Nordic Council of Ministers

Pharmaceuticals in Northern environments; what, where and how much?

Content

Preface

This report presents the outcome of the Nordic Council of Ministers' founded project "Pharmaceuticals in Northern environments; what, where and how much?". This Nordic project has been led by Pernilla Carlsson in close collaboration with Kristín Ólafsdottir and Arndís Sue-Ching Löve (Háskóli Íslands), Johan Lindberg (RISE, Sweden), Susanne Vävare (Ålands landskapsregering), Christian Vogelsang, Mona Eftekhar Dadkhah and Malcolm Reid (NIVA). Everyone has contributed with data and statistics from their respective country on pharmaceutical sales statistics and waste water treatment plant (WWTP) processes. Literature review, reporting, calculations of human excretion and WWTP removal efficiency have mainly been conducted by Christian Vogelsang, Mona Eftekhar Dadkhah, Kristín Ólafsdottir, Arndís Sue-Ching Löve, Malcolm Reid and Pernilla Carlsson. We thank everyone involved for a very good cooperation.

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Summary

The present study has investigated and collected sales statistics of pharmaceuticals in Sweden, Norway and Iceland. A literature review of waste water treatment plants (WWTP) and the efficiency of different WWTP techniques was conducted and combined with a literature review of metabolization of pharmaceuticals in humans. These data have been linked and used for calculations of the amount of pharmaceuticals and their metabolites that actually reaches the aquatic recipient. The most common used pharmaceuticals differ slightly between the Nordic countries investigated, although many of them are common in all of the countries.

Since pharmaceuticals often are metabolised to a large extent within the body and thereafter excreted as metabolites into the WWTPs, an efficient removal of the little fraction of parental compounds still present does not take into account any metabolites released into the aquatic environment. A future recommendation is to include metabolites of pharmaceuticals in environmental impact studies to be able to assess and account for the chemicals that actually pass through a WWTP to the aquatic environment.

Sammendrag

Denne studien har samlet og undersøkt salgsstatistikk for legemidler i Sverige, Norge og Island. Litteraturundersøkelser av effektiviteten ved forskjellige typer renseverk og metabolisering av legemidler i mennesker er utført og kombinert for å kunne estimere hvor mye legemidler og metabolitter som går ut årlig fra renseverk i Norden og inn i det akvatiske miljøet.

Det er ikke avdekket noen store, vesentlige forskjeller i forbruk av legemidler i de undersøkte landene, selv om det varierer hvilke legemidler som er de aller mest brukte.

Mesteparten av legemidlene metaboliseres ofte i kroppen og det er derfor mer metabolitter enn hovedstoff som oftest havner i renseverkene. En høy renseeffektivitet av hovedstoffet er dermed ikke enslydende med at mye av den totale massen hovedstoff og metabolitter faktisk rensens bort før det når det miljøet. Våres anbefaling er derfor at studier i fremtiden bør se mer på utslipp av metabolitter til det akvatiske miljøet, noe som er ekstra viktig mhp. eventuelle miljøeffekter av metabolitter.

Tittel: Legemidler i Norden; hva, hvor og hvor mye?

År: 2019

Forfattere: Pernilla Carlsson, Kristín Ólafsdottir (Háskóli Íslands), Arndís Sue-Ching Löve (Háskóli Íslands), Christian Vogelsang, Mona Eftekhar Dadkhah, Johan Lindberg (RISE), Malcolm Reid
Utgiver: Nordisk Ministerråd

1. Introduction

1.1 WWTPs and treatment principles

Wastewater treatment plants (WWTPs) are designed to meet their discharge permits focusing on the removal of suspended solids (SS) (i.e. particulate matter) and nutrients such as biodegradable organic matter, phosphorous or nitrogen depending on the local treatment requirements. The discharge permits are stricter in regions that are considered as sensitive to eutrophication than in so-called normal areas, which is the case for the Baltic Sea, Kattegat and Skagerrak and their associated freshwater catchment areas. As stated in the EU Directive 91/271/EEC, all discharges from agglomerations >2,000 person equivalents (PE) to normal and sensitive areas need to undergo secondary treatment, which implies a minimum of 70% removal of the biological oxygen demand (BOD_5) and 75% removal of the chemical oxygen demand (COD_{Cr})[1] . Discharges from agglomerations >10,000 PE to sensitive areas also need to comply with a minimum removal of total phosphorous of 80% (90% in the Norwegian regulations) and/or a minimum removal of 70% removal of total nitrogen[2]. These requirements imply relatively advanced biological and/or chemical treatment. In Norway, chemical treatment has been the preferred treatment method (Figure 1), focusing on the removal of phosphorus rather than BOD5. Hence, if phosphorous removal by chemical treatment is already applied (complying with a minimum of 90% removal of total P), secondary treatment is only required when a major upgrading to the WWTP is planned. Furthermore, nitrogen removal is only required in four distinct areas in Norway; Oslo, Lillehammer, Jessheim and Nordre Follo. In Sweden and Åland, the main treatment of waste water is tertiary treatment.

The permits regulating discharges to other areas than those mentioned above are in general less strict. Discharges from agglomerations of <10,000 PE to less sensitive areas (i.e. the Atlantic coast of Norway and Iceland) only need to apply simple sieving (≤1 mm pore size) or septic tank and complying with a minimum of 20% reduction in SS. For discharges from agglomerations of >10,000 PE to less sensitive areas secondary treatment is the standard. Moreover, if the discharge can be documented to not adversely affect the environment in terms of eutrophication or oxygen depletion due to a good water exchange, only primary treatment may be required, which implies a minimum of 20% removal of BOD_5 and 50% removal of SS.

1. Or discharge of a maximum of 25 mg O2/L as BOD5 and 125 mg O2/L as CODCr. There is also an optional limit of 70% removal of SS (<60 mg SS/L in effluent) for 2,000-10,000 PE and 90% removal of SS (<35 mg SS/L in effluent) for >10,000 PE.
2. Or discharge of a maximum of 2 mg P/L (1 mg P/L for agglomerations >100,000 PE) and 15 mg N/L (10 mg N/L for agglomerations >100,000 PE).

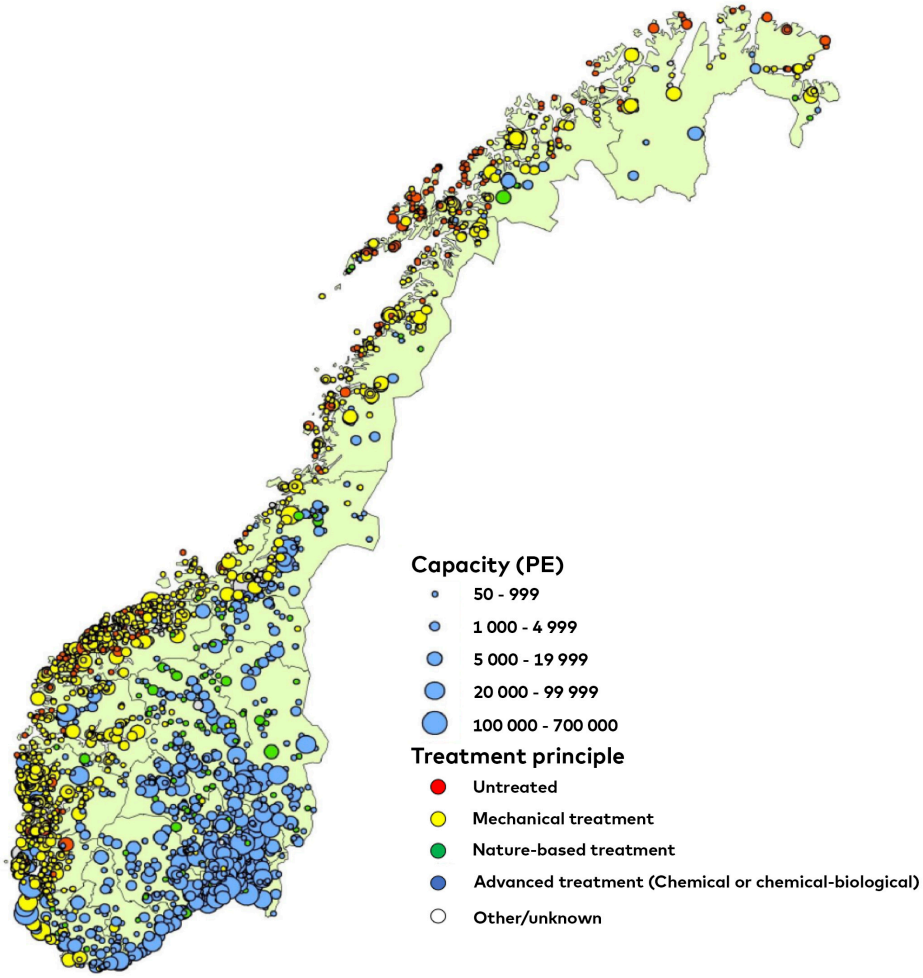

Figure 1. Overview of applied treatment principles and capacities in Norway (Berge and Sæther, 2018).

1.2 Pharmaceuticals

Recent studies have shown that the Baltic Sea receives about 1,800 tonnes of pharmaceuticals each year and the cleaning efficiency of parent compounds are often low (Vieno et al., 2017). On top of this, information regarding the environmental fate of the metabolites of these pharmaceuticals are very scarce. Some metabolites may deconjugate back to the parental compound (Celiz et al., 2009; Ternes et al., 1999) while others might very likely have a biological impact also as metabolites. Pharmaceuticals are, by obvious reasons, designed to have an impact in a biological system. However, little is known about any potential side effects apart from e.g. sex hormones and their interaction with fishes (Perrault 2003). As with all environmental pollutants, it is important to keep in mind that volume and toxicity are not necessarily correlated; certain compounds might be used in small quantities, but still have a high toxicity.

1.3 Aim of study

The project aims to investigate and quantify what, where and how much pharmaceuticals are released to the surrounding water bodies through waste water treatment plants in Iceland, Sweden, Åland and Norway. We will focus on the mostly used pharmaceuticals in each country and literature data on WWTP efficiencies on the respective compounds.

2. Methods

All pharmaceuticals are classified according to the Anatomical Therapeutic Chemical (ATC) system according to their anatomical main group, therapeutic and pharmacological subgroup and chemical substance. Compounds listed with several modes of action (i.e. same chemical compound, different ATC codes) were combined in this report. Usage of pharmaceuticals in the Nordic countries were provided as Defined Daily Doses (DDD). A DDD is defined as "the assumed average maintenance dose per day for a drug used on its main indication in adults". These numbers were recalculated into kilogram/year based on information from WHO (2019). More information regarding ATC system and DDDs can be found in e.g. Sakshaug et al. (2018) and from WHO (2019).

2.1 Collection of consumption data for pharmaceuticals

2.1.1 Iceland

Information on 40 most sold prescription pharmaceuticals in Iceland 2017 and 2018 was provided by the Medicines Registry from the Directorate of Health. This list provided a total number of nationwide defined daily doses (DDD) of sold prescription drugs. The DDD of each drug was converted to kg sold per year by using the doses defined by the WHO Collaborating Centre for Drug Statistics Methodology (WHO) 2019. The number of sold units of pharmaceuticals sold over the counter (OTC) in 2018 were provided by the Icelandic Medicines Agency. The units sold were converted into kg per year. The OTC data was combined with data on prescription drugs. Pharmaceuticals used by hospitals are not included in these numbers and the medication brought into the country by more than 2.3 million tourists per year is unknown (Ferdamalastofa, 2019). Iceland had 356,991 inhabitants as of 1 January 2019 (Statistics Iceland, 2019).

2.1.2 Norway

The Norwegian Institute of Public Health (FHI) was contacted and kindly provided statistics for annual usage in Norway of the active compounds. The data includes pharmaceuticals sold over the counter as well as prescriptions. Norway had 5,328,212 inhabitants as of 1 January 2019 (SSB, 2019).

2.1.3 Sweden

The Swedish Medical Products Agency (SMPA) was contacted and kindly provided statistics for annual usage in Sweden of the active compounds. The data includes pharmaceuticals sold over the counter as well as prescriptions. Sweden had 10,230,185 inhabitants as of 31 December 2018 (SCB, 2019).

2.1.4 Åland

Only data regarding usage of antibiotics were available for Åland. The waste water treatment in Åland is tertiary for the main population (ca 29,800 habitants in 2018), and water corresponding to 31,000 person equivalents (PE) are treated each year (personal communication with Lotsbroverket, and Susanne Vävare (Ålands landskapsregering)). This number accounts for industrial waste water as well. Some habitants are not connected to the main WWTP. Due to limited resources in the project, we choose not to do a specific calculation for Åland based on e.g. Swedish sales statistics. However, seen in a holistic, Scandinavian perspective, these 29,800 people would anyway be within the uncertainty of e.g. Åland's neighbour Sweden and hence, an additional calculation of Åland with sales statistics from its neighbour was considered to not be highly relevant to this report taken the general uncertainty into account.

2.2 Prediction of excretion rates and ratios between metabolites and parent compound

Information regarding metabolism and excretion of all investigated compounds were collected through a literature study (Table S1). Since details regarding which metabolites are formed and to which extent are often scarce, we have not done any calculations on metabolites released at this time since such numbers would involve very high uncertainty. We realize however, that the metabolites might be responsible for high effects in the environment just as, or even more than the parent compounds. These effects will need to be explored in a later study.

2.3 Applied wastewater treatment principles

Wastewater treatment principles ranges from no treatment (typically small, private sewages) to advanced biological and chemical methods. Mechanical cleaning (e.g. filtering of large particles) are the most common method in Iceland (68% of the population) and is also very common in large areas of Norway, although chemical and/or biological treatments are applied in Skagerrak and lake areas. Most treatment in Sweden includes biological/chemical steps. All waste water at Åland is treated with biological and chemical treatment. Each type of chemical/biological treatment applied will have different efficiency for individual pharmaceuticals due to different technological settings and their impact on individual pharmaceuticals. It was not possible to take all technological settings into account, in the present report, and there are large data gaps in cleaning efficiencies as well. Therefore, we applied a general approach where primary treatment means only mechanical treatment, and where secondary and tertiary treatments include chemical/biological treatment with an average efficiency based on literature data for each compound. Iceland only have chemical/biological treatment for about 2% of its population, from two small land-locked towns, Egilstaðir and Hveragerði. Due to other data limitation, we have not taken those 2% into account and all treatment in Iceland has been set to mechanical/no treatment. The calculations for Norway have taken secondary and tertiary treatment efficiencies into account since a much larger percentage of waste water is treated compared to Iceland. Similar calculations were done for Sweden. We applied the Norwegian statistics regarding untreated water to

take into account small, rural villages where waste water may not be treated before reaching a recipient in Sweden.

Compounds where data on WWTP efficiency exists were divided into three classes; low (<10% removal efficiency), medium (50%) and high (90%). The amount of parental compound entering the WWTPs were based on human excretion data (Table S1) and the cleaning efficiency (low/medium/high) percentages for these compounds were then applied using the calculations to estimate the release of parent compounds from the WWTPs into the recipient, depending on treatment. Since the treatment efficiency will depend on different techniques, biological/chemical/physical conditions, we applied a low-medium-high percentage instead of an exact value, since it will be too dependent on other factors.

2.3.1 Norway

NIVA has access to discharge details from all domestic WWTPs in Norway that have reported to the municipality-government reporting system (KOSTRA). Reported treated wastewater volumes in 2017 from 310 WWTPs with a treatment capacity >2,000 PE were used in the calculations of the yearly discharge estimates. With a total treatment capacity of 6.67 million PE and ca. 648 million m^3 of treated wastewater, these WWTPs represented 90% of the total treatment capacity and ca. 98% of all treated wastewater reported in 2017 from all WWTPs ≥50 PE in Norway. All reported sewer overflows from the same WWTPs were also included, amounting to ca. 17 million m^3 wastewater. Volume-wise, the WWTPs that applied combined chemical and biological treatment dominated with 42% (Table 1) of the different parent pharmaceutical compounds and sewer overflows. The discharge estimates from Norwegian WWTPs are based on 2017 data.

Table 1. Summary of number of WWTPs applying different wastewater treatment principles and associated volumes treated.

Treatment	Iceland		Norway (>2000 PE)		Sweden		Åland	
	#	Volume (mill. m^3/y)	#	Volume (mill. m^3/y)	#	Volume (mill. m^3/y)	#	Volume (mill. m^3/y)
None		30%	-	17.1 (2.6%)				
Septic tank			3	0.32				
Mechanical		68%	108	84.4 (21%, incl. CEPT)				
CEPT*			5	52.7				
Chemical		0%	90	206.1 (31%)				
Biological		2.4%	10	26.2 (3.9%)				
Biological-chemical			86	277.4 (42%)		Close to 100%		Close to 100%

Note: **CEPT = Chemically enhanced primary treatment.*

2.4 Predictions of expected compound-specific treatment efficiencies

Compound-specific removals by the treatment principles typically applied by the WWTPs in the countries participating in the current survey (see Table 1) were predicted based on available scientific literature.

2.5 Calculations of the estimated annual discharges of pharmaceuticals

Information on excretion of pharmaceuticals and their major metabolites was obtained from the following articles: Baselt (2017), Brunton et al. (2018), Moffat et al., (2011), Stanczyk et al. (2013), Shoupe and Haseltine (1993) and WHO (2006 and 2018). Treatment efficiencies were collected through a literature review (Appendix; Table S2).

The country-specific annual discharges, M_C, were calculated from the estimated fraction of the excreted parent compound that would pass the WWTPs:

$$M_C = C_n * f_{p,n} * (1 - f_{R,n})$$

, where M_C is the annual discharge of the parent compound to recipients in country C, is the country-specific consumption of compound n, is the fraction of compound n that is excreted as the parent compound, and is the fraction of compound n that is expected to be removed by the WWTPs treatment in country C:

$$f_{R,C,n} = f_{mech,n} + f_{chem} * R_{chem,n} + f_{biol} * R_{biol,n} + f_{chem\text{-}biol} * R_{chem\text{-}biol,n}$$

, where f_{mech}, f_{chem}, f_{biol} and $f_{chem\text{-}biol}$ are the respective fractions of municipal wastewater that are treated by WWTPs where the main treatment principle is mechanical, chemical, biological or chemical-biological, and $R_{mech,n}$, $R_{chem,n}$, $R_{biol,n}$ and $R_{chem\text{-}biol,n}$ are the respective removal ratios of compound n by WWTPs applying the indicated treatment principles.

3. Results

3.1 Consumption data for pharmaceuticals

Iceland was able to provide sales statistics for both 2017 and 2018. For all calculations, the 2018 statistics were used unless something else is stated since 2018 was used for the other countries. However, Iceland 2017 statistics are included in this report in the appendix (Table S3). All sales statistics used for calculations (2018 numbers) are shown in Table 2–4 for Iceland, Norway and Sweden. No sales statistics were available for Åland alone and is therefore not presented here. Diclofenac was listed with different ATC codes for Sweden compared to Iceland and Norway.

Table 2. The 38 most used pharmaceuticals in Iceland 2018.

ATC index	Active substance	mg/DDD	Millions DDD/ Iceland	kg sold/year
N02BE01	Paracetamol + OTC	3000	3	16,205
N02AJ06	Codeine and paracetamol	100 + 3,000	2	6,520
M01AE01	Ibuprofen OTC	1,200	No info	4,351
B01AC06	Acetylsalicylic acid + OTC	160	19	4,304
R06AA02	Diphenhydramine OTC	200	No info	1,962
C07AB02	Metoprolol	150	4	537
N06AB06	Sertraline	50	6	320
M01AH01	Celecoxib	200	2	302
N06AX16	Venlafaxin	100	3	302
C09DA01	Losartan and diuretics	50	5	241
C07AB03	Atenolol	75	3	228
C09CA01	Losartan	50	4	220
C03CA01	Furosemide	40	5	215
A02BC05	Esomeprazole	30	7	200
R06AX26	Fexofenadine	120	2	194
C10AA05	Atorvastatin	20	9	190
C09CA03	Valsartan	80	2	181
A02BC01	Omeprazole	20	8	177
C10AA01	Simvastatin	30	6	170
N05CF01	Zopiclone	7.5	19	143
C09DA03	Valsartan and diuretics	80	1	114

C01DA14	Isosorbide mononitrate	40	3	111
N06AX11	Mirtazapine	30	4	107
A02BC04	Rabeprazole	20	4	79
C03EA01	Hydrochlorothiazide and potassium-sparing agents	25	3	76
N06BA04	Methylphenidate	30	2	74
C09AA02	Enalapril	10	6	62
N06AB04	Citalopram	20	3	56
N06AB10	Escitalopram	10	5	53
N06AB03	Fluoxetin	20	3	52
C08CA01	Amlodipine	5	8	42
R06AD02	Promethazine	25	2	41
B01AF01	Rivaroxaban	20	1	28
N05CF02	Zolpidem	10	2	21
M05BA04	Alendronic acid	10	2	16
C09AA05	Ramipril	3	2	4
G03AA07	Levonorgestrel and ethinylestradiol	1.5 + 0.025	3	4
B03BA01	Cyanocobalamin	1	4	4
G04CA02	Tamsulosin	0.4	2	1
H03AA01	Levothyroxine sodium	0.15	5	1

Table 3. The 35 most used pharmaceuticals in Norway 2018.

ATC-code	Active substance	mg/DDD	Millions DDD/ Norway	Kg sold/year
N02BE01	Paracetamol	3,000	84	252,850
A10BA02	Metformin	2,000	29	58,287
M01AE01	Ibuprofen	1,200	31	37,658
B01AC06	Acetylsalicylic acid	160	121	19,324
J01CE02	Phenoxymethylpenicillin	2,000	5	10,000
M01AE52	Naproxen	500	19	9,500
C10AA05	Atorvastatin	20	173	3,458
N02AX02	Tramadol	300	8	2,400
A02BC02	Pantoprazole	40	54	2,155
J01CA08	Pivmecillinam	600	3	1,800
C10AA01	Simvastatin	30	60	1,796

N02AJ06	Codeine*	100	15	1,500
A02BC05	Esomeprazole	30	48	1,446
C09CA01	Losartan	50	28	1,409
M01AB05	Diclofenac	100	11	1,100
R06AE07	Cetirizine	10	67	670
C09CA06	Candesartan	8	64	512
N05BA04	Oxazepam	50	9	450
M01AE52	Esomeprazole	20	19	380
N06AB10	Escitalopram	10	38	379
N05CF01	Zopiclone	7.5	48	361
C08CA01	Amlodipine	5	65	327
H02AB06	Prednisolone	10	22	220
R06AX27	Desloratadine	5	43	216
R05DA01	Ethylmorphine	50	3	150
C09AA05	Ramipril	2.5	58	144
A01AA01	Sodium fluoride	1.1	55	61
R01AA07	Xylometazoline	0.8	72	58
R03AC02	Salbutamol	0.8	23	18
C07AB02	Metoprolol	0.15	46	7
H03AA01	Levothyroxine sodium	0.15	49	7
G03AA07	Levonorgestrel	0.1	45	5
R01AD09	Mometasone	0.2	18	4
G03AA07	Ethinylestradiol	0.02	45	1
G03CA03	Estradiol	0.05	10	1

Note: ** In combinations with Paracetamol. Codeine figures here alone.*

Table 4. The 26 most used pharmaceuticals in Sweden 2018.

ATC-code	Active substance	mg/DDD	Millions DDD/ Sweden	kg sold/ year (2018)
N02BE01	Paracetamol	3,000	91	271,670
A06AD11	Lactulose	6,700	34	224,519
M01AE01	Ibuprofen	1,200	62	74,636
D02AE01	Carbamide***		18	17,636
B01AC06	Acetylsalicylic acid	160	96	7,381
C07AB02	Metoprolol	150	54	8,056
A02BC01	Omeprazole	20	162	3,243
C09CA01	Losartan	50	50	2,511
D08AC02	Chlorhexidine***		2	2,021
C03CA01	Furosemide	40	46	1,858
C10AA05	Atorvastatin	20	90	1,793
C09AA02	Enalapril	10	176	1,761
M02AA15	Diclofenac***		2	1,728
C10AA01	Simvastatin	30	39	1,161
N05CM06	Propiomazine*	25	38	950
C08CA01	Amlodipine	5	153	765
C09CA06	Candesartan	8	52	416
N05CF01	Zopiclone**	7.5	45	339
C05AA01, D07AA02	Hydrocortisone***		0.3	263
A06AG11	Sodium lauryl sulfoacetate***		0.3	261
C08CA02	Felodipine	5	47	234
A01AA01	Sodium fluoride***		0.1	95
N05CH01	Melatonin	2	48	95
R01AA07	Xylometazoline**	0.8	72	58
C05AA01	Hydrocortisone***		0.02	17
H03AA01	Levothyroxine sodium	0.15	97	15

Note:

**Exact DDD usage is not provided, it is ≥38,000 DDDs.*

***Consumer data from 2017.*

****mg/DDDs not provided, only information about units sold.*

3.2 Estimated human excretion rates for parent compound and associated metabolites

Table 5 shows fraction of pharmaceuticals being excreted as parents and metabolites in Norway. The ratios presented here are presented in more detail in Table S1 as well and used for calculations for all countries in the present study. In general, the majority of releases are metabolites of pharmaceuticals.

Table 5. Estimated annual human excretion of parent compounds and associated metabolites for Norway based on consumption data for 2018.

			Norway (2018)		
			C_{Norway}	$C_{Norway} * f_p$	$C_{Norway} * f_m$
ATC-code and name	f_p	f_m	kg/y	kg/y	kg/y
N02BE01 - Paracetamol	0.02	0.98	252,850	5,057	247,793
A10BA02 - Metformin	1.00	0.00	58,287	58,287	-
M01AE01 - Ibuprofen	0.05	0.95	37,658	1,883	35,775
B01AC06 - Acetylsalicylic acid	0.01	0.99	19,324	193	19,131
J01CE02 - Phenoxymethylpenicillin	0.30	0.70	10,000	3,000	7,000
M01AE52 - Naproxen	0.10	0.90	9,500	950	8,550
C10AA05 - Atorvastatin	0.02	0.98	3,458	69	3,389
N02AX02 - Tramadol	0.29	0.71	2,400	696	1,704
A02BC02 - Pantoprazole	0.01	0.99	2,155	22	2,133
J01CA08 - Pivmecillinam	0.60	0.4	1,800	1,080	720
C10AA01 - Simvastatin	0.01	0.99	1,796	18	1,778
N02AJ06 – Codeine*	0.11	0.89	1,500	165	1,335
A02BC05 - Esomeprazole	0.01	0.99	1,446	14	1,432
C09CA01 - Losartan	0.04	0.96	1,409	56	1,353
M01AB05 - Diclofenac	0.01	0.99	1,100	11	1,089
R06AE07 - Cetirizine	0.06	0.94	670	39	631
C09CA06 - Candesartan	0.26	0.74	512	133	379
N05BA04 - Oxazepam	0.01	0.99	450	4.5	446
M01AE52 - Esomeprazole	0.01	0.99	380	3.8	376
N06AB10 - Escitalopram	0.08	0.92	379	30	349
N05CF01 - Zopiclone	0.09	0.91	361	31	330
C08CA01 - Amlodipine	0.05	0.95	327	16	310

H02AB06 - Prednisolone	0.16	0.84	220	35	185
R06AX27 - Desloratadine	0.02	0.98	216	3.7	212
R05DA01 - Ethylmorphine	0.04	0.96	150	6.6	143
C09AA05 - Ramipril	0.02	0.98	144	2.9	141
A01AA01 - Sodium fluoride	0.76	0.24	61	46	15
R01AA07 - Xylometazoline	ND	ND	58	-	-
R03AC02 - Salbutamol	0.30	0.7	18	5.5	13
H03AA01 - Levothyroxine sodium		1.00**	7.4	-	7.4
C07AB02 - Metoprolol	0.03	0.97	6.9	0.21	6.7
G03AA07 - Levonorgestrel		1.00**	4.5	-	4.5
R01AD09 - Mometasone	0.01	0.99	3.6	0.036	3.6
G03AA07 - Ethinylestradiol	0.01	0.99	0.90	0.009	0.89
G03CA03 - Estradiol	0.06	0.94	0.50	0.32	3.47

Note: *f_p and f_m are the fractions of distributed parent compound excreted, and annual discharge of its metabolites, respectively.*

**Codeine in combinations with paracetamol; codeine figures here alone.*

***Levothyroxine sodium and levonorgestrel are assumed to not metabolise to any large extent.*

3.3 Expected compound-specific treatment efficiencies and annual discharges

Estimated removal efficiencies of the different pharmaceutical compounds by mechanical, chemical, biological and chemical-biological treatment processes are presented in Table 6. Data from this table are relevant mainly for Sweden, Åland and Norway, since Iceland lack chemical and biological treatments, except for in Egilsstaðir. However, the population in Egilsstaðir is only ~2% of the Icelandic population and are therefore not included in these estimates. Since no sales statistics were available for Åland, no further calculations have been made either. Based on the present data and the knowledge that Åland has tertiary treatment on its main WWTPs, a realistic estimate of released pharmaceuticals and metabolites could be based on sales statistics in Sweden, and the information in Table 6 regarding treatment efficiency for different pharmaceuticals.

Table 7–9 show how much of the most sold compounds in Iceland, Norway and Sweden that are excreted as parent compound and the treatment efficiency/ excreted parent compound for the different WWTPs in each country. The influent is the unmetabolised parent compound (for details on metabolisation, see Table S1). The effluent is the amount that, according to Table 6 would be degraded with a chosen treatment. Since most of the parent compounds are metabolised within the human body, a very low percentage of the original compound actually reaches the receiving water bodies. Tramadol (17%) and candesartan (15%) are the only pharmaceuticals on the Norwegian list where >10% of the distributed dose is expected to pass through humans and WWTPs undegraded. It is worth mentioning that these numbers do not take deconjugation of parental compounds into account and that the percentage might be different for other, less used pharmaceuticals. The numbers for Iceland are higher; >10% of a distributed parent compound are released from WWTPs for 10 of the compounds on the list. However, the Icelandic list contains more pharmaceuticals than the Norwegian list and those with high percentage of parent compound passing through the WWTPs are not on the Norwegian compound list.

Table 6. Estimated removal efficiencies of the different pharmaceutical compounds by mechanical, chemical, biological and chemical-biological treatment processes.

No	ATC code	Compound	Removal efficiency for treatment categories			
			Mechanical	Chemical	Biological	Chemical-Biological
1	N02BE01	Paracetamol	Low	High	High	High
2	A10BA02	Metformin	Low		High	High
3	M01AE01	Ibuprofen	Low	High	High	High
4	B01AC06	Acetylsalicylic acid	Low	High	High	High
5	J01CE02	Phenoxymethyl-penicillin	Low		High*	High
6	M01AE52	Naproxen	Low	Moderate	High	High
7	C10AA05	Atorvastatin	Low		High	High
8	N02AX02	Tramadol	Low	Low	Low	Low
9	A02BC02	Pantoprazole	Low		N**	N
10	J01CA08	Pivmecillinam	Low			
11	C10AA01	Simvastatin	Low		High	High
12	N02AJ06	Codeine	Low		Moderate*	
13	A02BC05	Esomeprazole	Low		High	High
14	C09CA01	Losartan	Low	Moderate	Moderate	Moderate
15	M01AB05	Diclofenac	Low	Moderate	Moderate	Moderate
16	R06AE07	Cetirizine	Low			
17	C09CA06	Candesartan	Low	Low	Low	Low
18	N05BA04	Oxazepam	Low	Low	Low	Low
19	M01AE52	Esomeprazole	Low			
20	N06AB10	Escitalopram	Low		High	High
21	N05CF01	Zopiclone	Low			
22	C08CA01	Amlodipine	Low		Mod-High***	
23	H02AB06	Prednisolone	Low		High	High
24	R06AX27	Desloratadine	Low			
25	R05DA01	Ethylmorphine	Low			
26	C09AA05	Ramipril	Low		Mod-High	Low-Mod-High
27	A01AA01	Sodium fluoride	Low			
28	R01AA07	Xylometazoline	Low			
29	R03AC02	Salbutamol	Low			
30	H03AA01	Levothyroxine	Low			

		Sodium			
31	C07AB02	Metoprolol	Low	Moderate	High
32	G03AA07	Levonorgestrel	Low		
33	R01AD09	Mometasone	Low		
34	A11CC05	Colecalciferol	Low		
35	G03AA07	Ethinylestradiol	Low	Moderate	Moderate
36	G03CA03	Estradiol	Low	High	High

Note: *Coloured backgrounds (green, orange, red) indicate that there exist data to support the claim.*

Green = results from several full scale WWTPs; high removal has been well documented with less advanced treatment, high removal may hence be assumed with more advanced treatment.

Orange = only results from 1–2 full scale plants or pilot scale studies exist.

Red = Predicted from modelling or chemical-physical properties.

** Based on modelling data.*

*** Formation of parent compound.*

****Only pilot plants.*

Table 7. Influent Table and effluent of the most used pharmaceuticals in Iceland 2018 as kg/year.

	Mechanical (68%)		Untreated (30%)	Total effluent (kg)	% of distributed parent released from WWTP
	Influent	Effluent	Effluent	Effluent	
Omeprazol	1	1	1	2	1%
Pantoprazole	1	1	0	1	1%
Rabeprazol	0	-	-	0	0%
Esomeprazole	1	1	1	2	1%
Acetylsalicylic acid	29	29	13	42	1%
Isosorbide mononitrate	2	2	1	2	2%
Furosemide	82	82	36	118	55%
Metoprolol	11	11	5	16	3%
Atenolol	136	136	60	197	86%
Amlodipine	1	1	1	2	5%
Ramipril	0.1	0.1	0.03	0.1	2%
Losartan	13	11	6	17	4%
Valsartan	163	163	72	234	79%
Simvastatin	1	1	1	2	1%
Atorvastatin	3	3	1	4	2%
Ethinylestradiol	0.01	0.01	0.01	0.02	1%
Levonorgestrel	0	-	-	0	0%
Levothyroxine sodium	0	-	-	0	0%
Ibuprofen	148	133	65	198	5%
Celecoxib	5	5	2	8	3%
Codeine*	488	488	215	703	11%
Paracetamol	220	220	97	318	2%
Zopiclone	8	8	4	12	8%
Sertraline	0.4	0.4	0.2	1	0.2%
Escitalopram	6	6	3	9	8%
Mirtazapine	0	-	-	0	0%
Venlafaxin	10	10	5	15	5%
Diphenhydramine	13	13	6	19	1%
Fexofenadine	125	125	55	181	93%

Methyphenidate	1	1	0.2	1	1%
Promethazine	0.1	0.1	0.02	0.1	0.2%
Fluoxetin	4	4	2	5	10%
Zolpidem	0.2	0.2	0.1	0.3	1%
Alendronic acid	11	11	5	16	98%
Tamsulosin	0.1	0.1	0.02	0.1	9%
Hydrochloro-thiazide**	49	49	22	71	93%
Enalapril	10	10	4	14	23%
Rivaroxaban	7	7	3	10	35%

Note: *The total amount released in Icelandic waters take percentage of population with certain treatment (given in parentheses) into account. The headlines show how much (percentage) of the national sewage that is treated by which treatment, while the two last columns show the sum of the total effluent and total amount of parent compound released nationwide.*

** In combinations with paracetamol. Codeine figures here alone.*

*** Including potassium-sparing agents.*

Table 8. Influent and effluent of the most used pharmaceuticals in Norway 2018 as kg/year.

	Mechanical (21%)		Chemical (31%)		Biological (3.9%)		Chemical-biological (42%)		Untreated (2.6%)	Total	
	Infl.	Effl.	Infl.	Effl.	Infl.	Effl.	Infl.	Effl.	Effl.	Effl.	Ratio of TADPC*
Paracetamol	1,045	940	1,567	157	199	20	2,109	211	130	1,458	0.58 %
Metformin	12,043	10,839	18,066	n.e.	2296	n.e.	24,307	2431	1,502	14,771	25 %
Ibuprofen	389	350	584	58	74	7.4	785	79	49	543	1.44 %
Acetylsalicylic acid	40	36	60	6	7.6	0.76	81	8.1	5.0	56	0.29 %
Phenoxymethyl-penicillin	620	558	930	n.e.	118	11.8	1,251	125	77	772	7.7 %
Naproxen	196	177	294	147	37	3.74	396	40	24	392	4.1 %
Atorvastatin	14	13	21	n.e.	2.7	0.27	29	3	1.8	18	0.51 %
Tramadol	144	129	216	194	27	24.7	290	261	18	627	26 %
Pantoprazole	4.5	4	6.7	n.e.	0.8	1.70	9.0	18	0.56	24	1.12 %
Pivmecillinam	223	201	335	n.e.	43	n.e.	450	n.e.	n.e.	n.e.	
Simvastatin	3.7	3	5.6	n.e.	0.7	0.071	7.5	0.7	0.46	5	0.26 %
Codeine	34	31	51	n.e.	6.5	3.3	69	n.e.	4.25	38	2.5 %
Esomeprazole	3.0	3	4.5	n.e.	0.6	0.06	6.0	0.6	0.37	4	0.26 %
Losartan	12	10	17	9	2.2	1.11	24	12	1.45	34	2.4 %
Diclofenac	2.3	2	3.4	2	0.4	0.22	4.6	2.3	0.28	7	0.59 %
Cetirizine	8.0	7	12	n.e.	1.5	n.e.	16	n.e.	1.00	8	1.23 %
Candesartan	28	25	41	37	5.2	4.7	56	50	3.43	120	23 %
Oxazepam	0.9	0.8	1.4	1	0.2	0.16	1.9	1.7	0.12	4	0.90 %
Esomeprazole	0.8	0.7	1.2	n.e.	0.1	n.e.	1.6	n.e.	0.10	1	0.21 %
Escitalopram	6.3	5.6	9.4	n.e.	1.2	0.12	13	1.3	0.78	8	2.1 %
Zopiclone	6.3	5.7	9.5	n.e.	1.2	n.e.	13	n.e.	0.79	6	1.80 %
Amlodipine	3.4	3.0	5.1	n.e.	0.6	0.32	6.8	n.e.	0.42	4	1.16 %
Prednisolone	7.3	6.5	10.9	n.e.	1.4	0.14	15	1.5	0.91	9	4.1 %

Desloratadine	0.8	0.7	1.1	n.e.	0.1	n.e.	1.5	n.e.	0.09	1	0.36 %
Ethylmorphine	1.4	1.2	2.0	n.e.	0.3	n.e.	2.8	n.e.	0.17	1	0.93 %
Ramipril	0.6	0.5	0.9	n.e.	0.1	0.057	1.2	0.6	0.07	1	0.88 %
Sodium fluoride	9.6	8.6	14	n.e.	1.8	n.e.	19	n.e.	1.19	10	16.1 %
Xylometazoline	12	10.8	18	n.e.	2.3	n.e.	24	n.e.	1.49	12	21 %
Salbutamol	1.14	1.0	1.71	n.e.	0.22	n.e.	2.3	n.e.	0.14	1	6.4 %
Levothyroxine Sodium	0.000	0.0	0.000	n.e.	0.000	n.e.	0.000	n.e.	0.000	0	0.00 %
Metoprolol	0.043	0.038	0.064	n.e.	0.008	0.0041	0.086	0.009	0.005	0	0.82 %
Levonorgestrel	0.000	0.000	0.000	n.e.	0.000	n.e.	0.000	n.e.	0.000	0	0.00 %
Mometasone	0.007	0.007	0.011	n.e.	0.001	n.e.	0.015	n.e.	0.001	0	0.21 %
Colecalciferol	0.000	0.000	0.000	n.e.	0.000	n.e.	0.000	n.e.	0.000	0	0.00 %
Ethinyl-estradiol	0.002	0.002	0.003	n.e.	0.000	0.00018	0.004	0.002	0.000	0	0.44 %
Estradiol	0.007	0.006	0.010	n.e.	0.001	0.00013	0.013	0.001	0.001	0	1.63 %

** TADPC = total of annually distributed parent compound*

Note 1: *Total amount discharged from the WWTPs shown are not including the "unknown" discharges, particularly from the chemical treatment plants, due to lack of data and research on this. Note that the given discharges are therefore potentially significantly smaller than the actual discharges. These estimated discharges are marked in red.*

Note 2: *The influent to each type of treatment plant is the ratio of the total sum of all excreted unmetabolised parent compound (Table 5) that is expected to be received by this type of treatment based on the ratio of the Norwegian population served by this type of treatment plant (percentages shown in heading). The effluent is the estimated residual amount that, according to Table 6, would not be removed applying that type of treatment. The two last columns show, in order, the sum of the parent compound in all effluents from all WWTPs and the percentage that this represents of the total annually distributed parent compound in Norway.*

Table 9. Influent and effluent of the most used pharmaceuticals in Sweden 2018 as kg/year.

	Chemical-biological (97%)		Untreated (3%)	Total	% of distributed parent released from WWTP
	Influent	Effluent	Effluent	Effluent	
Sodium fluoride	70	70	2	72	76%
Omeprazol	31	31	1	32	1%
Acetylsalicylic acid	149	15	5	20	0.1%
Furosemide	1,009	1,009	31	1,041	56%
Metoprolol	234	117	7	124	2%
Amlodipine	37	19	1	20	3%
Losartan	97	49	3	52	2%
Candesartan	105	94	3	98	23%
Simvastatin	11	1	0	1	0.1%
Atorvastatin	35	17	1	18	1%
Levothyroxine sodium	0	0	0	0	0%
Diclofenac	17	15	1	16	1%
Ibuprofen	3,620	362	112	474	1%
Paracetamol	5,270	527	163	690	0.3%
Zopiclone	28	28	1	29	9%
Xylometazoline	0	0	0	0	0%
Enalapril	393	393	12	405	23%
Lactulose	217,783	217,783	6,736	224,519	100%
Sodium lauryl sulfoacetate	253	253	8	261	100%
Hydrocortisone	271	271	8	280	100%
Felodipine	227	227	7	234	100%
Carbamide	17,107	17,107	529	17,636	100%
Chlorhexidine	1,961	1,961	61	2021	100%
Melatonin	92	92	3	95	100%
Propiomazine	922	922	29	950	100%

Note: *The influent is the unmetabolised parent compound (for details on metabolisation, see Table S1). The effluent is the amount that, according to Table 6 would be degraded with a chosen treatment (headlines in the table). The total amount released in Swedish environment take percentage of population with certain treatment (given in parentheses) into account. The two last columns show the sum of the total effluent and total amount of parent compound released nationwide.*

4. Discussion

Since most of the pharmaceuticals investigated in this study are metabolised to a large extent in the human body to metabolites, any percentage of "cleaning efficiency" close to 100% for these compounds does not take metabolites into account. However, no/very little research on the removal efficiency of metabolites (as well as re-formation of parental compounds) was found and could therefore not be included in this study. Table S2 is a literature review of treatment efficiencies and techniques. However, the efficiency of some techniques will vary with intensity/effect (e.g. UV-light, ozone etc) applied and hence, some treatment efficiencies are presented with a rather large range.

It is important to keep in mind that high usage and release is not necessary the same as high environmental impact. Paracetamol is one of the most used compounds in all investigated countries, but 98% of paracetamol is metabolised, mainly to glucuronic acid (50–60% of the metabolites) and sulfuric acid (25–35%) in humans before excretion. There is little evidence that these metabolites would have a high environmental impact (Stuer-Lauridsen et al., 2000). However, there are pharmaceuticals with much lower volume consumed/year, but with a higher environmental impact potency, e.g. hormones such as contraceptives (ethinylestradiol and estradiol) (Adeel et al., 2017). Hence, waste water treatment efficiencies should be focused on those compounds and their metabolites.

Table 10. Top three pharmaceuticals sold (usage), excreted from humans (influent WWTP) and released into the aquatic environment (effluent WWTP) in Iceland, Norway and Sweden.

Country	Usage	Influent WWTP	Effluent WWTP
Iceland	Paracetamol, codeine in combination with paracetamol, ibuprofen	Codeine (alone), paracetamol, valsartan	Codeine (alone), paracetamol, valsartan
Norway	Paracetamol, metformin, ibuprofen	Metformin, paracetamol, phenoxymethyl-penicillin	Metformin, tramadol, naproxen
Sweden	Paracetamol, lactulose, ibuprofen	Lactulose, carbamide, paracetamol	Lactulose, carbamide, chlorhexidine

As Table 10 shows, paracetamol is the most commonly used pharmaceutical across the investigated Nordic countries. However, paracetamol is metabolised to a high degree in humans (Table S1) and hence, the most released compounds are other compounds from the sales list. Overall, there were only minor differences between the countries. There are measurements of released pharmaceuticals from WWTPs at Åland (and Sweden) available (Haikonen et al., 2018). The largest pharmaceutical releases in Åland were diclofenac (1,500 ng/dm^3), metoprolol (1,300 ng/dm3), oxazepam (680 ng/dm^3) and carbamazepine (640 ng/dm^3).

4.1 Data restrictions

Most studies available on treatment efficiency of pharmaceuticals in waste waters are focusing on removal of the parent compound, i.e. the distributed active compound. Hence, even with a reported high treatment efficiency, it might in reality be a high treatment efficiency of a small fraction of the compound, while the treatment efficiency on its metabolites remains unknown or not reported. Some metabolites might undergo deconjugation back to the parental compound in a WWTP such as e.g. tramadol (Douziech et al., 2018). These reactions are not well known and were outside the scope of the present report. Other compounds, such as e.g. diclofenac, are (to certain extent) used dermally and hence, the amount excreted and/or washed off unmetabolized are not known or estimated in the present report.

One source of pharmaceuticals into the environment that has not been considered is shipping, i.e. large cruise ships. Due to their capacity and amount of ships in certain popular regions, this might have a larger or comparable impact on the environment compared to the visited (small) village. However, the uncertainty factors are large, and this will need a thorough assessment which includes demography of passengers as well.

5. Conclusion

As can be seen from this report, the highest quantity of sold parental compounds are metabolised in the human body to a large extent, and they are excreted as metabolites. However, little is known about WWTP efficiency on metabolites or the impact of metabolites on the aquatic ecosystem.

Some compounds, e.g. tramadol may deconjugate from the metabolite and back to parental compound, and hence be released as a biologically active compound.

When environmental impacts are assessed, metabolites should be taken into account. Also, only the sales statistics does not provide enough information regarding which compounds that actually reach the aquatic environment. When WWTPs are planned and/or upgraded, pharmaceuticals and other environmental pollutants should be accounted for and suitable measurements to remove pharmaceuticals should be implemented when feasible.

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References

Adeel, M., Song, X., Wang, Y., Francis, D., Yang, Y., 2017. Environmental impact of estrogens on human, animal and plant life: A critical review. Environment International 99, 107–119. Available at: https://doi.org/10.1016/j.envint.2016.12.010

Baselt, R.C., 2017. Disposition of toxic drugs and chemicals in man. 11th. ed., Seal Beach, California: Biomedical publications.

Brunton, L.L., Hilal-Dandan, R., Knollmann, B.C., (Eds.), 2018. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed.

Botero-Coy, A.M., Martínez-Pachón, D., Boix, C., Rincón, R.J., Castillo, N., Arias-Marín, L.P., Manrique-Losada, L., Torres-Palma, R., Moncayo-Lasso, A., Hernández, F., 2018. 'An investigation into the occurrence and removal of pharmaceuticals in Colombian wastewater.' Science of The Total Environment 642, 842–853. Available at: https://doi.org/10.1016/j.scitotenv.2018.06.088

Celiz, M.D., Tso, J., Aga, D.S., 2009. Pharmaceutical metabolites in the environment: analyticalchallenges and ecological risks. Environmental Toxicology and Chemistry 28, 2473–2484. Available at: https://doi.org/10.1897/09-173.1

Comber, S., Gardner, M., Sörme, P., Leverett, D., Ellor, B., 2018. Active pharmaceutical ingredients entering the aquatic environment from wastewater treatment works: A cause for concern? Science of The Total Environment 613–614, 538–547. Available at: https://doi.org/10.1016/j.scitotenv.2017.09.101

Douziech, M., Conesa, I.R., Benítez-López, A., Franco, A., Huijbregts, M., van Zelm, R. 2018. Quantifying variability in removal efficiencies of chemicals in activated sludge wastewater treatment plants - a meta-analytical approach. Environmental Science: Processes & Impacts. 20:171-182. Available at: https://doi:10.1039/c7em00493a.

Ejhed, H., Fång, J., Hansen, K., Graae, L., Rahmberg, M., Magnér, J., Dorgeloh, E., Plaza, G., 2018. The effect of hydraulic retention time in onsite wastewater treatment and removal of pharmaceuticals, hormones and phenolic utility substances. Science of The Total Environment 618, 250–261. Available at: https://doi.org/10.1016/j.scitotenv.2017.11.011

Falås, P., Andersen, H.R., Ledin, A., Jansen, J. la C., 2012. Occurrence and reduction of pharmaceuticals in the water phase at Swedish wastewater treatment plants. Water Science and Technology 66, 783–791. Available at: https://doi.org/10.2166/wst.2012.243

Ferdamalastofa. Retrieved 19.12.2019. Available at: www.ferdamalastofa.is/en

Gracia-Lor, E., Sancho, J.V., Serrano, R., Hernández, F., 2012. Occurrence and removal of pharmaceuticals in wastewater treatment plants at the Spanish Mediterranean area of Valencia. Chemosphere 87, 453–462. Available at: https://doi.org/10.1016/j.chemosphere.2011.12.025

Greenham, R.T., Miller, K.Y., Tong, A., 2019. Removal efficiencies of top-used pharmaceuticals at sewage treatment plants with various technologies. Journal of Environmental Chemical Engineering 7, 103294. Available at: https://doi.org/10.1016/j.jece.2019.103294

Gurke, R., Rößler, M., Marx, C., Diamond, S., Schubert, S., Oertel, R., Fauler, J., 2015. Occurrence and removal of frequently prescribed pharmaceuticals and corresponding metabolites in wastewater of a sewage treatment plant. Science of The Total Environment 532, 762–770. Available at: https://doi.org/10.1016/j.scitotenv.2015.06.067

Haikonen, K., Fång, J., Thorsén, G. 2018. Mikroplaster och läkemedel Mariehamns Stad 2017 – Datasammanställning. IVL Svenska Miljöinstitutet.

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. Available at: https://doi.org/10.1016/j.chemosphere.2003.07.001

Kosma, C.I., Lambropoulou, D.A., Albanis, T.A., 2015. Occurrence of metformin and guanylurea in wastewaters in Greece. 14th International Conference on Environmental Science and Technology, Rhodes, Greece.

Moffat, A.C.O., David M., Widdop, B., Watts, J., (Eds.), 2011. Clarke's Analysis of Drugs and Poisons. 4th ed.

Ottmar, K.J., Colosi, L.M., Smith, J.A., 2012. Fate and transport of atorvastatin and simvastatin drugs during conventional wastewater treatment. Chemosphere 88, 1184–1189. Available at: https://doi.org/10.1016/j.chemosphere.2012.03.066

Perreault, H.A.N, Semsar, K., Godwin, J. 2003. Fluoxetine treatment decreases territorial aggression in a coral reef fish. Physiology & Behaviour 79. Available at: https://doi.org/10.1016/S0031-9384(03)00211-7

Radjenovic, J., Petrovic, M., Barceló, D., 2007. Analysis of pharmaceuticals in wastewater and removal using a membrane bioreactor. Analytical and Bioanalytical Chemistry 387, 1365–1377. Available at: https://doi.org/10.1007/s00216-006-0883-6

Roberts, J., Kumar, A., Du, J., Hepplewhite, C., Ellis, D.J., Christy, A.G., Beavis, S.G., 2016. Pharmaceuticals and personal care products (PPCPs) in Australia's largest inland sewage treatment plant, and its contribution to a major Australian river during high and low flow. Sci. Total Environ. 541, 1625e1637. Available at: https://doi.org/10.1016/j.scitotenv.2015.03.145

Sakshaug, S., Strøm, H., Berg, C., Salvesen Blix, H., Litleskare, I., Granum, T. 2018. Drug Consumption in Norway 2013–2017. ISBN: 978-82-8082-916-0. Norwegian Institute of Public Health

Shoupe, D., Haseltine, F. P., (Eds.), Contraception. 1993 New York : Springer-Verlag, 1993. – xiii, 261 p. Available at: https://doi.org/10.1007/978-1-4612-2730-4

Silva, L.J.G., Pereira, A.M.P.T., Meisel, L.M., Lino, C.M., Pena, A., 2014. A one-year follow-up analysis of antidepressants in Portuguese wastewaters: Occurrence and fate, seasonal influence, and risk assessment. Science of The Total Environment 490, 279–287. Available at: https://doi.org/10.1016/j.scitotenv.2014.04.131

Stanczyk, F.Z., Archer, D.F., Bhavnani, B.R., 2013. Ethinyl estradiol and 17β-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment. Contraception, 87, 706-727. Available at: https://doi.org/10.1016/j.contraception.2012.12.011

Statistics Iceland. Retrieved 19.12.2019. www.statice.is.

Statistiska centralbyrån (SCB). Retrieved 19.12.2019. www.scb.se.

Statistisk sentralbyrå (SSB). Retrieved 19.12.2019.www.ssb.no.

Stuer-Lauridsen, F., Birkved, M., Hansen, L.P., Holten Lutzhoft, L.-C., Halling-Sorensen, B., 2000. Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. Chemosphere 40, 783–793. Available at: https://doi.org/10.1016/S0045-6535(99)00453-1

Ternes, T.A., 1998. Occurrence of drugs in German sewage treatment plants and rivers1Dedicated to Professor Dr. Klaus Haberer on the occasion of his 70th birthday.1. Water Research 32, 3245–3260. Available at: https://doi.org/10.1016/S0043-1354(98)00099-2

Ternes, T.A., Kreckel, P., Mueller, J., 1999. Behaviour andoccurrence of estrogens in municipal sewage treatment plants—II. Aerobic batch experiments with activated sludge. Science of Total Environment 225, 91–99. Available at: https://doi.org/10.1016/S0048-9697(98)00335-0

Vieno, N., Hallgren, P., Wallberg, P., 2017. Pharmaceuticals in the aquatic environment of the Baltic Sea region – A status report (No. Volume No. 1), Emerging Pollutants in Water Series. HELCOM.

Wang, J., Wang, S., 2016. Removal of pharmaceuticals and personal care products (PPCPs) from wastewater: A review. Journal of Environmental Management 182, 620–640. Available at: https://doi.org/10.1016/j.jenvman.2016.07.049

World Health Organization, 2006. Assessment of zopiclone.

WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. 2019; Available at: https://www.whocc.no/atc_ddd_index/.

Yu, Y., Wu, L., Chang, A.C., 2013. Seasonal variation of endocrine disrupting compounds, pharmaceuticals and personal care products in wastewater treatment plants. Sci. Total Environ. 442, 310e336. Available at: https://doi.org/10.1016/j.scitotenv.2012.10.001

Zhao, X., Chen, Z., Wang, X., Shen, J., Xu, H. 2014. Applied Microbiological Biotechnology. 98: 9843. Available at: https://doi.org/10.1007/s00253-014-5923-0

Appendix

Table S1. Urinary/fecal excretion of chosen pharmaceuticals.

ATC-code and name	% excreted of dose (as parent)	Total excreted % incl. metabolites	Metabolite names (only if easily available)	Minor metabolites	Comments
A01AA01 - Sodium fluoride	69–83%	50% urine, 6–10% feces, 13–23% sweat	No metabolism		Applies to fluoride
A02BC01 - Omeprazol	<1%	76% urine, 17% feces	5-hydroxymethyl esomeprazole and its glucuronide, 5-carboxy esomepazole and its glucuronide		
A02BC02 - Pantoprazole	<1%	71% urine, 18% feces	O-demethylated-pantoprazole-sulfate conjugate (major metabolite)	oxidized or reduced -S- of the o-demethylate-pantoprazole-sulfate conjugate	
A02BC04 - Rabeprazol		90% urine, 10% feces	Primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites		
A02BC05 - Esomeprazole	<1%	76% in urine, 17% feces	5-hydroxymethyl esomeprazole and its glucuronide, 5-carboxy esomeprazole and its glucuronide		
A10BA02 - Metformin	100%	52% urine	No metabolism		52% oral availability. No metabolism
A11CC05 – Cholecalciferol		intravenously inj: 16% urine, 49% feces	8 different glucuronide conjugates		
B01AC06 - Acetylsalicylic acid	<1%	100% urine	5% salicylic acid and conjugates, 80% salicyluric acid, 10% salicylphenolic glucuronide, 5% salicylacyl glucuronide	di- and tri-hydroxy derivatives of salicylic acid (gentisic acid)	
C01DA14 -	2%		17% 2-glucuronide of		

Isosorbide mononitrate			parent, 37% isosorbide		
C03CA01 - Furosemide	Intravenously (iv): 56%	Oral distribution: 55% urine and 35% feces.			
iv: 83% in urine, 8% in feces	11% furosemide glucuronide, 2% norfurosemide				
C07AB02 - Metoprolol	3%	99,6% in urine	60% demethylated acid derivative (I), 10% oxidative deaminated derivative (II), 10% aliphatic hydroxylated derivative (III)		
C07AB03 - Atenolol	88%	39% urine, 36% feces	2% atenolol glucuronide, 2–3% hydroxyatenolol		
C08CA01 - Amlodipine	<5%	59% urine, 23% feces	5.9% amlodipine dehydrogenation to M9. M9 underwent oxidative deamination to M10 (2.3%)	Seven minor metabolites	
C09AA05 - Ramipril	<2%	56% urine, 39% feces	>10% ramiprilat + two diketopiperazine rearrangement products		
C09CA01 - Losartan	4%	35% urine, 60% feces	6% carbolic acid metabolite (EXP3174), several sidechain hydroxy derivatives and N-glucuronides of both losartan and EXP3174		
C09CA03 - Valsartan	9.8% urine, 71% feces	13% urine, 86% feces	9% valeryl-4-hydroxy valsartan		
C09CA06 - Candesartan	26% candesartan	33% urine, 67% feces	26% candesartan, 8% O-desmethyl candesartan,		Applies to candesartan cilexetil, candesartan is a metabolite of cand. cil.
C10AA01 - Simvastatin	<1%	13% urine, 60% feces	Simvastatin acid (major form)	Other hydrolysis products	
C10AA05 - Atorvastatin	<2%	<2% urine, mainly excreted in bile	O- and p-OH atorvastatin		All three are active and can excist in acid or lactone forms
G03AA07 – Ethinyl-estradiol	<1%	38% urine, 62% feces	Ethinylestradiol glucuronides and		

			ethinylestradiol sulfate		
G03AA07 – Levonorgestrel		20 to 67% urine, 21–34% feces	Reduction, hydroxylation, and conjugation (glucuronidation and sulfation), Oxidation occurs primarily at the C2α and C16β positions, while reduction occurs in the A ring		
G03CA03 - Estradiol	5.2–7.5%	54% urine, 6% feces	13–30% estrone glucuronide, 2-2.6–10.1% hydroxyestrone, 2.0–5.9% estriol, and 1.0–2.9% 16α-hydroxyestrone		
H02AB06 - Prednisolone	16%		3,3% prednisone, 5,5% 20β-OH-prednisolone, 4,7% 6β OH-prednisolone, 3,5% 20α OH-prednisolone		
H03AA01 – Levothyroxine sodium		50% urine, 11% feces	7% thyronine, 17% thyroacetic acid	T4 and conjug. T4, T3	
J01CA08 - Pivmecillinam	60%	75% orally absorbed	N-formyl derivative. Hydrolysis of the β-lactam ring also occurs.		
J01CE02 - Phenoxymethyl-penicillin	30%	49% urine, 32% feces	35–70% penicilloic acid	Hydroxylated metabolites	Good absorption after oral adm.
M01AB05 - Diclofenac	<1%	35-65% in urine, 15-45% feces	4-hydroxy diclofenac (major)		
M01AE01 - Ibuprofen	1-9%	90% urine, 1% feces	35% 2-carboxy ibuprofen and conjugates, 26% 2-hydroxy ibuprofen and conjugates	30% 1-hydroxy ibuprofen, 3-hydroxy ibuprofen and conjugates	>90% oral availability
M01AE52 - Esomeprazole	<1%	76% urine, 17% feces	5-hydroxymethyl esomeprazole and its glucuronide, 5-carboxy esomepazole and its glucuronide		
M01AE52 - Naproxen	10%	87% urine, 2.3% feces	60% conjugated naproxen, 5% O-desmethylnaproxen, 23% conjugated o-desmethylnaproxen		conjugated naproxen & O-desmethylnaproxen => naproxen during treatment.
M01AH01 - Celecoxib	2,60%	27% urine, 58% feces	20% carboxylic acid derivative		
N02AJ06 – Codeine*	5–17%	95% urine	10–21% conjugated norcodeine, 5–13%	Trace of norcodeine	

			conjugated morphine and 32–46% conjugated codeine	and morphine	
N02AX02 - Tramadol	29%	90% urine, 10% feces	20% O-desmethyltramadol and conjugated o-desmethyltramadol, 17% nortramadol, 20% free and conjugated o-desmethylnortramadol		
N02BE01 – Paracetamol**	2%	85–90% urine	50-60% glucuronic acid, 25–35% sulfuric acid, 3% cysteine	4–5% methoxy acetaminophen	
N05BA04 - Oxazepam	<1%	>66% in urine	61% oxazepam glucuronide, <5% as hydroxylated oxazepam		
N05CF01 - Zopiclone	7-10%	80% urine	11% zopiclone-N-oxide, 15% N-desmethyl zopiclone		75–80% bioavailable oral
N06AB06 - Sertraline	<0,2%	40–45% urine	deaminated, hydroxylated and conjug. sertraline and norsertraline		
N06AB10 - Escitalopram	8%	32% urine (citalopram)	10% N-desmethyl escitalopram	N,N-didesmethyl escitalopram	
N06AX11 - Mirtazapine		75% urine, 25% feces	Quaternary ammonium glucuronide of mirtazapine and the glucuronides of 8-hydroxy-mirtazapine		
N06AX16 - Venlafaxin	5%	87% urine	29–48% o-desmethyl venlafaxin, 0.2-7.4% norvenlafaxin, 6–19% di-norvenlafaxin		
R01AA07 - Xylometazoline		Not known	Not known		Not known
R01AD09 - Mometasone	<1%	8% urine, 74% feces	6B-OH metabolite, dechlorinated metabolite		Extensively metabolized
R03AC02 - Salbutamol	28% after inhalation in urine, 32% in urine after oral intake.	Inhalation: 70% urine, 10% feces. Oral: 75% urine, 4% feces.	48% 4-O-sulfate conjugate (oral), 1–2% glucuronide salbutamol		
R05DA01 - Ethylmorphine	4.4%	>76% urine	41% ethylmorphine-6-glucuronide, 12% morphine-3-glucuronide, 4.6% norethyl-morphine-6-glucuronide, 4.6% normorphine, 4.3% norethylmorphine, 3.3% morphine-6-glucuronide, 1.3% normorphine-		

			glucuronide, 0.8% morphine
R06AA02 – Diphen-hydramine	1%	49–64% urine	N-acetyl-N-desmethyl diphenhydramine,diphenylmetoxyaceticacid. Both conjugated with glycine and glutamine.
R06AE07 - Cetirizine	5.8%	70% urine, 10% feces	O-dealkylated parent is the only identified metabolite
R06AX26 - Fexofenadine	95%	80% feces, 11% urine	No information available
R06AX27 - Desloratadine	1.7%	41% urine, 47% feces	22% conjugated 3-OH-desloratadine, 5.7% conjugated di-OH-desloratadine

Note: *References for data presented in this table are mainly Baselt (2017), Brunton et al. (2018) and Moffat et al., (2011). References for certain compounds are: Stanczyk et al. (2013); ethinylestradiol and estradiol, Shoupe and Haseltine (1993); levonogestrel and WHO (2006 and 2018); zopiclone. Numbers provided are the average estimate given in the references if nothing else is stated.*

** In combinations with Paracetamol. Codeine figures here alone.*

*** Overdose of paracetamol: Higher levels of cysteine and mercapturic acid conjugates (up to 55%) and the parent compound (up to 14%).*

Table S2. Summary of the WWTP efficiency literature survey.

ATC code and compound	Treatment process	Treatment category	Removal efficiency (%)	Reference	Comments
N02BE01 - Paracetamol	Modified Bardenpho process	Secondary	99	Wang et al., 2016	Wastewater treatment plant, Bardenpho process is a continuous-flow suspended-growth process with alternating anoxic/aerobic/ anoxic/aerobic and modified BP is BP with addition of an initial anaerobic zone.
	Primary clarification + aerated tank with Fe(II)chloride precipitation	Primary+ secondary	>99	Ternes, 1998	German municipal sewage treatment plants/4 metabolites were measured in rivers and water streams.
	Areated grit removal tank and sedimentation +CAS	Primary + secondary	Hospital 87 (Mean) Wastewater 97 (Mean)	Kosma et al., 2010	Municipal and hospital Wastewater treatment plant in Greece
	Modelling	Secondary STP prediction	56	Khan and Ongerth, 2004	Wastewater treatment plant/ modeling/ looked at Metabolites as well
A10BA02 - Metformin	10 Different technologies used at 22 different WTP	From primary to secondary	40 (mean), 10–95 (25–75 percentile)	Greenham et al., 2019	Wastewater treatment plant (12 pharmaceuticals and 2 metabolites) paraxanthine (the primary metabolite of caffeine), and cotinine (the primary metabolite of nicotine)
	of caffeine), and cotinine (the primary				

	metabolite of nicotine).				
			93.8	Falås et al., 2012	
	8 WWTPs: all primary treatment, CAS with N removal, disinfection	Primary+ secondary	78–99	Kosma et al., 2015	8 Wastewater treatment plant in Greece/looked at Metformin and its bilogical transformation guanylurea.
	Modelling	Secondary STP prediction	44	Khan and Ongerth, 2004	Wastewater treatment plant/ modeling/ looked at Metabolites as well
M01AE01 - Ibuprofen	Areated grit removal tank and sedimentation +CAS	Primary + secondary	Hospital 58 (Mean) Wastewater 77 (Mean)	Kosma et al., 2010	Municipal and hospital Wastewater treatment plant in Greece
	Grit channels + primary clarifies + conventional activated sludge	Primary+ secondary	99.7	Wang et al., 2016	Wastewater treatment plant
	Primary treatment + Orbal oxidation ditch + UV disinfection	Primary+ secondary+ tertiary	60-90	Wang et al., 2016	Wastewater treatment plant
	CAS-wastewater treatment plant	Secondary	82.5	Radjenovic et al., 2007	Wastewater treatment plant
	Primary clarification + aerated tank with Fe(II)chloride precipitation	Primary+ secondary	90 (ave)	Ternes, 1998	German municipal sewage treatment plants/4 metabolites were measured in rivers and water streams.
	Modelling	Secondary STP prediction	52	Khan and Ongerth, 2004	Wastewater treatment plant/ modeling/ looked at Metabolites as well
	Mean of 44	Primary	17	Comber et al.,	Wastewater

	WWTPs in UK			2019	treatment plant
	Mean of 44 WWTPs in UK	Primary + secondary	96	Comber et al., 2019	Wastewater treatment plant
B01AC06 – Acetyl-salicylic acid	Primary clarification + aerated tank with Fe(II)chloride precipitation	Primary+ secondary	81 (ave)	Ternes, 1998	German municipal sewage treatment plants/4 metabolites were measured in rivers and water streams.
	Modified Bardenpho process	Secondary	92	Yu et al., 2013	
	Modelling	Secondary STP prediction	53	Khan and Ongerth, 2004	Wastewater treatment plant/ modeling/ looked at Metabolites as well
J01CE02 - Phenoxymethylpenicillin		Secondary STP prediction	67	Khan and Ongerth, 2004	Wastewater treatment plant/modeling/ looked at Metabolites as well
M01AE52 - Naproxen	Modified Bardenpho process	Secondary	94	Wang et al., 2016	Wastewater treatment plant
	Grit channels + primary clarifies + conventional activated sludge	Primary+ secondary	96.2	Wang et al., 2016	Wastewater treatment plant
	CAS-wastewater treatment plant	Secondary	85.1	Radjenovic et al., 2007	Wastewater treatment plant
	Primary clarification + aerated tank with Fe(II)chloride precipitation	Primary+ secondary	66 (ave)	Ternes, 1998	Wastewater treatment plant
	Areated grit removal tank and sedimentation +CAS	Primary + secondary	Hospital 48 (Mean) Wastewater 62 (Mean)	Kosma et al., 2010	Municipal and hospital Wastewater treatment plant in Greece
		Secondary STP	58	Khan and	Wastewater

		prediction		Ongerth, 2004	treatment plant/ modeling/ looked at Metabolites as well
C10AA05 - Atorvastatin	10 Different technologies used at 22 different WTP	From primary to secondary	50 (mean), -15–100 (25–75 percentile)	Greenham et al., 2019	Wastewater treatment plant (12 pharmaceuticals and 2 metabolites) paraxanthine (the primary metabolite of caffeine), and cotininee (the primary metabolite of nicotine).
	CAS	Secondary	86	Ottmar et al., 2012	Synthetic wastewater
N02AX02 - Tramadol	Coarse bar, fine screen, grit and fat trap, primary clarifier, biological N removal and chemical precipitation	Primary + secondary	1 (+/- 10)	Gurke et al., 2015	Wastewater treatment plant/looked at metabolites as well
A02BC02 - Pantoprazole	CAS	Secondary	100 (found 0.1-0.02 µg/L in all effluent samples; <0.004 µg/L in influents)	Gracia-Lor et al., 2012	3 Wastewater treatment plants in Spain
C10AA01 - Simvastatin	CAS	Secondary	86	Ottmar et al., 2012	Synthetic wastewater
		Secondary STP prediction	97	Khan and Ongerth, 2004	Wastewater treatment plant/ modeling/ looked at Metabolites as well
	Pilot plants (Fixed bed bioreactor, bio filter (trickling filter), fluidized bed bio reactor)	Secondary	84-93	Ejhed et al., 2018	Pilot treatment plant
N02AJ06 - Codeine	Modelling	Secondary STP prediction	23	Khan and Ongerth, 2004	Wastewater treatment plant/modeling/ looked at

					Metabolites as well
A02BC05 and M01AE52 -Esomeprazole	Primary treatment, CAS with N removal, disinfection	Primary+ secondary	>93	Kosma et al., 2017	Wastewater treatment plant, looked at metabolites
C09CA01 - Losartan	Bar screen, fat trap, CEPT (Bogota)	Advanced primary	8	Botero-Coy et al., 2018	Wastewater treatment plant
	Bar screen, fat trap (Medellin)	Primary	35	Botero-Coy et al., 2018	Wastewater treatment plant
	Coarse bar, fine screen, grit and fat trap, primary clarifier, biological N removal and chemical precipitation	Primary + secondary	55 (+/- 7)	Gurke et al., 2015	Wastewater treatment plant/looked at metabolites as well
M01AB05 - Diclofenac	Bardenpho process	Secondary	80	Wang et al., 2016	Wastewater treatment plant
	Primary treatment +Orbal oxidation ditch+ UV disinfection	Primary+ secondary+ tertiary	10–60	Wang et al., 2016	Wastewater treatment plant
	CAS-wastewater treatment plant	Secondary	50,1	Radjenovic et al., 2007	Wastewater treatment plant
	Primary clarification + aerated tank with Fe(II)chloride precipitation	Primary+ secondary	69 (ave)	Ternes, 1998	German municipal sewage treatment plants/4 metabolites were measured in rivers and water streams.
		Secondary STP prediction	30	Khan and Ongerth, 2004	Wastewater treatment plant/ modeling/ looked at Metabolites as well
	Areated grit removal tank and sedimentation +CAS	Primary + Secondary	Hospital 15 (Mean) Wastewater 20 (Mean)	Kosma et al., 2010	Municipal and hospital Wastewater treatment plant in Greece

	Mean of 44 WWTPs in UK	Primary	24	Comber et al., 2019	Wastewater treatment plant
	Mean of 44 WWTPs in UK	Primary + secondary	48	Comber et al., 2019	Wastewater treatment plant
	Mean of 44 WWTPs in UK	Primary + secondary + tertiary	56	Comber et al., 2019	Wastewater treatment plant
C09CA06 - Candesartan	Coarse bar, fine screen, grit and fat trap, primary clarifier, biological N removal and chemical precipitation	Primary + secondary	0 (+- 10)	Gurke et al., 2015	Wastewater treatment plant/looked at metabolites as well
N05BA04 - Oxazepam	Pilot plants (Fixed bed bioreactor, bio filter (trickling filter), fluidized bed bio reactor)	Secondary	-34–24	Ejhed et al., 2018	Pilot treatment plant
N06AB10 - Escitalopram	6 WWTPs: CAS, biofiltration (1 plant)	Tertiary	35–100	Silva et al., 2014	Wastewater treatment plants in portugal
	2 WWTPs: CAS, trickling filter	Secondary	100	Silva et al., 2014	Wastewater treatment plants in Portugal
C08CA01 - Amlodipine	Pilot plants (Fixed bed bioreactor, bio filter (trickling filter), fluidized bed bio reactor)	Secondary	45–90	Ejhed et al., 2018	Pilot treatment plant
H02AB06 - Prednisolone	Pilot scale granular sludge MBR	Secondary	98.5	Zhao et al., 2014	Pilot experiment with synthetic wastewater
C09AA05 - Ramipril	10 Different technologies used at 22 different WTP	From primary to secondary	85 (mean), 70–100 (25–75 percentile)	Greenham et al., 2019	Wastewater treatment plant (12 pharmaceuticals and 2 metabolites) paraxanthine (the primary metabolite of caffeine), and cotinine (the primary metabolite of nicotine).

	Coarse bar, fine screen, grit and fat trap, primary clarifier, biological N removal and chemical precipitation	Primary + secondary	7 (+- 10)	Gurke et al., 2015	Wastewater treatment plant/looked at metabolites as well
	Pilot plants (Fixed bed bioreactor, bio filter (trickling filter), fluidized bed bio reactor)	Secondary	43–87	Ejhed et al., 2018	Pilot treatment plant
C07AB02 - Metoprolol	Grit channels + primary clarifies + conventional activated sludge	Primary+ secondary	52.9	Roberts et al., 2016	
	CAS-wastewater treatment plant	Secondary	No removal	Radjenovic et al., 2007	Wastewater treatment plant
	Primary clarification + aerated tank with Fe(II)chloride precipitation	Primary+ secondary	83 (ave)	Ternes, 1998	German municipal sewage treatment plants/4 metabolites were measured in rivers and water streams.
		Secondary STP prediction	42	Khan and Ongerth, 2004	Wastewater treatment plant/ modeling/ looked at Metabolites as well
G03AA07 - Ethinylestradiol	Mean of 44 WWTPs in UK	Primary	4	Comber et al., 2019	Wastewater treatment plant
	Mean of 44 WWTPs in UK	Primary + secondary	46	Comber et al., 2019	Wastewater treatment plant
	Mean of 44 WWTPs in UK	Primary + secondary + tertiary	51	Comber et al., 2019	Wastewater treatment plant
	Pilot plants (Fixed bed bioreactor, bio filter (trickling filter), fluidized bed bio reactor)	Secondary	69–89	Ejhed et al., 2018	Pilot treatment plant

G03CA03 - Estradiol	Mean of 44 WWTPs in UK	Primary	3	Comber et al., 2019	Wastewater treatment plant
	Mean of 44 WWTPs in UK	Primary + secondary	89	Comber et al., 2019	Wastewater treatment plant
	Mean of 44 WWTPs in UK	Primary + secondary + tertiary	95	Comber et al., 2019	Wastewater treatment plant
	Pilot plants (Fixed bed bioreactor, bio filter (trickling filter), fluidized bed bio reactor)	Secondary	41–99	Ejhed et al., 2018	Pilot treatment plant

Note: *References for the table: (Botero-Coy et al., 2018; Comber et al., 2018; Ejhed et al., 2018; Falås et al., 2012; Gracia-Lor et al., 2012; Greenham et al., 2019; Gurke et al., 2015; Khan and Ongerth, 2004; Ottmar et al., 2012; Radjenovic et al., 2007; Silva et al., 2014; Ternes, 1998; Wang and Wang, 2016)*

Kosma et al., 2015, Roberts et al., 2016, Yu et al., 2013, Zhao et al., 2014.

Table S3. Total amount of the forty largest drug groups (ATC code 5th level) in Iceland 2017, and total amount sold.

ATC index	Active substance	mg/DDD	DDD - Nationwide	Total kg sold per year - Nationwide
N02BE01	Paracetamol	3,000	2,708,631	8,126
N02AJ06	Codeine and paracetamol	100 + 3,000	2,392,907	7,418
A12BA01	Potassium chloride	3,000	2,434,618	7,304
B01AC06	Acetylsalicylic acid	160	24,067,400	3,851
C07AB02	Metoprolol	150	3,385,681	508
N06AB06	Sertraline	50	5,912,026	296
N06AX16	Venlafaxin	100	2,800,336	280
C07AB03	Atenolol	75	3,297,469	247
C09DA01	Losartan and diuretics	50	4,327,616	216
C03CA01	Furosemide	40	5,192,244	208
C09CA03	Valsartan	80	2,499,469	200
C09CA01	Losartan	50	3,698,852	185
C10AA01	Simvastatin	30	6,081,326	182
R06AX26	Fexofenadine	120	1,485,375	178
A02BC05	Esomeprazole	30	5,649,794	169
C10AA05	Atorvastatin	20	8,466,810	169
A02BC01	Omeprazole	20	7,637,942	153
N05CF01	Zopiclone	7.5	19,440,122	146
M01AB05	Diclofenac	100	1,381,291	138
C09DA03	Valsartan and diuretics	80	1,582,042	127
C01DA14	Isosorbide mononitrate	40	2,806,302	112
N06AX11	Mirtazapine	30	3,692,367	111
C03EA01	Hydrochlorothiazide and potassium-sparing agents	25	3,241,900	81
A02BC04	Rabeprazole	20	3,953,972	79
N06BA04	Methyphenidate	30	2,101,624	63
N06AB04	Citalopram	20	2,885,871	58
C09AA02	Enalapril	10	5,516,485	55
B03BB01	Folic acid	10	5,100,550	51
N06AB03	Fluoxetin	20	2,536,778	51
N06AB10	Escitalopram	10	4,892,524	49
R06AD02	Promethazine	25	1,601,492	40
C08CA01	Amlodipine	5,0	7,588,030	38

N05CF02	Zolpidem	10	2,068,750	21
M05BA04	Alendronic acid	10	1,493,016	15
G03AA07	levonorgestrel and ethinylestradiol	1.5 + 0.025	2,715,552	4
C09AA05	Ramipril	2.5	1,654,200	4
B03BA01	Cyanocobalamin	1.0	3,627,000	4
A10BB12	Glimepiride	2.0	1,541,340	3
H03AA01	Levothyroxine sodium	0.15	4,886,889	1
G04CA02	Tamsulosin	0.4	1,745,840	1

About this publication

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