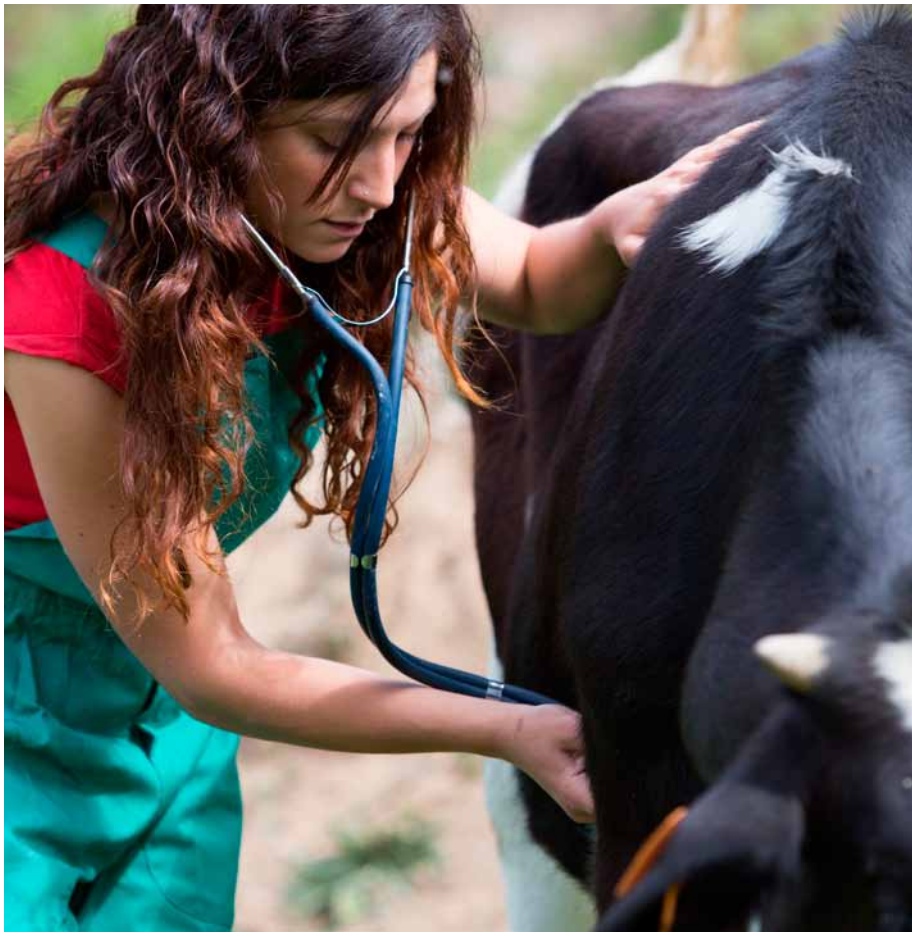


Figure 4. *Amount and fraction of municipal waste landfilled in HELCOM EU-member states. Data from Eurostat for year 2017 (Eurostat, 2019). Left axis shows percentage landfilled and right y-axis thousand tons landfilled.*

Photo: Shutterstock



Diclofenac is authorized for veterinary use in Estonia and Latvia, however likely used in small amounts.

Emissions due to veterinary use

Veterinary use leading to emissions to soil or wastewater is another potential source of diclofenac in the environment. Diclofenac is authorized for veterinary use in Estonia for cattle, pigs and horses and in Latvia for horses only (EMA, 2014). The veterinary medicinal products is called Reuflogin and is used for reduction of inflammation and fever in diseases of the respiratory system, the urogenital system and mammary gland and musculoskeletal disorders (EMA, 2014). For the purpose of writing the current report, the HELCOM secretariat requested information regarding veterinary use of diclofenac from the HELCOM Contracting Parties. Information was provided by Sweden, Estonia, Latvia and Poland. No information from other Contracting Parties has been submitted. In Sweden, there is no marketing authorization for diclofenac as veterinary medicinal product. However, veterinarians may prescribe human medicines to animals but there are no indications that this occurs (Therese Ringbom, Swedish Medical Products Agency). Estonia confirms that Reuflogin is used as veterinary medicine, but does not report on amounts used (Martin Ott, Department of the Marine Environment). Latvia reports authorization of Reuflogin solution for injections, however last import was in 2012 and then only 6 packages (Anete Kubliņa, Latvijas Vides, ģeoloģijas un meteoroloģijas centrs LVGMC). Poland confirms that no veterinary medicinal products containing diclofenac are on the Polish market (Agata Święcka, Ministry of Maritime Economy and Inland Navigation). This information indicates that veterinary use is likely a negligible source of diclofenac emitted in the Baltic Sea region.

Emissions due to human use

The major emission route for pharmaceuticals in the environment is generally believed to be via human excretion after consumption (UNESCO HELCOM, 2017). Pharmaceuticals are eliminated from the human body after complete or partial conversion to water-soluble metabolites or as unchanged parent compounds (see e.g. overview in (Vieno and Sillanpää, 2014)). Metabolites that are hydrolysable conjugates are often rapidly converted back (hydrolyzed) to parent compounds in the sewers. The fraction orally administered diclofenac that is excreted as unchanged drug or as hydrolysable conjugate (i.e. that contributes to diclofenac concentrations in wastewater) is ca 0.17 (Kehrein et al., 2015; Khan and Ongerth, 2004), meaning a large fraction of the total sales volume does not reach the sewers but are biotransformed in the human body (Falås et al., 2012). The corresponding excretion rates of other NSAIDs such as ibuprofen and naproxen are 0.25 and 0.7, respectively (Saunders et al., 2016). When diclofenac is administered topically in the form of a cream, ca 6-7% of the active ingredient is absorbed through the skin (Davies and Anderson, 1997), the remainder is washed off the skin or adsorbed to the clothing, and hence a large fraction of diclofenac in creams does not pass though the human body, and may thus end up in the WWTP. A case study from St Petersburg indicates that ca 170 kg diclofenac is applied on skin out of ca 700 kg consumed in total (HELCOM, 2018). If all topically administered diclofenac washed off from the skin or attached to the clothing would reach the wastewater (via showers and washing machines), a rough estimation based on these numbers is that ca 60% of all diclofenac reaching the St Petersburg WWTPs would originate from cream formulas, although this form of diclofenac represents a lower fraction of the total consumed mass. It is thus plausible that a large fraction of dermally applied diclofenac will reach the sewers via washing machines and showers.

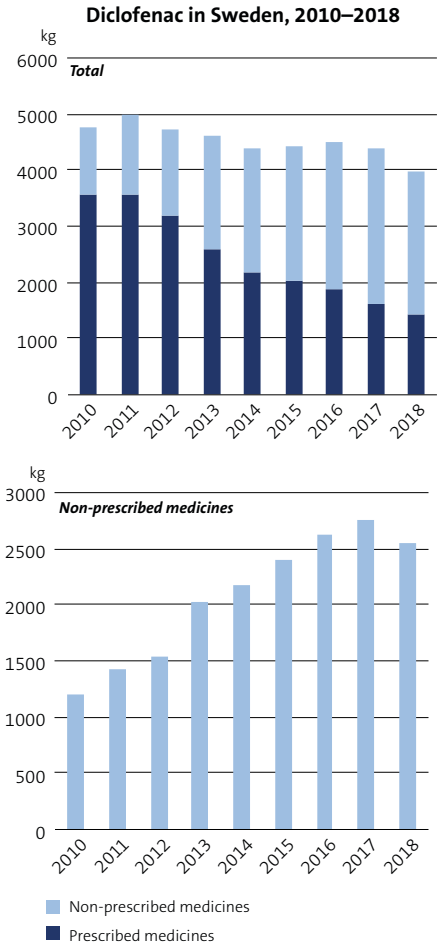


Figure 5. *Sold diclofenac in Sweden 2010-2018 in kg, in total (top) and in non-prescribed medicines (bottom). Note that the graphs show the same data for non-prescribed medicines, and that the use of non-prescribed diclofenac increased between 2010 and 2017.*

The reported mass includes all forms of diclofenac (pills, gels, etc.). In 2018, 70% (1800 kg) of the non-prescribed mass was sold in products for topical use (gels, spray, plasters). The mass was calculated from number of sold packages and data on amount API per package. Data provided by Therese Ringbom, Swedish Medical Products Agency. Population in Sweden 2018 was ca 10 million people.

Time trends

Sales and human consumption

Diclofenac is one of the most sold painkillers globally (Lonappan et al., 2016). The use of diclofenac in comparison to other NSAIDs varies in different countries. A study from 2013 including 15 high/middle/low income countries globally showed that diclofenac represented ca 30% of sold NSAIDs defined daily doses (DDD), i.e. more than the sold daily doses of ibuprofen, mefenamic acid and naproxen together (McGettigan and Henry, 2013). Information on estimated sold masses of pharmaceuticals (active pharmaceutical ingredients) in the Baltic Sea region show that diclofenac appears to be the 15th most sold human drug (UNESCO HELCOM, 2017). The data were from five HELCOM countries (Estonia, Finland, Germany, Russia, Sweden), and show that the share of NSAIDs sales reported in mass was for ibuprofen 83%, naproxen 11% and diclofenac 6% (out of the top 3 NSAIDs) (UNESCO HELCOM, 2017). Converted to DDDs (DDDs for diclofenac = 0.1, ibuprofen 1.2 and naproxen 0.5 g according to WHO at https://apps.who.int/medicinedocs/en/d/Js4882e/8.6.html), the share of top 3 NSAIDs total DDDs is instead 38% diclofenac, 47% ibuprofen and 15% naproxen. Diclofenac is hence the second most commonly sold/used NSAID in these countries, although the consumed mass is considerably lower than for ibuprofen and naproxen due to a lower recommended dose of the active ingredient.

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Emissions to wastewater after human use is the major source of diclofenac in the Baltic Sea.

Diclofenac is a popular over the counter drug in many countries but is also commonly prescribed. However, it has been shown that diclofenac has lower cardiovascular safety compared to other NSAIDs and cardiovascular risks similar to another NSAID that has previously been withdrawn (Fosbøl et al., 2010). The information on the risks has been available to regulators since the mid 2000's (McGettigan and Henry, 2013). Stable or slightly declining numbers of prescriptions were observed in England, Australia and Canada between 2006 – ca 2011 (McGettigan and Henry, 2013). Also in Sweden, the sold amount of prescribed diclofenac has declined during 2010 – 2018 (Figure 5). This decline has however largely been compensated by increased sold amounts non-prescribed over the counter (Figure 5).

Several Baltic Sea countries publish information regarding consumption of pharmaceuticals given in defined daily doses (DDD)/1000 inhabitants/day (Figure 6). DDDs are defined for each ATC code in the WHO Anatomical Therapeutic Chemical Classification System. According to WHO, the DDD is "the assumed average maintenance dose per day for a drug used for its main indication in adults" (https://www.whocc.no/ddd/definition_and_general_considera/). One DDD is assigned per ATC code and route of administration. Note that no DDD is defined for topical products, and hence any reported consumption expressed in DDDs does not include use of gels and creams containing diclofenac. For human use of diclofenac there are six different ATC codes, since there are several strengths and routes of administration with different therapeutic uses (https://www.whocc.no/atc/structure_and_principles/). However, only the ATC codes M01AB05 and M01AB55 (combination products) are assigned with a DDD, for both codes the DDD is 0.1 g (see online database https://www.whocc.no/atc_ddd_index/ , accessed 311019).

Photo: Voy/Mostphotos

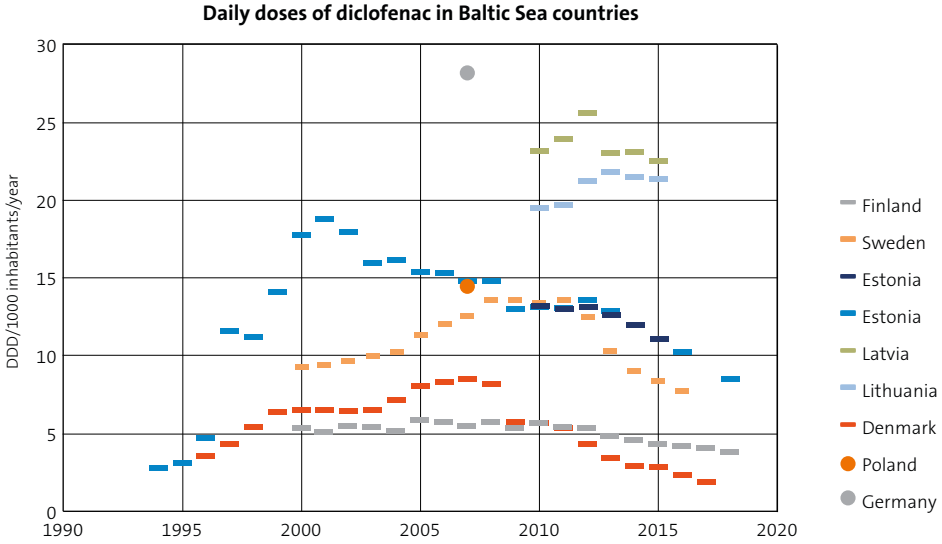

Figure 6. *Defined daily doses (DDD)/1000 inhabitants/year for Baltic Sea countries. The ATC codes included are given below. The ATC code that contributes the majority of the total DDDs in all countries is M01AB05. For Estonia, data were available from two different sources that differed slightly. Note that topical use of diclofenac (e.g. in gels) is not included as these applications lack a DDD.*

Data sources		
Finland	M01AB05 + M01AB55	http://raportit.nam.fi/raportit/kulutus/laakekulutus_e.htm
Sweden	diclofenac	Kristensen et al. 2019 (Kristensen et al., 2019)
Estonia	MO1AB05+MO1AB55	http://www.ravimiamet.ee/en/statistics-medicines (Statistical Yearbooks)
Latvia	MO1AB05+MO1AB55	http://www.ravimiamet.ee/en/statistics-medicines (Baltic Statistics on Medicines)
Lithuania	MO1AB05+MO1AB55	http://www.ravimiamet.ee/en/statistics-medicines (Baltic Statistics on Medicines)
Estonia	MO1AB05 + MO1AB80 diclofenac+misoprostol + M01AB82 diclofenac+ omeprazole(O)	http://www.ravimiamet.ee/en/statistics-medicines (20 Years of Statistics on Medicines in Estonia)
Denmark	M01AB05+M01AB55	http://www.medstat.dk/en#tabs-0
Poland	diclofenac	Schröder et al. 2016 (Schröder et al., 2016)
Germany	diclofenac	Schröder et al. 2016 (Schröder et al., 2016)

The trends in DDDs/1000 inhabitants for diclofenac appear to be declining for all countries during the last few years. Note however that Figure 6 does not include topical use of diclofenac; diclofenac gels can be bought in all European countries without prescription (Therese Ringbom, Swedish MPA). In Sweden, the mass of diclofenac sold as topical products was ca 1800 kg out of nearly 4000 kg sold in total in 2018 (Therese Ringbom, Swedish MPA). For Estonia and Denmark the declining trend in DDDs/1000 inhabitants/year for oral applications can be seen several years back in time. In Estonia, a prescription is required for many diclofenac products since 2007 (Lember et al., 2016), however pills with low dose can be purchased without prescription in pharmacies. Little information is available on consumption in Poland, where diclofenac containing medicines can be bought also in e.g. grocery stores, but seems to be similar to the Estonian and Swedish levels of consumption. Finland and Denmark (where orally administrated diclofenac is not sold without prescription) appear to have a comparatively low per capita consumption, whereas Germany, Latvia and Lithuania have higher consumption. It is notable that many environmental samples with reported

high concentrations of diclofenac are from Germany (see e.g. monitoring data from 2016 https://www.umweltbundesamt.de/en/topics/water/rivers/active-pharmaceutical-ingredients-api#textpart-1), where the per capita and absolute consumption of diclofenac also appears to be in the high end of the observed range for HELCOM countries. Diclofenac for oral use can be bought without prescription in German pharmacies, and a rising use of non-prescribed painkillers in general has been observed in Germany (Sarganas et al., 2015). Observed concentrations in Latvian and Lithuanian inland waters are comparatively low despite a high per capita consumption; however, the number of data points on environmental occurrence for these countries is low and several factors can potentially explain low concentrations such as the population density, time of year for sampling, where the samples were collected, hydrological factors etc.

The total sales of diclofenac (excluding topical use) during years 2000 - 2016, expressed in DDD/1000 inhabitants/year, has recently been assessed for the five Nordic countries (Kristensen et al., 2019). Total NSAID sales, which thus includes other products than those containing diclofenac, increased in all countries during this time period: in Sweden by 48%, in Finland by 24%, and in Denmark by 2%. Sales of diclofenac however decreased in Sweden by 16%, in Finland by 20% and in Denmark by 64%. Oral formulations of diclofenac is sold only by prescription in Finland and Denmark, in Sweden 33% of total sales are over the counter (Kristensen et al., 2019). It has recently been announced that oral applications of diclofenac will require a prescription in Sweden after 2020 due to the human health risks. The authors of the Nordic study noted that prescribed diclofenac decreased in Denmark 2008–2009, and this was likely due to a Danish study of human health hazards of diclofenac, which was widely reported in media, and the subsequent action by the Danish Medicines Agency that withdrew the authorization to sell diclofenac over the counter (Kristensen et al., 2019). Note that at the same time in Sweden (year 2009), some non-prescribed drugs, including diclofenac for topical use, became available for sale in grocery stores etc. (see e.g. https://lakemedelsverket.se/malgrupp/Apotek--handel/Recept-fritt-i-affarerna/Listor/). Swedish prescriptions of diclofenac decreased (and naproxen prescriptions increased) when diclofenac was replaced by naproxen on the Wise List, which is a list for recommended essential medicines for common diseases in patients in the Stockholm County Council, in 2012 (Kristensen et al., 2019). No warning regarding diclofenac was issued by Nordic national medicine agencies (except in Denmark) until 2013 (Kristensen et al., 2019). Warnings from the European Medicines Agency have been issued in 2005 and 2013, the European Society of Cardiology recommended to stop use of diclofenac in 2016 (Kristensen et al., 2019). The authors of the Nordic study recommend education and active dissemination of guidelines and changes in reimbursement systems to promote prescription of other NSAIDs, and stricter regulations of over the counter sales. Note that this study does not discuss diclofenac sales of products intended for topical use, and hence the reductions in total diclofenac sales may be overestimated. In fact, the sales of non-prescribed diclofenac increased in Sweden 2010 – 2017 (Figure 5) and a large fraction of this is in the form of gels/creams (70% in 2018).

Photo: Sten-Åke Stenberg/Mostphotos

In addition to actions taken to reduce consumption of diclofenac to protect human health, a few actions are taken due to environmental concern that may explain declining use. It can be noted that the discovery of the link between diclofenac and vulture extinction in Asia (Oaks et al.,

2004) in the mid 2000's has given the substance a bad reputation long before diclofenac was eventually suggested as a priority substance under the WFD in 2013. This proposal was however declined and diclofenac was instead put on the WFD Watch List in order to get more monitoring data on environmental occurrence of diclofenac. The data generation under the Watch List is considered sufficient (Loos et al., 2018), and a decision regarding diclofenac's status as a priority substance or not is underway. However, the process is currently stalled due to other priorities of the European Commission (e.g., the Fitness Check of the WFD). No EU-wide regulation of this over the counter drug is currently in place. HELCOM has requested information regarding any national measures to reduce emissions of diclofenac in the member countries, however there appears to be few measures implemented except for monitoring, and the Swedish and Danish measures mentioned above.

Emissions from WWTPs

Average effluent concentrations of diclofenac reported in the scientific literature are highly variable and are commonly in the range of 2 ng/L to 2500 ng/L with maximum concentrations 120 – 4700 ng/L (reviewed by (Vieno and Sillanpää, 2014)). Diclofenac metabolites are also present in high (several hundreds of ng/L) levels. The UNESCO/HELCOM Pharmaceuticals report from 2017 describes a compilation of data provided by HELCOM Contracting Parties (UNESCO HELCOM, 2017). In this dataset, average concentrations of diclofenac in WWTP effluents were reported to be approximately 1000 ng/L (this was the 14th highest average concentration in effluents in the dataset), with maximum diclofenac concentrations reported exceeding 10 000 ng/L. Another more recent HELCOM data call on pharmaceuticals in WWTP effluents showed that the average concentration was 2510 ng/L (max 17200 ng/L)(CWPharma project, 2019).

Few time trend analyses of diclofenac in WWTP effluents in the Baltic Sea region have been published. Loads of several pharmaceuticals including diclofenac in effluents have been calculated for the Swedish WWTP Ryaverket in Gothenburg for the years 2006 – 2015 (Paxéus et al., 2016). The authors attributed the observed tendency of increasing loads over this time period to advertising and consequently increasing topical use of diclofenac, however without providing support for this theory. The authors also noted that the availability of many non-prescribed pharmaceuticals has increased in Sweden since 2009 when selling these products outside the pharmacies was allowed (Paxéus et al., 2016).

Environmental concentrations

No clear long-term temporal trends at European level can be discerned in the data deriving from the Watch List monitoring, although the highest mean concentrations in freshwater and marine waters were apparently observed ca 2011-2012 (Loos et al., 2018; UBA, 2017). Monitoring of diclofenac in the German River Rhine between 1997 and 2006 showed no clear trend, which was consistent with the constant prescription numbers during this time period (Sacher et al., 2008). The temporal variation observed was large, and not clearly related to average water flows in the river (Sacher et al., 2008). Large variations in measured concentrations at the same station at different time points were also observed in a Swedish screening campaign with water sampled in autumn 2012 and spring 2013.

Several factors strongly influence the environmental concentrations of diclofenac, which are highly variable over space and time. Concentrations of diclofenac in river water exhibit seasonal patterns. Lower surface water concentrations during summer months, as observed in the European dataset from the Watch List monitoring (Loos et al., 2018), can be expected due to higher light intensity leading to faster photodegradation (Buser et al., 1998), low flow conditions and potentially seasonal variations in emissions.

Mean measured concentrations in Polish rivers that were about 2-5 times lower in summer than in winter have been reported in 2016 (HELCOM, 2018). Significantly lower concentrations in summer have also been observed in Rhine, where the highest concentrations were observed during January – March and the lowest July - September (Sacher et al., 2008). In addition, the transport of diclofenac in the Rhine was lower from April to September, a pattern that has been observed also in Sweden (Daneshvar et al., 2010). The authors of the German study did not attribute the increased river transport in winter to higher use (as prescriptions were constant over seasons) or variations in water flow (as concentrations also increased in winter), but hypothesized that the removal efficiency in WWTPs was seasonally varying (Sacher et al., 2008). The authors of the Swedish study attributed the higher winter transport to lower transformation; sales statistics of diclofenac in the region did not show seasonal variation (Daneshvar et al., 2010). A French study of seasonality in riverine diclofenac concentrations suggests higher removal during low flow (i.e. summer) conditions due to increased residence time and temperatures (Aminot et al., 2016). Decreasing diclofenac concentrations can also occur due to a higher percentage of effluent in the river at low flow conditions (Kunkel and Radke, 2012). It is hence important to consider what time of year that the sampling was conducted when comparing analyses of diclofenac in the environment.

The spatial and temporal variation of diclofenac concentrations has been assessed in several modeling studies. Concentrations of diclofenac in river networks are highly variable due to location of WWTPs and dilution factors as illustrated by two modeling studies of diclofenac in the Ruhr (Germany) and Tamar (UK) catchments (Johnson et al., 2007; Kehrein et al., 2015). Concentrations in the river networks increase sharply downstream WWTPs, and are effectively diluted when tributaries with less contaminated water flows into the main river, and photolysis causes a steady decline in between point sources along the river (Kehrein et al., 2015). Models also predict that the temporal variability is large due to variations in flow conditions and emissions, meaning diclofenac levels below and above the EQS are observed and/or predicted in the same river stretch at different time points (Kehrein et al., 2015; Wallberg et al., 2016).

Conclusions

The major source of diclofenac to waterways in the Baltic Sea region is emissions via municipal wastewater treatment plants. A large fraction of ingested diclofenac is transformed in the human body, but due to high amounts used the mass that reaches the sewers is significant and concentrations are high compared to several other pharmaceuticals. A relatively large proportion of diclofenac in wastewater may originate from topical use as the major fraction of the dermally applied dose does not pass

through the body and is therefore not transformed. The importance of this pathway for diclofenac through WWTPs to the Baltic Sea however needs more investigation. The removal efficiency of diclofenac in conventional WWTPs is variable, but moderate (in general 20-40%).

Diclofenac is not used as a veterinary medicine in most Baltic Sea countries, and the volume used where this is practiced appears low. Veterinary use should therefore not be an important source of diclofenac to the environment.

Incorrect disposal of diclofenac is difficult to assess, but incorrectly disposed diclofenac may in many cases end up in municipal waste that is either incinerated or landfilled. Since diclofenac is usually not sold in liquid formulations, it is less likely to be deliberately flushed down the drain. Landfill leachates are not likely to be a significant source of diclofenac in waterbodies in the Baltic Sea region in general.

The consumption of diclofenac in pills has declined or stabilized in most Baltic Sea countries in recent years. This is probably due to the human health hazards related to diclofenac consumption that have been highlighted both nationally and at European level, and led to recommendations to substitute diclofenac-based pharmaceutical products by safer alternatives, although this may mainly have had an effect on prescribed diclofenac. It is not clear how non-prescribed sales are influenced by these measures. In Sweden for example, the sales of non-prescribed diclofenac have increased since 2010. There are large national differences in the per capita use of orally administered diclofenac, with Germany, Latvia and Lithuania having a particularly high use. Time trends in consumption of non-prescribed diclofenac and diclofenac in formulas for dermal use are current knowledge gaps.

Observed concentrations of diclofenac are highly variable, making status assessments uncertain. For inland waters, the dilution factors and locations of WWTPs influence concentrations in rivers. A seasonality in riverine concentrations is commonly observed, with higher concentrations in winter. Reported concentrations in freshwater in HELCOM countries are commonly in the range of the proposed EQS of 50 ng/L, and reported concentrations in sea water are also in many cases close to the EQS of 5 ng/L suggested for marine waters.

No statistically significant time trends can be observed for diclofenac in surface water due to the high variability in observed concentrations compared to estimated decline in emissions from human consumption. Considering the declining or stabilized levels of oral use of diclofenac in recent years, and short residence time of diclofenac in the environment, concentrations in surface waters can be expected to slowly decline in the coming years. However, the importance of dermally applied diclofenac for levels in WWTPs and time trends in sales of these products need to be assessed to settle this conclusion.

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References

Alygizakis, N.A., Gago-Ferrero, P., Borova, V.L., Pavlidou, A., Hatzianestis, I., Thomaidis, N.S., 2016. Occurrence and spatial distribution of 158 pharmaceuticals, drugs of abuse and related metabolites in offshore seawater. Sci. Total Environ. 541, 1097–1105.

Aminot, Y., Le Menach, K., Pardon, P., Etcheber, H., Budzinski, H., 2016. Inputs and seasonal removal of pharmaceuticals in the estuarine Garonne River. Mar. Chem. 185, 3–11.

aus der Beek, T., Weber, F., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A., 2016. Pharmaceuticals in the environment—Global occurrences and perspectives. Environ. Toxicol. Chem. 35, 823–835.

Avdeef, A., Box, K.J., Comer, J.E.A., Hibbert, C., Tam, K.Y., 1998. pH-Metric logP 10. Determination of liposomal membrane-water partition coefficients of Ionizable drugs. Pharm. Res. 15, 209–215.

BIO Intelligence Service, 2013. Study on the environmental risks of medicinal products, Final Report prepared for Executive Agency for Health and Consumers. Available at https://ec.europa.eu/health/sites/health/files/files/environment/study_environment.pdf.

Bound, J.P., Voulvoulis, N., 2005. Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. Environ. Health Perspect. 113, 1705–1711.

Buser, H.-R., Poiger, T., Müller, M.D., 1998. Occurrence and fate of the pharmaceutical drug diclofenac in surface waters: rapid photodegradation in a lake. Environ. Sci. Technol. 32, 3449–3456.

Caban, M., Szaniawska, A., Stepnowski, P., 2016. Screening of 17α-ethynylestradiol and non-steroidal anti-inflammatory pharmaceuticals accumulation in Mytilus edulis trossulus (Gould, 1890) collected from the Gulf of Gdańsk. Oceanol. Hydrobiol. Stud. 45, 605–614.

Coll, C., Bier, R., Li, Z., Langenheder, S., Gorokhova, E., Sobek, A., n.d. Association between aquatic micropollutant degradation and river sediment bacterial communities. Submitted.

Cuklev, F., Kristiansson, E., Fick, J., Asker, N., Förlin, L., Larsson, D.G.J., 2011. Diclofenac in fish: blood plasma levels similar to human therapeutic levels affect global hepatic gene expression. Environ. Toxicol. Chem. 30, 2126–2134.

CW Pharma project, 2019. Brief analysis on results from HELCOM data-call on micropollutants – Pharmaceuticals. Document presented at the 11th Meeting of the Working Group on Reduction of Pressures from the Baltic Sea Catchment Area 23-25 Oct 2019.

Daneshvar, A., Svanfelt, J., Kronberg, L., Weyhenmeyer, G.A., 2010. Winter accumulation of acidic pharmaceuticals in a Swedish river. Environ. Sci. Pollut. Res. 17, 908–916.

Davies, N.M., Anderson, K.E., 1997. Clinical pharmacokinetics of diclofenac. Clin. Pharmacokinet. 33, 184–213.

EC, 2012. European Commission 2011/0429 (COD) Proposal for a Directive of the European Parliament and of the Council amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. https://ec.europa.eu/smart-regulation/im.

EC, 2011. European Commission. Technical Guidance for Deriving Environmental Quality Standards, Guidance Document No: 27 under the Common Implementation Strategy for the Water Framework Directive (2000/60/EC).

Ek, C., Winkens Pütz, K., Danielsson, S., Faxneld, S., 2019. Screening for pharmaceuticals, phthalates and polycyclic aromatic hydrocarbons (PAHs) in bivalves sampled along the Swedish coast.

EMA, 2014. European Medicines Agency. Opinion of the Committee for Medicinal Products for Veterinary Use pursuant to Article 30(3) of Regulation (EC) No 726/2004. Online. As viewed 161019 https://www.ema.europa.eu/en/documents/other/opinion-committee-medicinal-produ.

Eurostat, 2019. Municipal waste generation and treatment, by treatment method. Online. As viewed 161019. https://ec.europa.eu/eurostat/web/waste/municipal-waste-generation-and-treatment-by-treatment-method [WWW Document].

Falås, P., Andersen, H.R., Ledin, A., Jansen, J.L.C., 2012. Occurrence and reduction of pharmaceuticals in the water phase at Swedish wastewater treatment plants. Water Sci. Technol. 66, 783–791.

Fick, J., Lindberg, R.H., Kaj, L., Brorström-Linden, E., 2014. Results from the Swedish National Screening Programme 2010 Subreport 3. Pharmaceuticals. Available at: https://www.ivl.se/webdav/files/Rapporter/B2014.pdf.

Fosbøl, E.L., Folke, F., Jacobsen, S., Rasmussen, J.N., Sørensen, R., Schramm, T.K., Andersen, S.S., Rasmussen, S., Poulsen, H.E., Køber, L., 2010. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among healthy individuals. Circ. Cardiovasc. Qual. Outcomes 3, 395–405.

Giordano, F., Rossi, A., Pasquali, I., Bettini, R., Frigo, E., Gazzaniga, A., Sangalli, M.E., Mileo, V., Catinella, S., 2003. Thermal degradation and melting point determination of diclofenac. J. Therm. Anal. Calorim. 73, 509–518.

Gobas, F.A.P.C., de Wolf, W., Burkhard, L.P., Verbruggen, E., Plotzke, K., 2009. Revisiting bioaccumulation criteria for POPs and PBT assessments. Integr. Environ. Assess. Manag. An Int. J. 5, 624–637.

HELCOM, 2018. Diclofenac. HELCOM pre-core indicator report. Online. as viewed 161019, http://www.helcom.fi/Core%20Indicators/Diclofenac%20HELCOM%20pre-core%20indicator%202018.pdf. ISSN: 2343-2543.

Ikkere, L.E., Perkons, I., Sire, J., Pugajeva, I., Bartkevics, V., 2018. Occurrence of polybrominated diphenyl ethers, perfluorinated compounds, and nonsteroidal anti-inflammatory drugs in freshwater mussels from Latvia. Chemosphere 213, 507–516.

Johnson, A.C., Dumont, E., Williams, R.J., Oldenkamp, R., Cisowska, I., Sumpter, J.P., 2013. Do concentrations of ethinylestradiol, estradiol, and diclofenac in European rivers exceed proposed EU environmental quality standards? Environ. Sci. Technol. 47, 12297–12304.

Johnson, A.C., Keller, V., Williams, R.J., Young, A., 2007. A practical demonstration in modelling diclofenac and propranolol river water concentrations using a GIS hydrology model in a rural UK catchment. Environ. Pollut. 146, 155–165.

Kehrein, N., Berlekamp, J., Klasmeier, J., 2015. Modeling the fate of down-the-drain chemicals in whole watersheds: New version of the GREAT-ER software. Environ. Model. Softw. 64, 1–8.

Khan, S.J., Ongerth, J.E., 2004. Modelling of pharmaceutical residues in Australian sewage by quantities of use and fugacity calculations. Chemosphere 54, 355–367.

Kristensen, K.B., Karlstad, Ø., Martikainen, J.E., Pottegård, A., Wastesson, J.W., Zoega, H., Schmidt, M., 2019. Nonaspirin nonsteroidal antiinflammatory drug use in the Nordic countries from a cardiovascular risk perspective, 2000–2016: A drug utilization study. Pharmacother. J. Hum. Pharmacol. Drug Ther. 39, 150–160.

Kunkel, U., Radke, M., 2012. Fate of pharmaceuticals in rivers: deriving a benchmark dataset at favorable attenuation conditions. Water Res. 46, 5551–5565.

Kusturica, M.P., Tomas, A., Sabo, A., 2016. Disposal of unused drugs: Knowledge and behavior among people around the world, in: Reviews of Environmental Contamination and Toxicology Volume 240. Springer, pp. 71–104.

Lapworth, D.J., Lopez, B., Laabs, V., Kozel, R., Wolter, R., Ward, R., Vargas-Amelin, E., Besien, T., Claessens, J., Delloye, F., 2018. Developing a groundwater watch list for substances of emerging concern: a European perspective. Environ. Res. Lett.

Lember, E., Pachel, K., Loigu, E., 2016. Modelling diclofenac and ibuprofen residues in major Estonian seaside cities. J. Water Secur. 2.

Li, Z., Sobek, A., Radke, M., 2016. Fate of pharmaceuticals and their transformation products in four small European rivers receiving treated wastewater. Environ. Sci. Technol. 50, 5614–5621.

Lonappan, L., Brar, S.K., Das, R.K., Verma, M., Surampalli, R.Y., 2016. Diclofenac and its transformation products: environmental occurrence and toxicity-a review. Environ. Int. 96, 127–138.

Loos, R., Marinov, D., Sanseverino, I., Napierska, D., Lettieri, T., 2018. Review of the 1 st Watch List under the Water Framework Directive and recommendations for the 2 nd Watch List. Publ. Off. Eur. Union 1–267.

McGettigan, P., Henry, D., 2013. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. PLoS Med. 10, e1001388.

Nödler, K., Voutsa, D., Licha, T., 2014. Polar organic micropollutants in the coastal environment of different marine systems. Mar. Pollut. Bull. 85, 50–59.

Oaks, J.L., Gilbert, M., Virani, M.Z., Watson, R.T., Meteyer, C.U., Rideout, B.A., Shivaprasad, H.L., Ahmed, S., Chaudhry, M.J.I., Arshad, M., 2004. Diclofenac residues as the cause of vulture population decline in Pakistan. Nature 427, 630.

Paxéus, N., Bester, K., El-Taliawy, H., 2016. Temporal variations and trends in loads of commonly used pharmaceuticals to large wastewater treatment plants in Sweden, a case study (Ryaverket). Water Sci. Technol. 73, 3049–3056.

Persson, M., Sabelström, E., Gunnarsson, B., 2009. Handling of unused prescription drugs—knowledge, behaviour and attitude among Swedish people. Environ. Int. 35, 771–774.

Posselt, M., Mechelke, J., Rutere, C., Coll, C., Jaeger, A., Raza, M., Meinikmann, K., Krause, S., Sobek, A., Lewandowski, J., Horn, M., Hollender, J., Benskin, J.P., 2020. Bacterial Diversity Controls Transformation of Wastewater-Derived Organic Contaminants in River-Simulating Flumes. Submitted.

Qi, C., Huang, J., Wang, B., Deng, S., Wang, Y., Yu, G., 2018. Contaminants of emerging concern in landfill leachate in China: A review. Emerg. Contam. 4, 1–10.

Radke, M., Maier, M.P., 2014. Lessons learned from water/sediment-testing of pharmaceuticals. Water Res. 55, 63–73.

Roos, A., Loso, K., Fång, J., 2017. Mätningar av läkemedelsrester i blod och urin från utter.

Sacher, F., Ehmann, M., Gabriel, S., Graf, C., Brauch, H.-J., 2008. Pharmaceutical residues in the river Rhine—results of a one-decade monitoring programme. J. Environ. Monit. 10, 664–670.

Sarganas, G., Buttery, A.K., Zhuang, W., Wolf, I.-K., Grams, D., Rosario, A.S., Scheidt-Nave, C., Knopf, H., 2015. Prevalence, trends, patterns and associations of analgesic use in Germany. BMC Pharmacol. Toxicol. 16, 28.

Saunders, L.J., Mazumder, A., Lowe, C.J., 2016. Pharmaceutical concentrations in screened municipal wastewaters in Victoria, British Columbia: A comparison with prescription rates and predicted concentrations. Environ. Toxicol. Chem. 35, 919–929.

Schmidt, M., Sørensen, H.T., Pedersen, L., 2018. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. bmj 362, k3426.

Schröder, P., Helmreich, B., Škrbic, B., Carballa, M., Papa, M., Pastore, C., 2016. Status of hormones and painkillers in wastewater effluents across several European states — considerations for the EU watch list concerning estradiols and diclofenac. Env. Sci Pollut Res 23, 12835–12866. https://doi.org/10.1007/s11356-016-6503-x

Schwaiger, J., Ferling, H., Mallow, U., Wintermayr, H., Negele, R.D., 2004. Toxic effects of the non-steroidal anti-inflammatory drug diclofenac: Part I: histopathological alterations and bioaccumulation in rainbow trout. Aquat. Toxicol. 68, 141–150.

Törneman, N., Hallgren, P., Bjarke, M., 2014. Occurrence of additional WFD priority substances in Sweden.

UBA, 2019. The database “Pharmaceuticals in the Environment” - Update and new analysis Final report. by Dusi Eike, Rybicki Marcus, Jungmann Dirk GWT-TUD GmbH, Dresden, Germany On behalf of the German Environment Agency. TEXTE 67/2019 Project No. 97778 FB000079. ISSN.

UBA, 2017. Dossier Diclofenac_Draft_JRC-2017_V4.1-GM(update 31-05-2017)_JRC 25June2017 as viewed on 16.10.19 at: https://circabc.europa.eu/w/browse/412c0e12-6235-497f-8607-2d8dc1d95da7.

UNESCO HELCOM, 2017. Pharmaceuticals in the aquatic environment of the Baltic Sea region – A status report. UNESCO Emerging Pollutants in Water Series – No. 1, UNESCO Publishing, Paris.

Vieno, N., Sillanpää, M., 2014. Fate of diclofenac in municipal wastewater treatment plant—a review. Environ. Int. 69, 28–39.

Wallberg, P., Wallman, P., Thoren, S., Nilsson, S., Christiansson, F., 2016. Behov av avancerad rening vid avloppsreningsverk - Finns recipienter som är känsligare än andra? Rapport för Naturvårdsverket.

Wärnersson, I., Larsson, J., 2007. Screening av läkemedelsresteri lakvatten, avloppsvattenoch slam i Blekinge län.

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