Reducing micropollutants with source control: substance flow analysis of 212 pharmaceuticals in faeces and urine

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Abstract Pharmaceuticals in the aquatic environment are raising concern. It is expected that many anthropogenic pharmaceuticals are largely excreted via urine; a popular argument for introducing urine source separation. However, to date, this assumption lacks verification. We close this gap with quantitative screening of official pharmaceutical data. We analysed the excretion pathways of 212 pharmaceuticals' active ingredients (AI), equalling 1,409 products. On average, 64% (±27%) of each AI was excreted via urine, and 35% (±26%) via faeces. In urine, 42% (±28%) of each AI was excreted as metabolites. However, these numbers need cautious interpretation. We found an extreme variability (1) between different therapeutic groups, (2) within some groups and (3) sometimes even between products of the same AI. We discuss various therapeutic groups and include Swiss sales' quantities. For instance, urine source separation could very effectively remove the highly sold and non-degradable x-ray contrast media: 94% (±4%) are excreted via urine. However, for different pharmaceuticals belonging to cytostatics, excretion via urine was 6–98%. Because of such large variability we advise caution to introduce the still imperfect urine separation technology solely because of pharmaceuticals. Nonetheless, together with other good arguments for this innovation, removal of pharmaceuticals is a welcome side effect.

Keywords Excretion; NoMix toilets; pharmaceuticals; screening; urine source separation; wastewater

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Introduction

Wastewater contains a cocktail of human pharmaceuticals and metabolites, which are only partially eliminated in treatment plants (Paxeus, 2004; Joss *et al.*, 2006). This issue has raised increasing concern, and advanced sanitation technologies will have to address the problems associated with these micropollutants. The European Medicines Agency recently proposed a procedure to assess the environmental risk from human medicinal products (EMEA, 2006). Despite such progress, the impact of pharmaceuticals on the environment often remain unclear. To date, the numbers of drugs in studies performed according to the EMEA (2006) guideline has been limited, the reasons being lack of data concerning the toxicity of medicals and their environmental concentrations (e.g. Ferrari *et al.*, 2004; Huschek *et al.*, 2004; Carlsson *et al.*, 2006). To bridge this phase of uncertainty, fast screening tools to identify pharmaceuticals that pose high risks can support decision making (Lienert *et al.*, 2007). Moreover, as long as so little is known, it seems justified to apply the precautionary principle (Rogers, 2003) to avoid drugs from entering the wastewater stream.

Source control could be an effective precautionary measure and an alternative to end-of-pipe upgrading of treatment plants (Larsen and Gujer, 2001; Joss *et al.*, 2006). Since anthropogenic organic chemicals are usually metabolised in the human body to a polar form with higher water solubility (Sheldon *et al.*, 1986), it is expected that many pharmaceuticals are excreted via kidneys and are highly concentrated in urine. This is a popular argument for introducing urine source separation (NoMix technology; Larsen *et al.*, 2004; also see

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www.novaquatis.eawag.ch). However, to date, quantitative data supporting this assumption are missing. This paper intends to fill this gap with a screening approach by conducting a material flow analysis based on a literature and data bank survey.

Materials and methods

Data collection

We conducted a literature search of 54 articles to select pharmaceuticals (active ingredients, AI) excreted by humans (Figure 1); many of them have been detected in wastewater. We excluded AI for veterinary or external applications, but included those externally applied substances that are substantially absorbed into the bloodstream (e.g. some eye drops). We compiled the excretion pathways via urine or faeces of the AI and if possible of their metabolites, from the Swiss Pharmaceutical Compendium (2006), which lists all authorised drugs in Switzerland (www.swissmedic.ch). We limited ourselves to this source for efficiency. For each AI (e.g. acetylsalicylic acid), we collected data for every mono-compound (e.g. alka-seltzer, aspirin) and combi-compound (e.g. treupel) product. We assigned each AI to a therapeutic group that treats the same or similar diseases (e.g. the group of analgesics contains six AI, one of them being acetylsalicylic acid). We compiled 454 AI from the literature, but had to exclude many (Figure 1). For instance, 50 AI only had qualitative data such as "mostly renal elimination". In the end, we were able to compile quantitative data for 212 AI, totalling 1,409 products. Additionally, we purchased the annual sales quantities of the top 100 most-sold pharmaceuticals in Switzerland in 2004 and of some additional pharmaceuticals (IMS, 2004).

Data handling

Often, we only found data for the excretion via urine. We assumed that only a negligible fraction is excreted via other pathways (e.g. skin, respiration) and subtracted the excretion via urine from 100% excretion to receive an average of the excretion via faeces. In some cases, metabolism data were given. Because metabolism details are not relevant for this study (summarised in Lienert *et al.*, 2007), we summed up all metabolites if more than

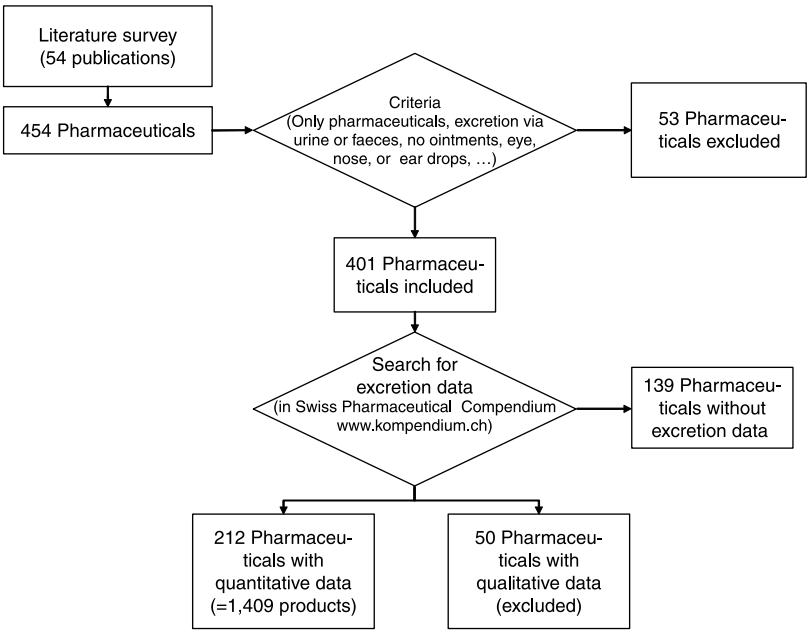

Figure 1 Procedure for collection of excretion data; numbers of pharmaceuticals (active ingredients, AI)

one were listed. Quantitative data on excretion and especially on metabolism via faeces were extremely scarce. Because of considerable inconsistencies in the data, we calculated basic statistics following defined rules. For each excretion pathway (e.g. "unchanged via urine") of each pharmaceutical (AI), we listed the given excretion of each product in an "average column". For some products the Pharmaceutical Compendium reported ranges; here we listed the minimal and maximal value in separate columns and calculated the average per product from these. In cases where an average as well as a minimal and maximal value were given, we listed all three in our database. If only a minimal or only a maximal value was given, we listed these in the respective column and also in the "average column". For each AI we then calculated the average from this "average column" over all products. In the following overview tables, we also list the smallest and largest values we found. The average and standard deviation were calculated from the "average column" only (i.e. excluding the columns with minimal and maximal values). For a better overview we also grouped the 212 AI into 56 therapeutic groups.

Data validation

Data were collected during 1.5 years. At the end of data collection, we randomly selected 10% of the 212 AI (= 1,409 products) and again verified their excretion data in the Swiss Pharmaceutical Compendium (2006). We found that the classifications into therapeutic groups in the compendium had altered in the mean time and corrected these. We only found one minor mistake in the excretion data (90% instead of 98%). Hence, we are confident that we achieved a high data quality, while it is important to bear in mind that the available data are generally inconsistent.

Results and discussion

Excretion over all 212 pharmaceuticals

On average, nearly two-thirds (64%) of each AI was excreted via urine, and one-third (35%) via faeces (Table 1). On average, 42% of each AI was metabolised; these metabolites were mainly excreted via urine. Based on our data, excretion via faeces occurred in the non-metabolised form. However, data on metabolism in faeces were very scarce (sample size for excretion of non-metabolised AI in feces = 14). These numbers need cautious interpretation. We found an extreme variability (1) between different therapeutic groups, (2) within some groups, and (3) sometimes even between products of the same AI. Minimal and maximal excretion values covered the entire range from 0 to 100%, and the standard deviations were large (Table 1). Some of this variability reflects biological variability, but much is caused by the large difference in physicochemical properties of the different pharmaceuticals. Additionally, sample sizes varied considerably; most data stemming from non-metabolised excretion via urine, but less from faeces and metabolites. This resulted in considerable discrepancies. For instance, the sum of unchanged and metabolised excretion via urine (35% + 42% = 77%) should equal the total excretion via urine (64%), which is clearly not the case (Table 1). To reduce uncertainty, we then compared different therapeutic groups.

Overview: excretion within therapeutic groups

We found 56 therapeutic groups, but 34 groups (with a total of 47 AI) consisted of <3 AI. Here, the mean fractions of total excretion via urine ranged from $<10\%$ (dimethicone, orlistat [xenical], everolimus, cyclosporine), to $>95\%$ (pyridostigmine, nitrofurantoin, bromocriptine, theophylline, fondaparinux sodium). In this list, the average total fraction excreted via urine was 64% ($\pm 30\%$), and 48% ($\pm 25\%$) of each AI was excreted as metabolites via urine.

Table 1 Excretion of 212 pharmaceuticals

	Urine									Faeces					
	Total (urine)			Unchanged (urine)			Metabolised (urine)			Total (faeces)			Unchanged (faeces)		
	min	av	max	min	av	max	min	av	max*	min	av	max	min	av	max
Excretion	0%	64%	100%	0.1%	35%	100%	1%	42%	124%	0%	35%	100%	0.30%	32%	100%
SD (N)		±27% (212)			±33% (132)			±28% (57)			±26% (212)			±34% (14)	

*This maximum >100% was caused by the addition of the excretion values of three metabolites of paracetamol given in the Swiss Pharmaceutical Compendium. Because we did not want to further manipulate data we decided to leave such inconsistencies.

Total percentages excreted via urine and faeces, and percentages excreted as parent compound (Unchanged) or in metabolised form.

Av, average of the "average column" (see Methods); min, minimal value detected for all pharmaceuticals; max, maximal value; SD, standard deviation of the average values; N, sample size (number of pharmaceuticals)

Table 2 Excretion pathways of 22 therapeutic groups (165 active ingredients, AI)

Therapeutic group		Total (urine) %				Unchanged (urine) %				Metabolised (urine) %				Total (faeces) %			
	N	min	av	max	SD	min	av	max	SD	min	av	max	SD	min	av	max	SD
Excretion >80% via urine																	
X-ray contrast media	9	90	94	100	±4	90	94	98	±3					0	6	10	±4
Analgesics	6	2	82	100	±17	1	28	85	±18	10	66	124	±35	4	18	45	±17
Antiepileptic drugs	4	50	81	100	±18	1	14	40	±22	16	33	50	±24	0	15	30	±12
Excretion >70% via urine																	
Hypnotic drugs	4	56	77	100	±18	1	13	25	±17	60	70	80	0	0	23	44	±18
Gastric acid inhibitors	4	40	74	90	±19	1	36	80	±35	1	15	20	±4	10	26	60	±19
Oestrogens	3	38	73	95	±31	1	9	17	±8	40	67	95	±38	5	27	83	±31
Antiviral drugs	8	14	71	100	±28	1	27	80	±36	10	45	88	±32	0	29	86	±28
Excretion >60% via urine																	
Antiphlogistics	8	30	67	82	±10	1	7	25	±12	30	53	70	±21	18	32	50	±10
Arterial vasodilators	6	1	67	99	±23	0	4	10	±4	33	42	50	±12	1	31	69	±22
Antidiabetic agents	3	35	67	100	±32	1	51	100	±70					0	28	65	±33
Vasodilatants	4	13	67	95	±36	1	10	28	±14	13	18	22	0	6	33	87	±37
Antidepressants	9	50	66	90	±12	2	5	31	±4	6	6	6	0	10	34	50	±12
Antiemetics	4	51	65	78	±9	4	7	12	±4	47	61	70	±12	21	31	41	±9
Betablockers	8	10	63	96	±28	4	33	77	±24	50	50	50	0	4	34	90	±26
Diuretic drugs	4	22	63	100	±16	22	38	95	±26	2	36	64	±32	11	37	57	±16
Glucocorticoids/Corticosteroids	6	8	63	98	±38	1	4	7	±4					2	30	88	±34
Antibiotics	33	8	61	100	±27	5	53	100	±29	5	20	40	±8	0	37	92	±26
Excretion >49% via urine																	
Antilipidaemics	5	6	59	100	±46					94	100	106	0	0	41	94	±46
Neuroleptics	5	23	53	92	±28	4	48	92	±62					8	47	77	±28
Antihypertensives	14	6	50	100	±26	1	29	70	±29	1	30	70	±28	5	48	94	±26
Cytostatics	13	6	49	98	±28	15	46	95	±27	1	6	11	0	2	51	94	±28
Gestagens	5	31	49	60	±11					60	60	60	0	40	51	69	±11
Average	8		66				28				43				32		
Standard Deviation	±6		±11				±23				±25				±11		
Total AI in Table 2 (N_{total})	165																

Groups contain ≧ 3 AI. Total percentages excreted via urine and faeces, and percentages excreted as parent compound (Unchanged) or in metabolised form.
Av, average of the "average column" (see Methods); min, minimal value detected for all AI in the respective therapeutic group; max, maximal value; SD, standard deviation of the average values; N, sample size (number of AI in therapeutic group).

The 22 therapeutic groups containing ≥3 AI are listed in Table 2 (= 165 AI). We do not show the excretion data for the non-metabolised AI via faeces, because we only found data in four groups (8 AI). In each of the 22 groups, on average at least 49% of an AI was excreted via urine (average of all groups 66% ± 11%; Table 2). Some therapeutic groups showed little variability between excreted fractions of the respective AI (e.g. standard deviation <12% for: x-ray contrast agents, antiphlogistics, antidepressants, antiemetics and gestagens). However, in others the variations were large (e.g., SD > 30% for: oestrogens, antidiabetic agents, vasodilatants, glucocorticoids/corticosteroids, and antilipidemics; Table 2).

Because of limited space we can only discuss the most interesting groups. However, we point out that there are quite a number of therapeutic groups with fairly large excretion via urine – and relatively low variability among the different AI in the group (Table 2). This, for instance, applies to hypnotic drugs (e.g. phenobarbital 100% excretion via urine) and gastric acid inhibitors, and, to a lesser extent (>60% excretion via urine, little variability), also to, for example, antidepressants (e.g. fluoxetine: 60% excretion via urine, 0.3 t sold in 2004; Figure 2), or antiemetics. Additionally, some groups would have a larger average excretion via urine, but contain one or two AI that are exceptions; e.g. antiviral drugs (two exceptions; amprenavir: 14% via urine; valaciclovir: 45%), arterial vasodilators (diltiazem: 31% via urine; pentaerithrityl tetranitrate: 55%), antidiabetics (acarbose: 35%),

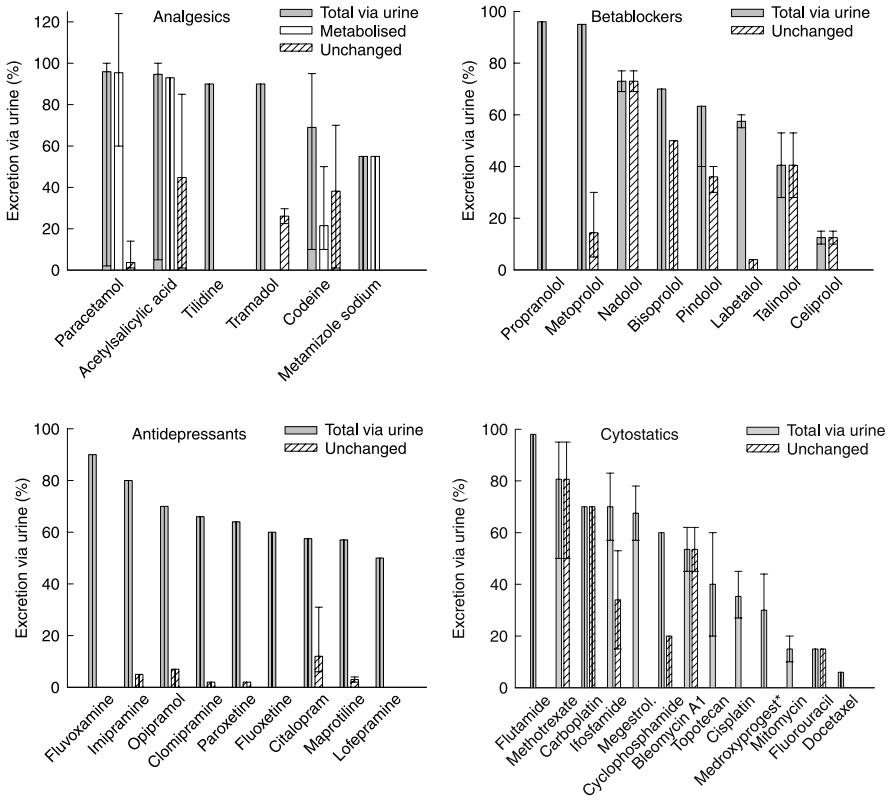

Figure 2 Excretion via urine of selected therapeutic groups. We show the average for each AI. Error bars denote the minimal and maximal value detected for each AI. We show the total fraction excreted via urine and the fraction of the non-metabolised parent compound (Unchanged). For clarity, we did not include excretion via faeces. If bars are missing, respective data were missing (e.g. no data on metabolism for the analgesic tilidine). For antidepressants, β-blockers, and cytostatics, metabolism data were missing for most AI. Cytostatics: cyclophosphamide includes cyclophosphane; ∗, medroxyprogesteronacetate

vasodilatants (sildenafil citrate: 13%) or β-blockers (see Figure 2). In these cases, separate collection of urine would help to keep a considerable amount of the human medicals away from the aquatic environment. In others, there was extreme variability: e.g. excretion via urine in the group that contained most AI, the antibiotics, ranged from 8% (erythromycin) to 100% (meropenem). The example of penicillin V (therapeutic group = antibiotics) illustrates the variability within one AI: 26–90% was excreted via urine, depending on product and manufacturers' information.

X-ray contrast media

Urine source separation could be a very effective measure to remove the x-ray contrast media from the wastewater stream, since 94% (±4%) selected for our study are excreted via urine. Iodinated X-ray contrast media are inert, which is reflected in the non-existing metabolisation (Table 2) and are strongly resistant to degradation, both by biological wastewater treatment (Joss *et al.*, 2006) and by ozonation (Ternes *et al.*, 2003). Moreover, several contrast agents appear on the list of the top 100 most-sold pharmaceuticals: iopromide (6.9 t sold in 2004), iohexol (4.6 t) and iomeprol (1.7 t). Additionally, iobitridol (3.8 t) and ioxitalamic acid (3.6 t) also appear on this list; these were not included in our study. However, of the latter one product is excreted to a large extent via faeces.

In a hospital pilot study in Berlin the implementation of NoMix toilets for separate collection of urine containing x-ray contrast media and a decentralised collection system with mobile transportable urine containers were theoretically evaluated (Pineau and Heinzmann, 2005). The mobile containers seemed to be most efficient, because this measure is easy to implement, whereas the installation of new sanitary devices is associated with costs and possibly other drawbacks. However, implementation of NoMix toilets would have the additional benefit of removing other pharmaceuticals contained in the urine of patients that were not assessed in the mentioned study.

Analgesics

Analgesics are among the most widely used pharmaceuticals. For instance, paracetamol is number one of the Swiss top 100 list (128 t sold in 2004); use of acetylsalicylic acid (47 t) and metamizole sodium (5 t) is also high. Urine source separation would be highly efficient to keep paracetamol and acetylsalicylic acid, as well as tilidine and tramadol, away from the aquatic environment (≥90% excretion via urine), but would only solve half the problem for metamizole sodium (Figure 2). The example of acetylsalicylic acid also illustrates the difficulties we encountered. The fraction of unchanged and metabolised excretion via urine should equal the total, which is not the case (45% + 93% ≠ 95%). The large variability of minimal and maximal excretion is also apparent, e.g. ranging from 2 to 100% for paracetamol.

Antiepileptic drugs

The two highly sold drugs carbamazepine and gabapentin (both 4.4 t sold in 2004), are excreted to 72 and 100%, respectively, via urine. Carbamazepine had a high environmental risk quotient in the related modelling study (Lienert *et al.*, 2007) and is degraded to <20% by biological wastewater treatment (Joss *et al.*, 2006). Here, urine source separation would be an interesting option.

Oestrogens

Oestrogens are known to induce long-term chronic effects in aquatic organisms (e.g. vitellogenin response of fish; Routledge *et al.*, 1998), even at very low concentrations. With 0.2 t sold in 2004, ethinyloestradiol does not appear in the top 100 list. At first

glance urine source separation seems to be promising for oestrogens, since 73% are excreted via urine (Table 2). However, we observed a large standard deviation (±31%), which is caused by the synthetic ethinylestradiol. This AI is contained in contraceptives, and only 38% is excreted via urine (40% as metabolites; maximally 17% unchanged). In contrast, oestradiol valerate and the natural hormone oestradiol are excreted to 90 and 92%, respectively, via urine. Oestradiol is mainly excreted in the metabolised form (no data on metabolism for oestradiol valerate). Moreover, degradation by conventional biological wastewater treatment can be expected to be better for the natural hormones oestradiol and oestrone (>90% removal rate; Joss *et al.*, 2006) than for the synthetic ethinyloestradiol (<90%). Hence, urine separation could only partially solve the problem of synthetic oestrogens in wastewater, while it would efficiently remove the natural oestradiol, which is degraded in wastewater treatment anyway.

Antiphlogistics

These drugs are extensively used (ibuprofen: 24 t sold in 2004; mefenamic acid: 19 t; diclofenac: 4.6 t). Ibuprofen and diclofenac had a high environmental risk quotient in the related modelling study (Lienert *et al.*, 2007). Urine source separation could remove about two-thirds of the AI of this group from the wastewater stream, with little variation between different compounds (Table 2). This seems to be fairly efficient, since such medicines are widely used throughout the population, and in these cases recovery from point sources such as hospitals would not be an effective measure. Moreover, since the degradation rates by biological treatment range from <20% for diclofenac and indomethacine, over 20–90% for naproxen, to >90% for ibuprofen (Joss *et al.*, 2006), this source control measure could effectively complement conventional wastewater treatment.

Antilipidaemics

Excretion via urine ranged from 6% (fluvastatin; simvastatin: 13%) to 100% (clofibrate; etofibrate: 95%; fenofibrate: 79%). Antilipidaemics are not on the 2004 top 100 sales list (fenofibrate: 0.4 t, clofibrate 0.02 t). Ecotoxicological modelling indicated that fenofibrate and bezafibrate have a fairly high environmental risk (Lienert *et al.*, 2007). Interestingly, modelling revealed that despite the large excretion via urine of fenofibrate and its metabolites, a much higher ecotoxicological risk was contained in faeces. This may be explained by the high lipophilicity of fenofibrate. Therefore, substance flow analyses as in this study are only an approximation of the effectiveness of urine separation, but will not give the right answer in all cases (see Lienert *et al.*, 2007 for a more thorough discussion).

Cytostatics

The cytostatics also exemplify the variability between AI of one therapeutic group (Figure 2). Total excretion via urine ranged from ≤15% (docetaxel, fluorouracil, mitomycin) to 98% (flutamide), with an average of 49% (±28%; Table 2). Our data indicate that many cytostatics are not metabolised. The sales figures are low (cyclophosphamide: 33 kg sold in 2004, methotrexate: 16 kg, mitomycin: 0.04 kg). However, they are aggressive compounds, designed to fight cancer, and deserve closer scrutiny in ecotoxicological studies. Mutagenicity is a probable effect, one source reporting of malformations in the offspring of freshwater molluscs caused by mitomycin (Nakano *et al.*, 2003). Hence, collection of the urine from patients treated with selected cytostatics could be an option, since urine separation could remove a large part of some, but certainly not all cytostatics.

Conclusions

The initial assumption that most pharmaceuticals are excreted with urine could be verified to a certain extent. However, we were also able to show that this statement is valid for some pharmaceuticals and therapeutic groups, but is not at all true for others. Some of the detected inconsistency reflects biological variability, but much is caused by the large difference in physicochemical properties of the pharmaceuticals. Moreover, just relying on mass balances does not necessarily correspond with the ecotoxicological relevance. Indeed, in the related modelling study of 42 drugs we found that although, on average, 70% of a pharmaceutical was excreted via urine, the environmental risk potential was estimated to be about equal in urine and faeces (Lienert *et al.*, 2007). However, we hypothesise that the pharmaceuticals in faeces, which are generally more lipophilic, might adsorb well to faecal matter and end up in the sludge (in Switzerland sludge is incinerated); this assumption should be experimentally verified in future studies. If it is true, the fraction of micropollutants in faeces might be better removable from wastewater than the hydrophilic fraction in urine – and a combination of the two measures might prove to be very effective.

Since the NoMix technology is still at an early stage, implementing urine source separation in real life is associated with some difficulty (e.g. concerning NoMix toilets). Therefore, we advise great caution about introducing the NoMix technology at this stage solely to solve the problem of pharmaceuticals in the aquatic environment. Separate collection of urine can contribute to keeping these substances away from wastewater, but it will not be the perfect solution. On the other hand, there are very good arguments for urine source separation; a main one being water pollution control with respect to nutrients (see Lienert *et al.*, 2007). Hence, if the NoMix technology is introduced for such reasons, facilitated removal of pharmaceuticals can be a very welcome side effect.

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