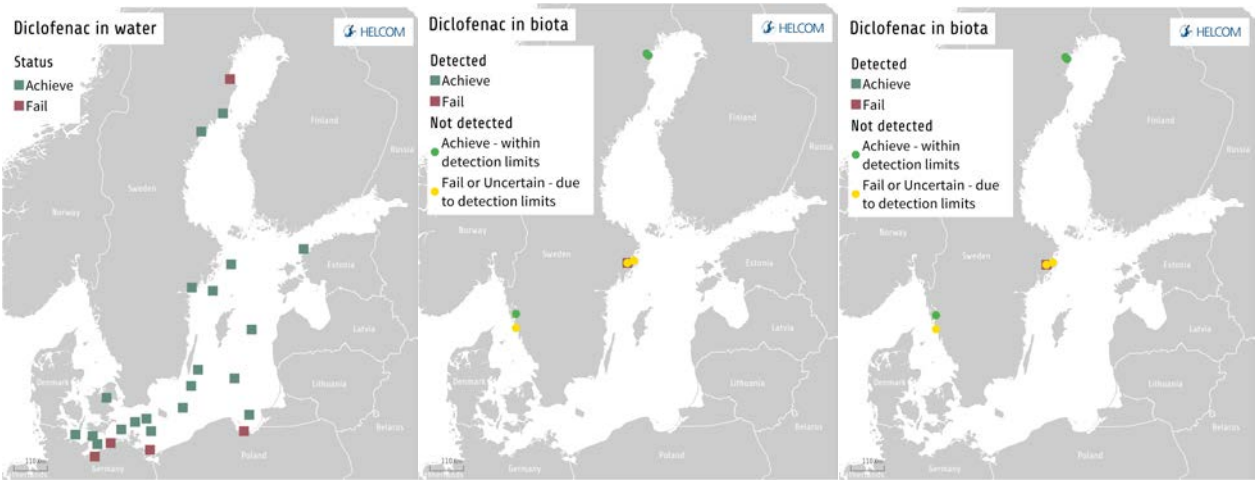
Diclofenac

This pre-core test indicator and its threshold values are yet to be commonly agreed in HELCOM and the presented thresholds are furthermore not currently approved EQS values, but provisional proposals.
The indictor is included as a test indicator for the purposes of the 'State of the Baltic Sea' report, and the results are to be considered as intermediate.

Key Message

Pharmaceuticals represent a major group of substances of emerging concern and it is vital that a detailed understanding of their distribution, role and fate in the environment is determined. This pre-core indicator targets the development of a status evaluation of the occurrence and concentrations of diclofenac in the Baltic Sea marine environment. Currently the distribution, role and fate of diclofenac in the Baltic Sea is not clearly understood, with limited information from few monitoring and screening studies available. Thus, while an initial overview is possible, accurate evaluations of the status of the environment cannot be made at this time. Defining trends and environmental status will only be possible after monitoring has been carried out to encompass the required spatial distribution and temporal periods. Furthermore, diclofenac was included in the EU first watch list under the Environmental Quality Standards Directive, requiring those HELCOM Contracting Parties who are also EU member states, to gather suitable monitoring data for the purpose of facilitating the development of appropriate methods and addressing any risk posed. It has recently been proposed that diclofenac be removed from this watch list since sufficient data has been collected and it remains to be clarified if diclofenac will be added to the list of priority substances.



Key message figure 1. Overview of sample location in Baltic Sea water (left and centre) and biota (right). Samples in which diclofenac were detected are indicated by squares, with colours indicating good (green) and not good (red) status. Circles indicate samples in which diclofenac was not detected, with colours indicating the analytical limit* certainty, green having analytical limits below the set threshold value (i.e. reliable) and yellow having analytical limits above the set threshold value or unknown (i.e. uncertain reliability).

*The term “analytical limit” is used in this report as no differentiation between LOD and LOQ could be assigned to the reported values in all cases.

Available data have indicated that the diclofenac concentration can be high close to waste water treatment plants (WWTPs, these often being the major point of entry to the Baltic Sea), of which a large number can be found situated in coastal regions (<20 km from the coast). High concentrations of diclofenac may also be detected in rivers draining into the Baltic Sea. Moreover, concentrations of diclofenac have been detected in water, sediments and biota in the Baltic Sea. Further data and analyses to determine the environmental effects of increased diclofenac concentrations, the dispersal from source, and the spatial distribution in water, sediments and biota are required to guide status evaluation.

The indicator is applicable in the waters of all countries bordering the Baltic Sea. The indicator is established and further monitoring data is currently being gathered. The current data coverage (temporal and spatial) is low and thus the results and confidence in the indicator evaluation are considered as intermediate.

Relevance of the core indicator

Pharmaceuticals represent a major group of substances of emerging concern and diclofenac, categorised in the therapeutic group of anti-inflammatory and analgesics, is both a widely used pharmaceutical in the Baltic Sea region and one of the most common pharmaceuticals currently detected in the environment (Unesco and HELCOM, 2017). Diclofenac remains one of the most used and most widely sold anti-inflammatory and analgesics in the region and it has been utilised for an extended period of time. It has been widely detected in aquatic environments (e.g. 50 countries) and at concentrations that can be indicative of detrimental environmental effects (Weber et al., 2014, Zang et al. 2008). In addition to its inclusion on the EU first watch list a recent data analysis indicated that diclofenac was among the 20 most sold pharmaceuticals in the Baltic Sea catchment area. Furthermore, it was also among the 20 pharmaceuticals with the highest concentrations in WWTP influent and effluent, showed very low levels of removal in conventional WWTP systems (circa 1%), and was among the 20 highest concentrations of measured pharmaceuticals detected in river water (Unesco and HELCOM, 2017). It has also been detected in Baltic Sea biota at levels above threshold values (e.g. in Perch, Hallgren and Wallenberg, 2015; Karlsson and Viktor, 2014) and previous studies have linked toxic effects in marine organisms to high concentrations of diclofenac.

Policy relevance of the core indicator

	BSAP segment and objectives	MSFD Descriptor and criteria
Primary link	Hazardous substances • Concentration of hazardous substances close to natural levels • Healthy wildlife	D8 Concentrations of contaminants D8C1 Within coastal and territorial and beyond territorial waters, the concentration of contaminants do not exceed the threshold values.
Secondary link	Hazardous substances • Fish safe to eat	D9 Contaminants in fish and seafood D9C1 The level of contaminants in edible tissues (muscle, liver, roe, flesh or other soft parts, as appropriate) of seafood (including fish, crustaceans, molluscs, echinoderms, seaweed and other marine plants) caught or harvested in the wild (excluding fin-fish from mariculture) does not exceed the threshold values.
Other relevant legislation: For some Contracting Parties the Water Framework Directive will be relevant and Diclofenac was added to the EU watch list. It is currently being reviewed to determine if it will be added to the priority list.		

Cite this indicator

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Diclofenac HELCOM pre-core indicator 2018 (pdf)

Results and Confidence

This pre-core test indicator and its threshold values are yet to be commonly agreed in HELCOM and the presented thresholds are furthermore not currently approved EQS values, but provisional proposals.
The indictor is included as a test indicator for the purposes of the 'State of the Baltic Sea' report, and the results are to be considered as intermediate.

A major source of pharmaceuticals in the environment is the excretion of active substances consumed by humans (and animals). Diclofenac enters WWTPs and is subsequently transferred to rivers and the marine environment, where biota can consequently be exposed. Current data indicate that in many instances pharmaceuticals, including diclofenac, are not effectively degraded in conventional WWTPs and are sufficiently persistent to pass through treatment processes and reach surface waters (Tixier et al., 2003). However, other sources have been shown or suggested, including the recreational use of waters (especially in lakes and rivers, Atlasi et al 2012) and the spreading of WWTP sludges on land (Lindim et al., 2016). Sources such as hospitals, pharmaceutical manufacturers, sewer overflow or leakage, septic tanks, agriculture and storm water run-off are also relevant to consider as potential pathways of introduction to the Baltic Sea.

The sections described below are considered to be potentially relevant compartments to analyse diclofenac for the evaluation of environmental status. A combined approach using monitoring or assessment of one or several of these may provide the most appropriate indicator approach.

Sales

In the HELCOM BASE pilot project sales statistics were collected for Russia on 87 pharmaceutical preparations registered for use in 2009-2010, including diclofenac. Calculations were made to estimate the total usage of diclofenac in the St.Petersburg region (HELCOM 2014). Four major forms of diclofenac containing pharmaceutical products were sold: creams, injections, pills and suppositories.

Sales of Non-Steroid Anti-Inflammatory creams for topical (external) application during one year (May 2012-April 2013) in Russia totalled 33.9 million packages. Voltaren and Diclak were the two leading products sold, with 4.7 million packages each. One 20 g unit of 1% Voltaren Gel contains 0.2 g diclofenac, with larger packages of 50g, 75g and 100 g also available on the market. Diclak gel is available as similar packages with a 1% concentration and as a 5% preparation in 50 g tubes. Yearly sales of Diclak corresponds to 2.13 tonnes of diclofenac. However, the proportion of Diklak sold with an active ingredient of either 5% or 1% is not known. Therefore, the total consumption of diclofenac for external application is estimated from these data as 14 million units per year, or 2.8 tonnes. Based on calculations, the external application use of diclofenac in St. Petersburg is estimated at 170 kg. Sales of pills, injections and suppositories by three leading brands are shown in Results table 1. The total annual consumption of diclofenac through pharmaceutical preparations other than creams for topical application is estimated at 20 tonnes, with an estimated sale of 27 million diclofenac units in 2011. In 2010 hospitals purchased 900,000 packages for injections and <100,000 in the form of pills, totalling an annual consumption of 20 tonnes (HELCOM 2014).

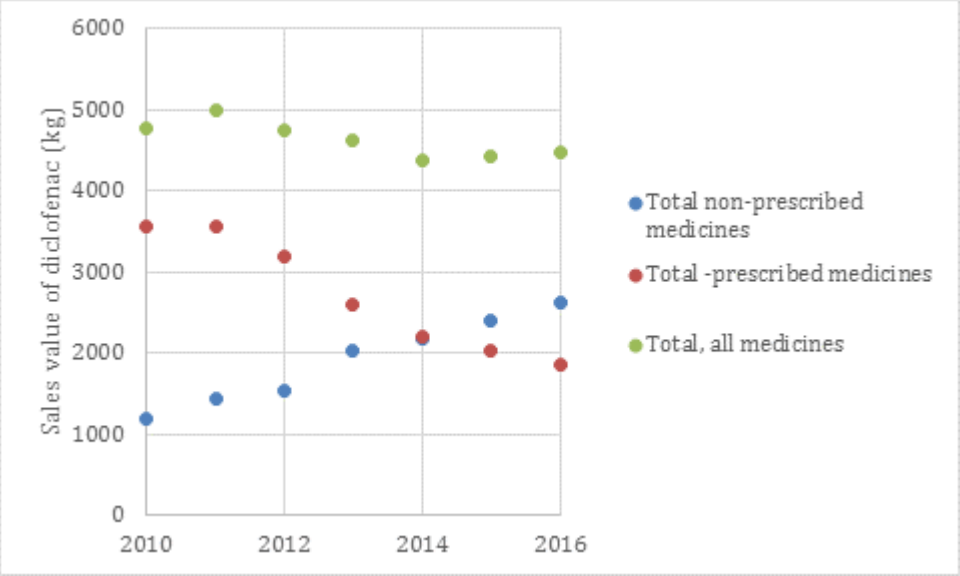
Results table 1. Indicative annual consumption of three brands of pharmaceutical preparations containing diclofenac in Russia (reproduced from HELCOM 2014).

	Injections (number of items)	Pills (number of items)	Suppositories (number of items)
Diclofenac	6,731,799	5,958,925	900,616
Ortophen	144,030	6,155,850	26
Voltaren	1,168,177	232,503	489,748
Diclofenac per package	0.5 g	1 g	0.5 g
Diclofenac per form	**4 tonnes**	**12 tonnes**	**0.75 tonnes**

Based on the above data the consumption of these pharmaceutical preparations for the St. Petersburg area is estimated to be 700 kg per annum. If all the diclofenac were to enter the sewage system, the concentrations could reach 850 ng/L (HELCOM 2014).

Similarly, in a recent data compilation covering reported data that encompassed circa 25% of the Baltic Sea catchment population it was estimated that diclofenac was amongst the 20 most sold pharmaceuticals in the region, with sales of >12 t /year (Unesco and HELCOM, 2017). In other studies changes in national consumption have also been documented, with a general increase in sales being observed (Baranauskaitė and Dvarionienė, 2014), though in instances were legislation has changed the opposite trend has also been observed (Lember et al., 2016).

Other trends in sales can also offer interesting insights into diclofenac usage that may be relevant for understanding how it is discharged into the environment. A summary of sales in Sweden between 2010 and 2016 indicated that while prescribed medication decreased the total sales value of diclofenac (kg) remained somewhat stable, with sales of non-prescribed medication increasing (Results figure 1).



Results figure 1. Annual sales value of diclofenac (kg) for the whole of Sweden, 2010-2016 as provided by the Swedish Medical Products Agency.

The modelling of diclofenac sales/usage, in conjunction with other variables such as WWTP removal rates, has also been successfully utilised in recent studies to estimate river area exceeding European environmental quality standards (Johnson et al., 2013), to consider future challenges in management (Baranauskaitė and Dvarionienė, 2014), and to follow annual trends and predict discharges to the Baltic Sea (Lember et al., 2016) or river basins (Lindim et al., 2016). The latter study was followed up with a detailed prediction on discharges to the Baltic Sea, including gaining high correlations with measured environmental data from the Stockholm region where wastewater effluent is discharged to the Baltic without significant river transport (Lindim et al., 2017).

Information on the sale of diclofenac is considered to be a potentially relevant proxy to be used in the evaluation of environmental status. However, reporting would be required for the entire catchment region and some understanding of the discrepancy between sales and use may need to be developed, as well as the consideration seasonal aspects (e.g. elevated usage during winter months) and population demographics (e.g. age).

Waste water treatment plants (WWTPs)

Diclofenac was regularly detected amongst the 20 highest pharmaceutical concentrations in WWTP waters and sludges (Results table 2), and conventional treatment methods generally showed no major removal of it during processing, circa 1% from the aqueous phase (Unesco and HELCOM, 2017). Low removal patterns in WWTPs have generally been observed previously, where concentrations of diclofenac decreased by 11 and 28% between influent and effluent waters (Andersson et al. 2006, Fick et al. 2011; Miljøministeriet, Naturstyrelsen, 2015), and in some cases effluent concentrations were higher than those in the influent waters (HELCOM 2014, Zorita et al., 2009). It has also been suggested that diclofenac may be capable of altering microbial communities within WWTPs with consequent effects of WWTP function (Kraigher et al., 2008). Moreover, recent studies comparing WWT processes have shown there to be a wide range of removal

rates dependent on the type of process employed and that environmental conditions at or surrounding individual WWTPs may have an influence (reviewed in Vieno and Sillanpää, 2014 and Lonappan et al., 2016). This phenomenon might be explained by the liberation of diclofenac from conjugated metabolites during bacterial treatment (HELCOM 2014), or by re-solubilisation of sediment/sludge associated diclofenac. In other words, diclofenac is partially present in the sewage in a conjugated form, due to the metabolic processes in the organism that first ingested the substance, the conjugates not being formed during the WWTP process (Peres and Bacrelo 2008), and may result in a re-release of diclofenac into the environment (Zorita et al., 2009).

Results table 2. Diclofenac concentrations from screening studies, scientific literature and data compilations. Ranges are given where data are from extensive spatial or temporal collection.

	WWTP influent (ng/L)	WWTP effluent (ng/L)	Reference
Denmark	Means of 60-370 Maximum 490	Means of 30-370 Maximum 380	Miljøministeriet, Naturstyrelsen (2015)
Estonia	Mean 1190 Maximum 3000	Mean 1630 Maximum 1840	Unesco and HELCOM, 2017
Finland	Mean: 939 Maximum: 3000 Mean: 368 Maximum: 933 Mean: 260 Maximum: 360 Means of 250-800	Mean: 884 Maximum: 2000 Mean: 1124 Maximum: 2755 Mean: 359 Maximum: 710 Means of 1000-2250 Maximum: 90 Mean: 50	Unesco and HELCOM, 2017 Lindholm-Lehto, 2016 Kavander, 2017 Lindholm-Lehto et al., 2016 Äystö et al., 2014
Germany	Mean: 420 Maximum: 640 2330	Mean: 810, Maximum: 2100 1300 ±100 1360 Mean: 3290, Maximum: 13000 Mean: 2444, Maximum: 4300 Mean: 3390 Maximum: 13000	Ternes 1998 Ternes et al. 2003 Quintana & Reemtsma 2004 Unesco and HELCOM, 2017 Unesco and HELCOM, 2017 Monitoring (2016) HELCOM DATA CALL
Latvia	Maximum: 1311 Maximum: 409	 Maximum: 1165 Means of 429-3280	Muter et al., 2017. NonHazCity project – unpublished Monitoring (2016) HELCOM DATA CALL
Sweden	 900-7000 100-670 190-540 290-560 Mean: 230	81-270 14–710 420-3900 200-700 100 220-230 290-390 Mean: 490	Lilja et al. 2010 Andersson et al. 2006 Fick et al. 2011 Andersson et al. 2006 Remberger et al. 2009 Bendz et al. 2005 Breitholtz et al., 2012* Zorita et al., 2009 Unesco and HELCOM, 2017

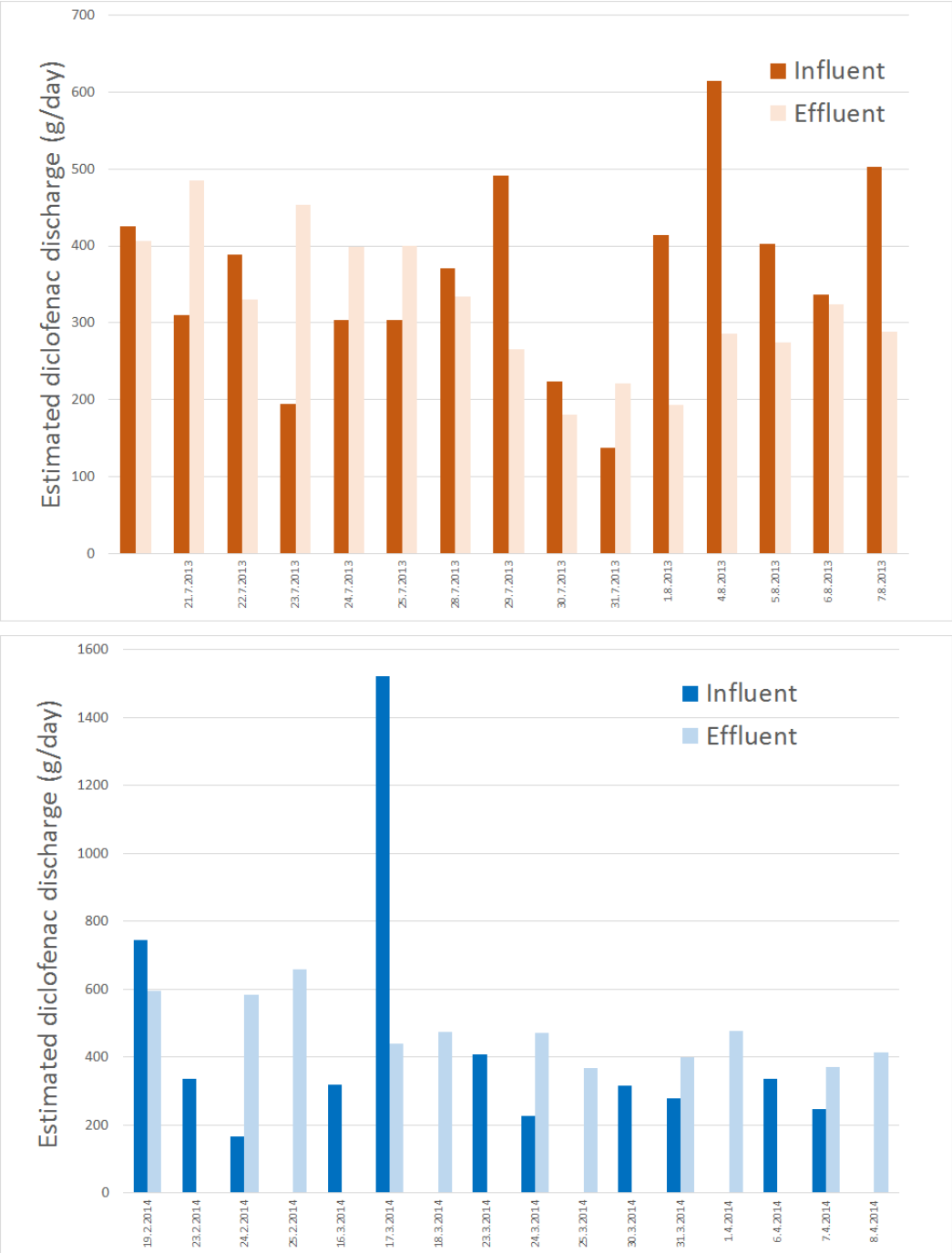
	Mean 676 Maximum 7000	Mean 158 Maximum 510 Mean 334 Maximum 5000 Mean 486 Maximum 840 Mean 2324 Maximum 2971 Mean 817 Maximum 1320	Unesco and HELCOM, 2017 Fick et al., 2015 Haglund, 2017 - unpublished. Haglund, 2015.
Russia	Mean 408 Maximum 741 Means of 350-620 Maximum 800	Mean 355 Maximum 514 Means of 510-550 Maximum 750	Unesco and HELCOM, 2017 HELCOM 2014

Note[1]: values for untreated sewage sludges for reporting HELCOM Contracting Parties were: mean: 79 ng/L and maximum: 250 ng/L. Untreated, digested and composted sludges contained diclofenac at circa 100, 100 and 10 µg/kg d.w., respectively (Unesco and HELCOM, 2017).

Note[2]: Reported data from HELCOM Contracting Parties include the following number of data items (number of individual WWTPs): Germany – 155 + 5 (11 and 5), Finland – 40 (13), Estonia – 6 (3), Denmark – 17 (6), and Sweden – 9 + >28 (3 and >4).

*Constructed wetlands, tertiary WWT process.

A detailed study of pharmaceuticals in the St Petersburg area, the HELCOM BASE pilot project, indicated that seasonal and environmental factors (e.g. rainfall) may also influence the discharge rates from WWTPs (HELCOM 2014). In summer months the average influent concentration was 408 ng/L (rage of 154-741 ng/L, equivalent to 138-615 g/day), whereas effluent discharge water concentrations were on average 355 ng/L (range of 154-514 ng/L, equivalent to 180-485 g/day). During winter the average concentration of diclofenac in effluent waters was higher than in summer, 530 ng/L (range 440-630 ng/L, equivalent to 369-658 g/day); despite the lower average influent concentrations of 350 ng/L (range 160-1700 ng/L, equivalent to 228-1205 g/day) (Results figure 2).

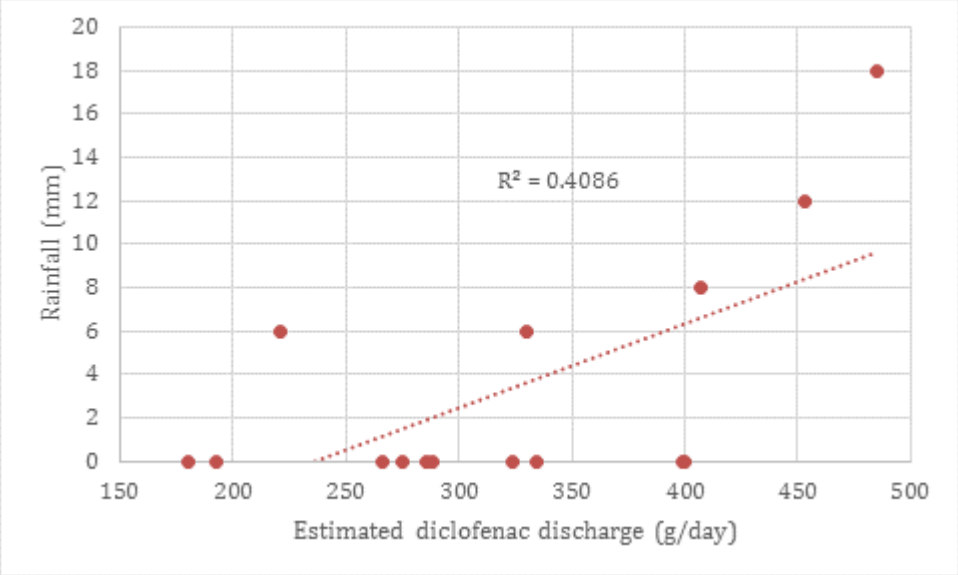


Results figure 2. Estimated summer (orange shades, top) and winter (blue shades, bottom) diclofenac discharge in influent (darker colours) and effluent (paler shades) at St. Petersburg WWTP.

This could relate to differences in the daily discharge estimates in effluent water in winter (average of 477 g/day) as compared to summer (average of 323 g/day), driven by increased use of diclofenac during the cold period of the year, but it is also possible that metabolites are more readily produced in summer or are hydrolysed back to diclofenac in winter via biological/chemical processes and/or that sludge/sediment bound diclofenac in WWTPs is re-released and enters effluent waters. Such dynamics could result in the retention

of higher concentrations of diclofenac within the WWTP during warmer summer months and stronger discharges during winter.

At the central waste water treatment plant in St. Petersburg the influent water is a mix of domestic wastewater and rainwater, thus meteorological conditions have an impact on water volumes in the process. Factors such as rainfall, which showed a potential correlation with effluent discharge concentrations (R^2 = 0.41, Results figure 3), may therefore influence the discharge rates (or concentrations in discharge waters), influencing the concentrations of diclofenac discharged and potentially the transfer distances from WWTPs.



Results figure 3. Correlation between diclofenac discharge in effluent waters and rainfall during summer sampling events at St. Petersburg WWTP.

This pilot study indicated that the concentration of diclofenac in the WWTP was only two times lower than a scenario in which all sold diclofenac were to enter the sewage system, and that the upper level of diclofenac discharged from the city of St. Petersburg to the Baltic Sea would be 1.1 kg/day, an annual load of circa 400 kg (HELCOM 2014). Averaging the load to the annual water volume of 78.9 km^3 (2,500 km^3/s) of the river Neva, gives an average expected surface water concentration of diclofenac in the water flowing into the Gulf of Finland of 4-5 ng/L (HELCOM 2014). This estimated concentration is close to the newly proposed threshold value of 5 ng/L, assuming that usage and discharge rates remain at the current level and that accumulation within the discharge zone does not take place over longer time periods.

Pathways – rivers

Rivers act as major pathways for the transport of diclofenac from WWTPs to the Baltic Sea environment and elevated concentrations have been detected in the waters of numerous rivers that subsequently enter the Baltic Sea (Results table 3).

Results table 1. Diclofenac concentrations in river waters and sediments from screening studies, scientific literature, and data compilations. The limit of quantification (LOQ) in the Swedish screenings studies was 10 ng L^{-1}

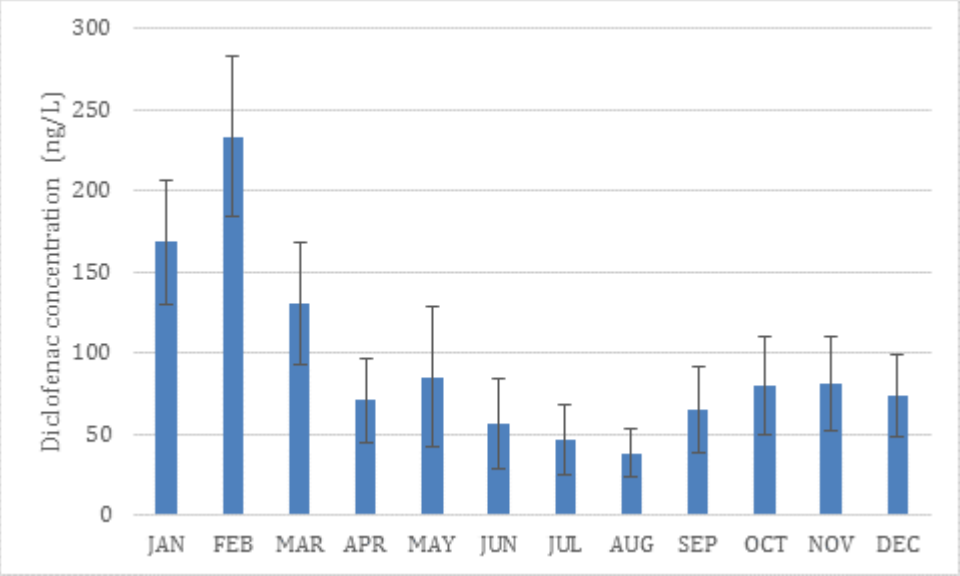
	Surface water (ng/L)	Sediment (µg/kg d.w.)	Reference
Compiled data, multiple countries	Mean: 133 Maximum: 2710		Unesco and HELCOM, 2017*
Denmark	Mean: 102 Maximum: 230 Mean: 76 Maximum: 230 Maximum: 300		Unesco and HELCOM, 2017* Miljøministeriet, Naturstyrelsen, 2015 Monitoring (2016) HELCOM DATA CALL
Estonia	Mean: 61 Maximum:130 Maximum:79		Unesco and HELCOM, 2017* Monitoring (2016) HELCOM DATA CALL
Finland	Mean: 23 Maximum: 55 Maximum:93 Means of 5.1 - 187		Unesco and HELCOM, 2017* Monitoring (2014-6) HELCOM DATA CALL Lindholm-Lehto et al., 2016
Germany	Median: 150 Maximum: 1200 Mean: 170 Maximum: 1950 Mean: 170 Maximum: 2710		Ternes 1998 Unesco and HELCOM, 2017* Monitoring (2015-6) HELCOM DATA CALL
Latvia	Maximum: 8.4		Reinholds et al., 2017
Lithuania	Mean: <10 (values below the LOQ)		Monitoring (2016) HELCOM DATA CALL
Poland	Slupia River, mean: 93 Mean: 94 Maximum: 665		Borecka et al., 2015 Monitoring (2016) HELCOM DATA CALL
Sweden	Uppsala: 28, 90, 290, 880 Maximum: 120 Circa 400-900 Maximum: 7.4 (Umeå river)	River Piteå: 3.5, 0.19, 0.85, 3.1	Fick et al. 2011 Bendz et al. 2005 Remberger et al. 2009 Lindim et al., 2016 Case study (2016) HELCOM DATA CALL

*This data compilation includes some of the data shown below for individual countries but is dominated by data from German rivers. Reported data from HELCOM Contracting Parties include the following number of data items (number of individual rivers): Germany – 1649 (124), Finland – 18 (4), Estonia – 12 (5), Denmark – 5 (4), and Sweden – 2 (2).

HELCOM DATA CALL Denotes data reported by countries in response to the HELCOM data call in Autumn 2017. This data represents additional data from the 2015-2016 data that has been collected since the data call for used as the basis for the Unesco and HELCOM, 2017 report. Data is summarised as maximum and mean values where possible, though 'less-than' values, where values are determined as less than the LOQ, are not currently included. Where 'less-than' values occurred no mean value is calculated and only a maximum value provided. The dates provided in brackets indicates the year(s) for which data are reported.

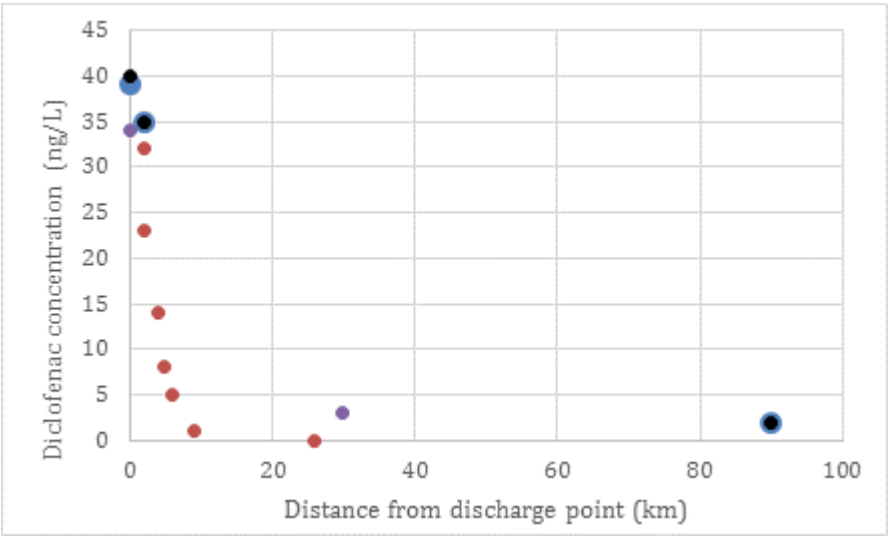
Initial data seems to indicate that concentrations detected in river waters may vary seasonally, peaking in January and February (Results figure 4). The reasons behind this could relate to levels of usage in these

months (i.e. higher usage in colder months) or to degradation and water treatment processes (e.g. the function of WWTPs or rainfall and discharge rates).



Results figure 4. Mean diclofenac concentrations in 15 Polish rivers sampled across the year (in 2016). Error bars represent Standard Error (SE), n =15.

Elevated concentrations have been recorded, particularly in the immediate vicinity of WWTPs, though the limited data that is currently available indicates that concentrations of diclofenac often decrease quite rapidly with distance from the point of discharge, i.e. WWTPs (Results figure 5); a factor that requires further detailed studies.



Results figure 5. Diclofenac concentrations in samples with increasing distance from the point of discharge. Data are shown for the River Aura (red)*, River Seinäjoki and Kyrö (blue)*, River Kyrönjoki (black)**, and River Aurajoki (purple)** (Vieno, 2007* and Lindqvist et al. 2005**). Concentrations upstream of the discharge points (discharge point being 0 km) were: 4, 0, 0 and 6 ng/L, respectively.

It should however be noted that concentrations above proposed threshold values have still been recorded in both Baltic Sea waters and in Baltic Sea biota. This foments a number of potentially important considerations, such as the importance of WWTPs in close proximity to Baltic Sea coastal waters, the lack a complete understanding of the fate of diclofenac (e.g. data on sediments along pathways and within the Baltic Sea), and the importance of targeted sampling and analysis. For example, targeting potential indicator species that may encounter highly elevated concentrations, i.e. those that are passive filter feeders or those that traverse the marine-freshwater gradient via breeding or feeding life phases, and subsequently feed into the marine food web, is of high importance.

Baltic Sea Environment

Water and sediments

Of the data compiled for the Status report on pharmaceuticals in the Baltic Sea (UNESCO and HELCOM, 2017), within the pharmaceutical category anti-inflammatory and analgesics, diclofenac was the most frequently detected substance in samples compiled from the marine environment; representing 257 water samples. The highest concentrations of 54 ng/L was recorded in the south-western Baltic. The substance was detected in 54 (21%) of water samples and exceeded the proposed threshold value for diclofenac concentration in 6 samples from south-western Baltic Sea. The analytical limit for 83 (32%) samples where diclofenac was not detected were unknown or were higher than the threshold value, meaning the absence of concentrations above the threshold non-detection cannot be assured.

The new HELCOM data call (PRESSRURE and State&Consevation 2017) allowed new data to be compiled on observation of diclofenac in open sea and coastal waters. Altogether 60 observation were reported for the period 2014 and 2017 (and not included in the Unesco and HELCOM 2017 report) were supplied by Denmark, Germany, Latvia, Poland and Sweden. Five observations where the threshold value was exceeded were identified in marine waters, though analytical limits mean that in several cases the status can not be assessed with complete certainty (Key message figure 1).The highest measured concentration - 15.6 ng/l – was observed in the south-west Baltic Sea. Exceedances of the threshold were also observed in the Gdansk basin and Bothnian Bay.

Analysis of diclofenac in in sediments is scarce, with 15 individual samples taken in coastal water of Sweden and Estonia during screening studies. The substance was detected in 4 (27%) samples from coastal waters in the Bothnian Bay, with the highest concentration of 3,5 µg /kg d.w. The analytical limit for the other samples tested was above 10 µg /kg d.w., thus the absence of concentrations above the threshold cannot be assured.

The compiled data were obtained either from regular monitoring observations or from screening studies and cover almost all sub-basins of the Baltic Sea. Nonetheless, a significant part of the data remains uncertain due methodological issues and the associated detection limits.

Biota

Data regarding concentrations of diclofenac in Baltic Sea biota is currently extremely limited. It has however been detected in bile samples from European perch (*Perca uviatilis*) in a small number of samples (5 of 50) in the Stockholm region. Concentrations ranged between 0.53 and 5.2 µg/kg w.w. (Karlsson and Viktor, 2014), above the proposed threshold level (1 µg/kg w.w.) in three of five cases.

Confidence in the indicator

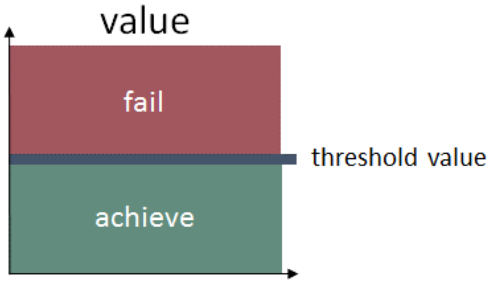
Currently data on diclofenac are obtained from a limited number of monitoring observations and mainly from screening studies, though coverage is inclusive of a large area of the Baltic Sea. Nonetheless, greater spatial and temporal coverage is required from all compartments with relevance to this indicator, especially the concentrations of diclofenac in Baltic Sea water and biota. Knowledge of how well samples represent a larger area (i.e. the appropriate HELCOM assessment units) needs to be developed to define the most suitable monitoring strategy and time series data will enable detailed trend based evaluations. Bearing in mind that diclofenac might be deposited to sediments, further detailed studies on fate and potential release/transfer are required. Furthermore, a high priority will be to focus the development of clear agreements regarding analytical methodologies to ensure the highest quality data can be obtained and that analytical limits do not prevent good status assessment within marine environments downstream of source discharge points.

Due to the fact that the monitoring of pharmaceuticals is generally at an early stage, no evaluation of the environmental status and no sub-basins spatial analysis has yet been made for this indicator. It is recommended that monitoring should be carried out for several years before a decisive status evaluation is done.

Thresholds and Status evaluation

This pre-core test indicator and its threshold values are yet to be commonly agreed in HELCOM and the presented thresholds are furthermore not currently approved EQS values, but provisional proposals.
The indictor is included as a test indicator for the purposes of the 'State of the Baltic Sea' report, and the results are to be considered as intermediate.

The EU Environmental Quality Standards for diclofenac is proposed as the threshold level for this indicator (see note below). An annual average Environmental Quality Standard (AA-EQS) in marine waters of 0.005 µg/l (5 ng/L) is proposed. A concentration of diclofenac in biota being below 1 µg kg^{-1} w.w., based on a value protective for avian predators (secondary poisoning), and of 0.007 µg/l (7 ng/L) for marine and freshwaters predators (secondary poisoning) is proposed (Thresholds figure 1).



Thresholds figure 1. Good status is achieved if the concentrations of diclofenac are below the defined threshold values.

The threshold values are in line with the scientific PNEC or NOEC values implying that no harmful effects can be found. However, as the issue is of an emerging nature, it is proposed that the threshold value would initially be evaluated as a trend (where data is suitable and accredited) so that no increase in diclofenac concentration from the current status would be allowed. This is in-line with the EU directive on environmental quality standards (2008/105/EC), Article 3, which states that long-term temporal trends should be assessed for substances that accumulate in sediment and/or biota.

Note: Environmental Quality Standards and thresholds proposed in this indicator document are taken from a draft ´EQS DATASHEET Environmental Quality Standard Dicolofenac´ document, a document that represents an EU/wide study (see Dossier Diclofenac reference). This document contains provisional proposals for EQS values. Since diclofenac has been suggested to be removed from the EU watch list, on the basis that enough data has been collected to determine if it is to be added to the priority list (or not), the thresholds used in this indicator are based simply on the most recent proposals made during the ongoing revision process. The process to determine the EQS thresholds and the position of diclofenac related to monitoring requirements remain to be finalised within the EU and until that has been clarified the most recent EQS proposals are maintained for the test thresholds applied in this indicator.

Assessment Protocol

This pre-core test indicator and its threshold values are yet to be commonly agreed in HELCOM and the presented thresholds are furthermore not currently approved EQS values, but provisional proposals.
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Due to the fact that no commonly agreed monitoring strategy has been developed for pharmaceuticals, only data from screening studies, scientific literature and data compilations are currently considered.

A number of factors of potential importance with respect to establishing suitable assessment protocols for this indicator include: 1) developing and confirming the accurate usage and potential of sales statistics, 2) gaining a better understanding of the environmental cycle of diclofenac, 3) developing a clearer understanding of diclofenac transformations in the environment and WWTPs, 4) detailed monitoring of WWTP discharge rates and diclofenac concentrations, 5) clarification of the apparent rapid decrease in diclofenac concentration in rivers (fate and sediment status) 6) temporal monitoring to determine longer term environmental impacts, 7) greater spatial monitoring, 8) enhanced monitoring of all relevant compartments (e.g. water, sediment and biota), 9) potential designation of target organisms for monitoring effort (e.g. benthic feeders, sedentary filter feeders, or species that traverse the marine-freshwater boundary), 10) the role of WWTPs in close proximity to the Baltic Sea coast, and 11) agreement on suitable analytical methodologies. Many of these factors are discussed in Lehtonen et al., (2014), and as greater spatial and temporal data emerges clear progress will be possible.

Assessment units

The indicator is tentatively to be evaluated on the HELCOM assessment unit level 4 (http://www.helcom.fi/action-areas/monitoring-and-assessment/monitoring-and-assessment-strategy), as the status of the marine environment is presumed to be affected mainly from WWTP related point sources. In screening studies, water concentrations failing to achieve good status have generally been found to drop over a distance of a few kilometres. As knowledge on the spatial extent of diclofenac dispersal, its fate, and its impact increases it may be possible to apply a more suitable assessment strategy. The indicator is in theory applicable in all assessment units throughout the Baltic Sea, as diclofenac is used in all HELCOM regions.

Relevance of the Indicator

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Hazardous substances assessment

The status of the Baltic Sea marine environment in terms of contamination by hazardous substances is assessed using several core indicators. Each indicator focuses on one important aspect of the complex issue. In addition to providing an indicator-based evaluation of the status of the Baltic Sea in terms of concentrations of diclofenac in the marine environment, this indicator may in the future be suitable for incorporation into the overall hazardous substances assessment, integrated in conjunction with the other hazardous substances core indicators.

Policy relevance

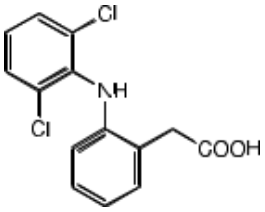
The Moscow Ministerial Declaration 2010 gives HELCOM a clear obligation to 'further assess the environmentally negative impacts of pharmaceuticals and other substances that are not monitored regularly, with the aim as a first step to assess in a coordinated manner their occurrence in the Baltic Sea and evaluate their impacts on the Baltic biota'. The commitment was followed up by the 2013 HELCOM Ministerial Declaration in which the Contracting Parties agreed to collect information on pharmaceuticals and assess the status of contamination of pharmaceuticals and their degradation products in the marine environment.

Diclofenac was included on the EU first watch list (2013/39/EU) with the stated aim being to gather monitoring data for the purpose of facilitating the determination of appropriate measures to address the risk posed by those substances. Inclusion on such watch list is done when there is insufficient data to assess potential negative impacts on the environment, the assertion being based on results from the prioritization process of hazardous substances under the WFD, research results and similar reports. For those HELCOM Contracting Parties that are also EU members the inclusion on the first watch list has required monitoring at selected representative monitoring stations for a 12-month period, a process that started in 2015 and has now been completed. The outcome of the review process based on this data collection will determine future requirements for those HELCOM Contracting Parties that are also EU members.

There are no current restrictions on the use of diclofenac in the Baltic Sea region, though in India for example, its use is being phased out due to the documented detrimental effects on vultures.

Furthermore, the monitoring of diclofenac and the development of the indicator may have direct relevance to policies related to WWTPs and pharmaceutical disposal/take-back initiatives.

Role of diclofenac in the ecosystem



Diclofenac is an active pharmaceutical ingredient belonging to a group called nonsteroidal anti-inflammatory drugs (NSAIDs) that works by reducing hormones that cause inflammation and pain in the body. This pharmaceutical is widely used in the Baltic Sea region, in the format of tablets to be ingested, injections and as creams for topical application.

Low removal rates and poor biodegradation have been reported, though reports on both seem to range dependant on specific condition (as reviewed in Vieno and Sillanpää, 2014). Consequently, effluent waters from some WWTPs can contain high concentrations. Introduction to the Baltic Sea is believed to take place primarily via this route, with rivers transferring diclofenac to the Sea. While concentrations have been shown to decrease rapidly in rivers diclofenac has also been detected in water samples far from known sources (HELCOM 2014).

The strongest evidence of the detrimental effects of diclofenac stems from the terrestrial environment. Residues of diclofenac causing kidney failure is considered to be the main cause for a decline of >95 % in the population of oriental white-backed vulture, one of the (previously) most common raptors in India and Pakistan (Oaks et al, 2004, Shultz et al, 2004; Reddy et al, 2006; Swan et al, 2006; Cuthbert et al, 2006, 2007).

In the aquatic environment diclofenac has been shown to bioaccumulate in fish (Brown et al. 2007; Schwaiger et al., 2004; Brozinski et al., 2013), including diclofenac metabolites (Kallio et al., 2010), and mussels (Ericson et al., 2010). Toxic effects have also been recorded, including kidneys disruption (Schwaiger et al., 2004; Triebskorn et al, 2004; Hoeger et al., 2005), damage to eggs and embryos (Hallare et al., 2004), and altered gene expression (Cuklev et al., 2011). In crabs diclofenac has been shown to cause disruption of osmoregulation (Eades & Waring 2010) and in broadcast spawning marine invertebrates it may have consequences for reproductive success (Zanuri et al., 2017). In mussels diclofenac has been shown to have a number of impacts. Early studies indicated that byssus strength (i.e. the ability to attach to substrates) was impaired and that energy was potentially diverted from growth and reproduction, with possible long term population effects (Ericson et al., 2010). More recent studies using biomarkers have shown a range of alterations indicative of: oxidative stress, gill and digestive gland damage, altered protein folding, impaired immunological response, and energy metabolism changes due to diclofenac or pollutant cocktail exposure (Schmidt et al., 2011; Schmidt et al., 2013, Turja et al., 2014; Gonzalez-Rey and Bebianno, 2014; Turja et al., 2015, Mezzelani et al., 2016). It has also been shown that mussels from more pristine environments were more strongly influenced and that recovery time differed (Kumblad et al., 2015) and suggested that this biomarker approach may offer promise as an environmental status indicator component (Löf et al., 2016). Furthermore, in many cases these impacts were observed at environmentally relevant concentrations and is some systems in the environment itself.

While the general consensus is that acute toxicity appears unlikely, there is significant concern that long term exposure, continual discharges (i.e. increasing environmental deposition), and local environmental factors may be key factors and that specific environmental zones or biological categories may be adversely influenced by diclofenac concentrations. Diclofenac has been shown to be susceptible to photo-degradation, though the process appears highly site-specific, and the breakdown compounds from this action may also be compounds of concern (Schmitt-Jansen et al., 2007). Furthermore, there is evidence to suggest that mixtures

of several hazardous compounds, as is commonly found in the environment, can have markedly stronger negative impacts (Cleuvers, 2004) and should be considered, particularly in the light of long term exposure, and that climate change alterations to the environment (e.g. ocean acidification) may influence the potency of diclofenac (Munari et al., 2016).

Human pressures linked to the indicator

	General	MSFD Annex III, Table 2a
Strong link		Substances, litter and energy - Input of other substances (e.g. synthetic substances, non-synthetic substances, radionuclides) – diffuse sources, point sources, atmospheric deposition, acute events
Weak link		

Monitoring Requirements

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Monitoring methodology

Diclofenac can be analysed in water and in fish plasma, and other biomarkers are rapidly being developed. Pharmaceuticals are generally present at very low concentrations in the environment, thus it is vital that selected analytical methods take analytical limits into consideration (see Unesco and HELCOM, 2017 for discussion). Agreement on methodology and the analytical procedure to carry out the designated analysis will be convened on by HELCOM Contracting Parties during further indicator development.

The HELCOM BASE pilot project carried out sampling in waste water treatment plants according to the following methodology:

- WWTP personnel carried out sampling
- In influent water by sampling over a 24-hour period on which the average was calculated. Effluent samples were grab samples taken on the same mornings.
- On several days, two samples were taken and analysed independently.
- Samples were collected by SRCES personnel immediately afterwards and extracted within 24 hours.
- $^{13}C_6$-Diclofenac was used as a surrogate standard and was introduced into the raw sample.
- Samples were analysed for Diclofenac using HPLC-HRMS.

Current monitoring

Diclofenac is currently not included in the regular environmental monitoring of any HELCOM Contracting Party, though EU member states have been obliged to monitor this substance and report collated data due to its inclusion on the first watch list of the EU priority substances. This process has now been completed and the data review and decision making process are underway. The substance is considered an emerging issue, and as such it has been included in some national screening programmes (e.g. Swedish EPA) and as extensive spatial and temporal data is reported this indicator will be updated.

Description of optimal monitoring

Due to the lack of coherent data from the marine environment and especially from biota, it is not possible to give recommendations on optimal monitoring at this time. Generally it can be stated that monitoring should be commenced in coastal areas close to cities with large wastewater treatment plants (WWTPs), particularly those within the coastal zone, and that intercalibration between all involved laboratories would be very beneficial.

Screening studies of surface water show concentrations generally dropping to below the threshold value at a distance of 10 km from WWTPs. It might be appropriate to monitor concentrations at the WWTP and at a specified distance from the plant in sea water and biota, however specifying the distance will require further work. The change of diclofenac concentration over a distance from source is highly dependent on the hydrological, hydro-chemical and hydro-biological regimes in the assessment unit. It might not be possible to provide guidelines as the appropriate design of the sampling strategy that would be generally applicable in all areas. However, it could be relevant to consider more closely the patterns in changing concentrations versus distance from source from several locations, to consider whether min-max and median values at a certain location or from several locations could be used when evaluating the status of the environment. Examining concentration trends over time more closely is also considered to be relevant.

The pilot study in the St Petersburg area carried out in the HELCOM BASE project (HELCOM 2014) clearly demonstrated the benefit from coupling environmental monitoring data with proxy data from pharmaceutical sales. However the pilot study underlines the importance of accessing high quality sales data for making relevant proxy evaluations. Improving the availability of this proxy data from pharmaceutical sales, would be a cost effective method to improve the knowledge base of the environmental status assessment of the Baltic Sea.

Data and updating

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Access and use

The data and resulting data products (tables, figures and maps) available on the indicator report can be used freely, given that the source is cited. The indicator should be cited as follows:

HELCOM (2018) Diclofenac. HELCOM pre-core indicator report. Online. [Date Viewed], [Web link].

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Metadata

The current data are very variable and somewhat disparate, being gathered from scientific publications, reports and data compilations. All sources are presented in the reference list where possible. The majority of measurements are from WWTPs, though some have been taken from rivers, estuaries and biota. Metadata will be updated in subsequent versions and made available via the HELCOM data and mapping services at that stage.

Data sources are referenced where possible. Monitoring data is often not published in the same formats as other reference material and where data is referenced as HELCOM DATA CALL then this data refers to data reported to HELCOM by national contact points for each individual country. All HELCOM countries reported data during the process and the 2017 DATA CALL (PRESSRURE and State&Consevation 2017) referenced above included the following information:

1) WWTP data from: Denmark (6 influent mean values, 6 effluent mean values, and 6 sludge mean values), Finland (28 influent values of which 3 were mean values, 31 effluent values of which 3 were mean values, and 2 sludge values of which one was a mean value), Germany (259 effluent values), Latvia (2 influent values, and 6 effluent values of which 5 were mean values), Sweden (17 effluent values, and 3 sludge values), and Russia (8 mean influent and 8 mean effluent values).
2) River data from: Denmark (17 items, of which 5 were 'less-than'[note below] values), Estonia (56 items, of which 54 were 'less-than' values), Finland (62 items, of which 25 were 'less-than' values, and 15 were mean values), Germany (2164 items, of which 1208 were 'less-than' values), Latvia 15 items, of which 14were 'less-than' values), Lithuania (4 items, of which 4 were 'less-than' values), Poland (180 items), and Sweden (8 items, of which 1was a 'less-than' value).
3) Open sea and coastal waters: All together 60 observation were reported for the period 2014 and 2017 with data supplied by Denmark, Germany, Latvia, Poland and Sweden. Only 3 observations out

of 60 had analytical limits higher than the threshold value identified for marine water. Presence of diclofenac in marine water was identified in 8 samples and the GES threshold was exceeded in 5 cases.

Note below This term is used for data that have values below the technical limits of quantification (LOQ) of the used equipment. It does not indicate anything in relation to the threshold values (for which river data are not compared in the current report) but these data are not included in the summary tables above. In the future these issues should be addresses to consider river data against possible threshold values and a suitable incorporation of 'less-than' value data in the assessment.

Contributors and references

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Contributors

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The HELCOM Correspondence Group on Pharmaceuticals (HELCOM GC PHARMA) has also contributed and reviewed this document.

Archive

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Diclofenac HELCOM pre-core indicator 2018 (pdf)

There are no previous versions of this indicator report at present.

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