Sources of Active Pharmaceutical Ingredients (APIs)

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Consumption & emissions of APIs

Human and veterinary consumption of APIs

- Antibiotics
- Antiepileptics
- Antihypertensives
- Asthma and allergy medications
- Gastrointestinal disease medications
- Hormones
- Metabolic disease medications
- Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics
- Other cardiovascular medicines
- Psychopharmaceuticals
- Veterinary medicines

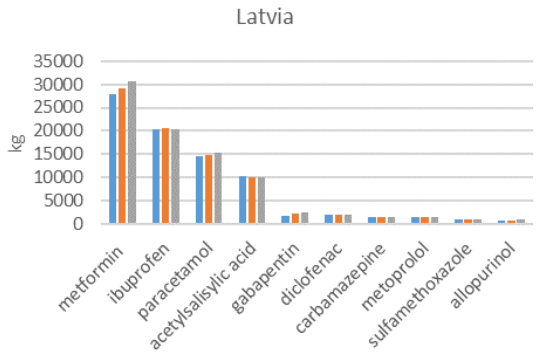
Emissions of APIs

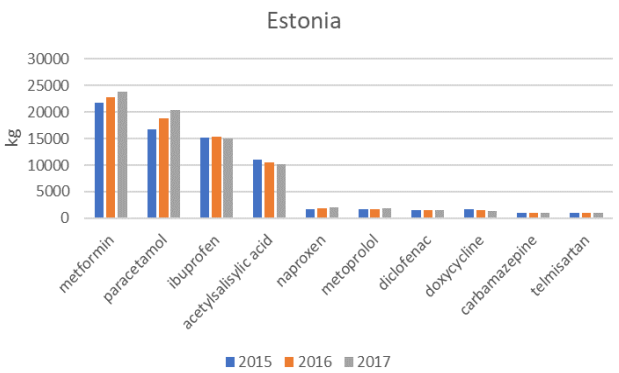
- Hospitals
- Manufacturing facilities of APIs
- Pig and poultry farms
- Fish farms
- Landfills
- Wastewater treatment plants (WWTPs)

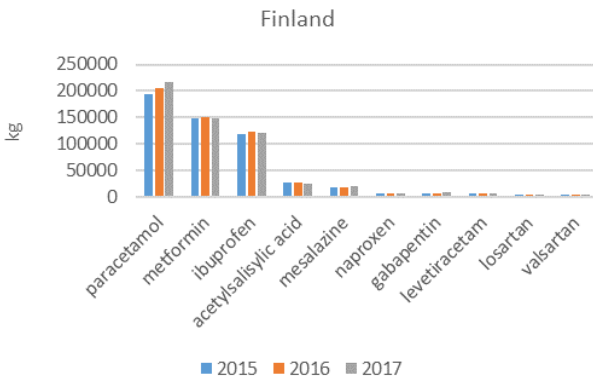
Human and veterinary consumption of APIs

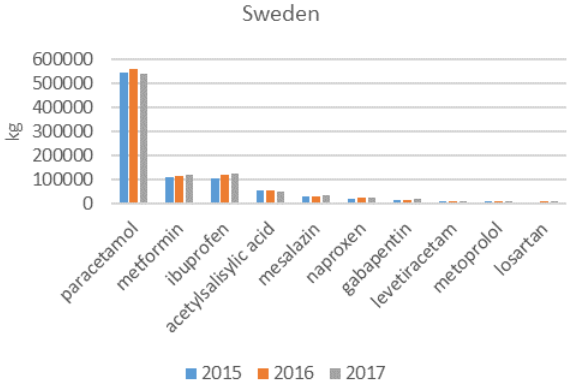
- Consumption data for 83 APIs were collected for the years 2015-2017.
- Difficult or impossible to obtain complete consumption data of APIs in mass units (in kg).
- Consumption of veterinary medicines was also collected through a questionnaire in collaboration with HELCOM.

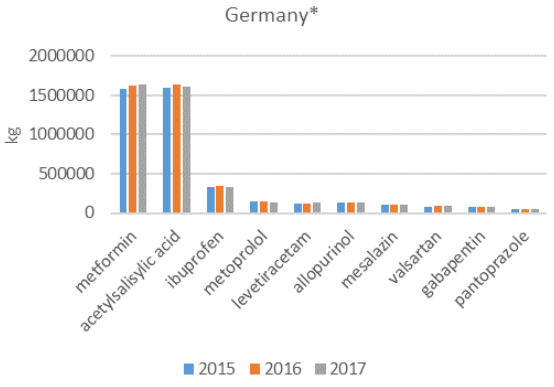
Top 10 consumed APIs







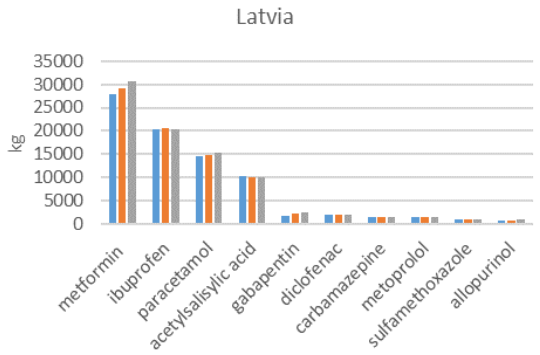


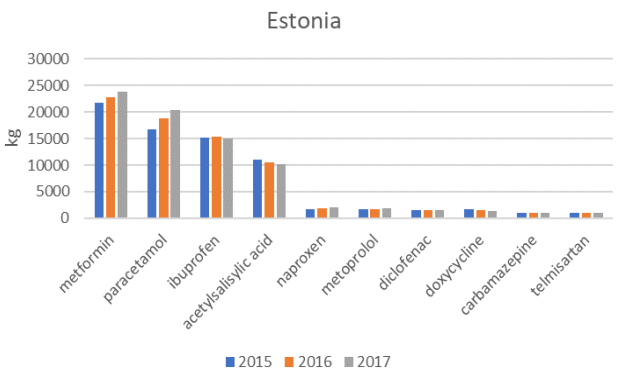


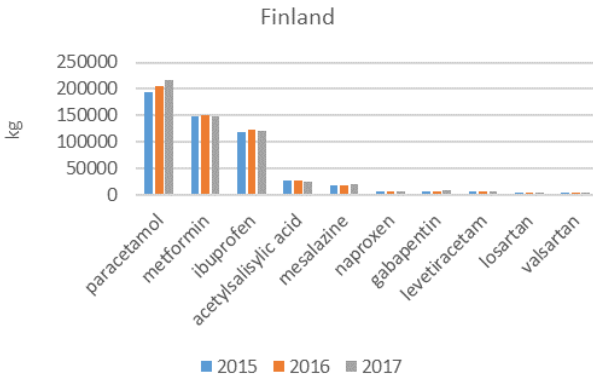
Most consumed of the studied APIs were used for:

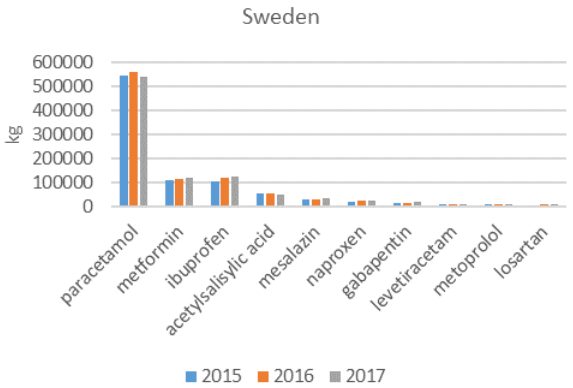
- type II diabetes – metformin,
- pain and fever – paracetamol and different non-steroidal anti-inflammatory drugs,
- epilepsy – levetiracetam and gabapentin,
- cardiovascular diseases – losartan, valsartan and metoprolol.

Top 10 consumed APIs



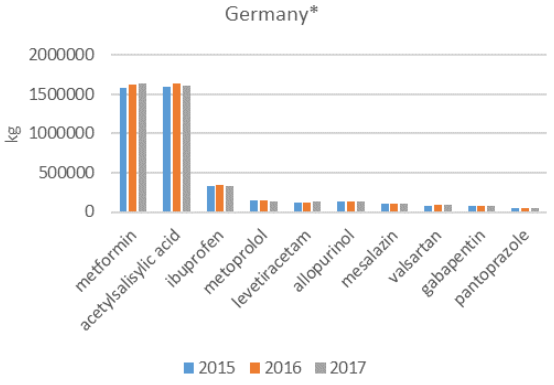






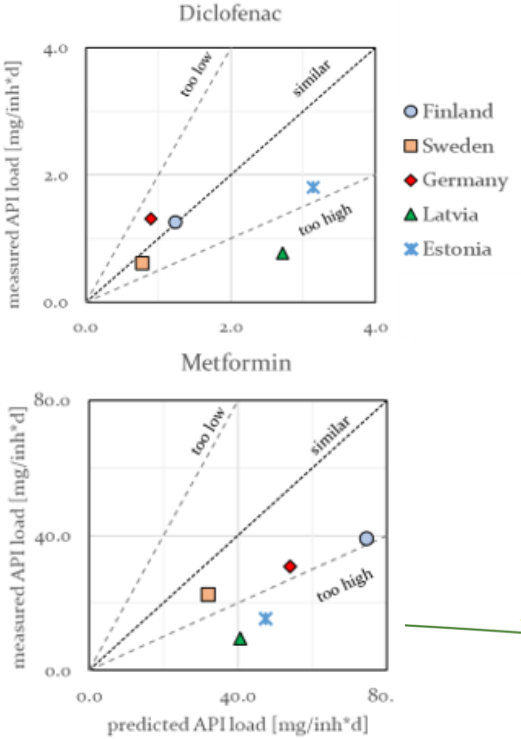
After intake, some medicines are metabolized, while others remain intact until they are excreted.

APIs and their metabolites are spread via the WWTPs to receiving aquatic environments.

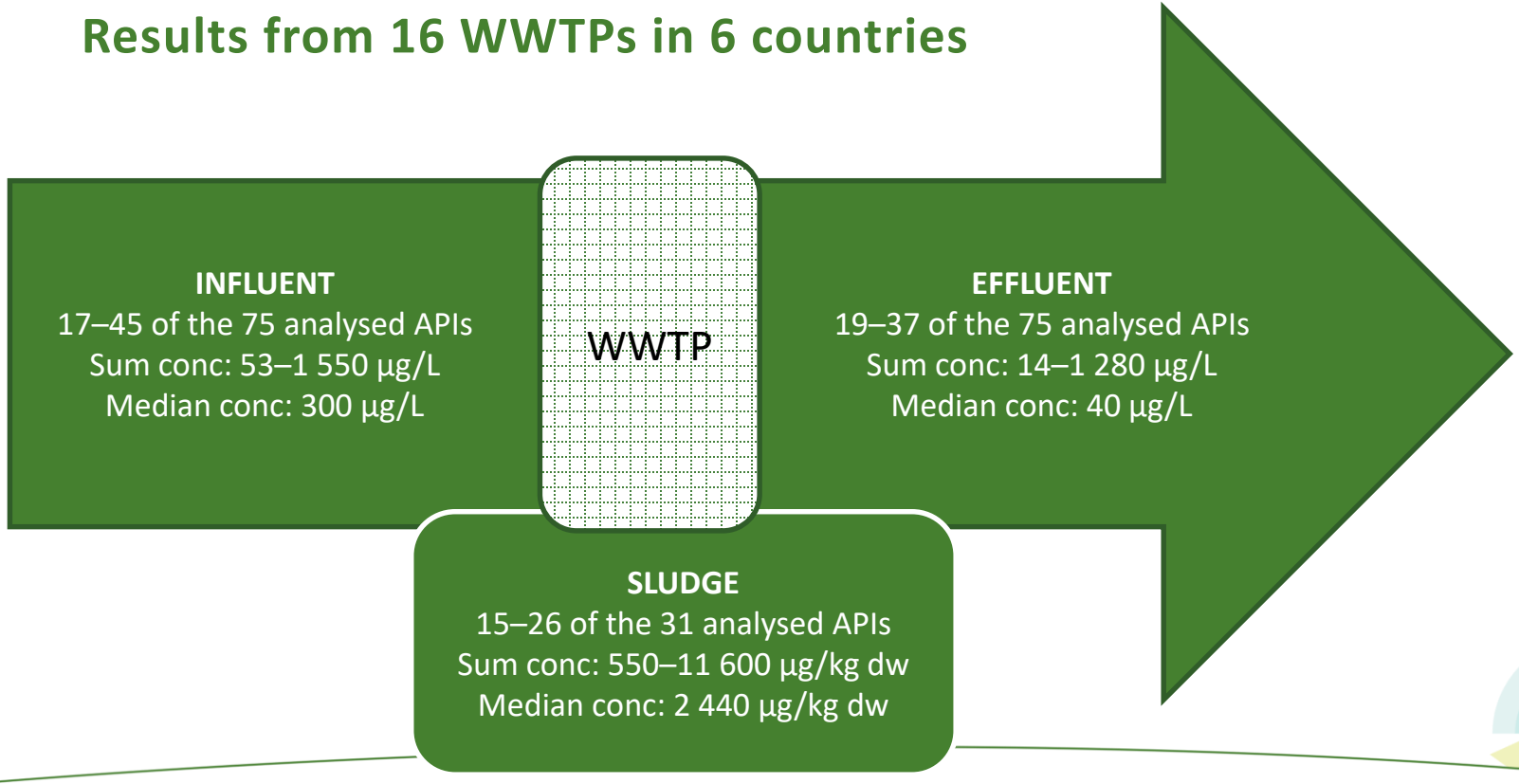


Can the countrywise consumption data be used to predict the load of APIs in wastewater influents?

- Good agreement for some APIs e.g. diclofenac and paracetamol in most countries.
- Over- or underestimation for some APIs e.g. metformin and carbamazepine.
- The agreement may be improved by including more comprehensive consumption data and measurements.



Results from 16 WWTPs in 6 countries



Most frequently detected APIs

17 APIs detected in ≥90% of the influents – 6 APIs found in all influents

- Caffeine, codeine, **diclofenac**, fluconazole, **gabapentin**, hydrochlorothiazide, **ketoprofen**, levetiracetam, mesalazine, **metformin, naproxen, oxazepam**, paracetamol, sulfamethoxazole, **trimethoprim**, valsartan and venlafaxine.
- Max conc: paracetamol (up to 1000 µg/L) in Finland and Sweden.

15 APIs detected in ≥90% of the effluents – 3 APIs found in all effluents

- Carbamazepine, citalopram, clarithromycin, **diclofenac**, erythromycin, fluconazole, hydrochlorothiazide, ketoprofen, **metoprolol**, naproxen, **oxazepam**, sotalol, tramadol, trimethoprim and venlafaxine.
- Max conc: ibuprofen and diclofenac (up to 44 µg/L) in Latvia and Estonia.

8 APIs were found in all sludge samples

- Diclofenac, carbamazepine, venlafaxine, metformin, caffeine, metoprolol, citalopram and sertraline.
- Max conc: telmisartan and ofloxacin (up to 8700 µg/kg dw) in Estonia and Finland.

Removal efficiencies of APIs

28 APIs with positive removal efficiencies.

APIs at least partly removed in conventional WWTPs. +

- APIs with high average removal efficiency (≥90%): allopurinol, caffeine, levetiracetam, mesalazine, metformin, nebivolol, olanzapine, paracetamol and simvastatin.

19 APIs with positive or negative removal efficiencies.

Removal efficiencies depended on the WWTP. +/-

3 APIs with negative removal efficiencies.

API emissions did not decrease in conventional WWTPs. -

- Metoprolol, primidone and ramipril.
- Another 7 APIs with zero or negative *average* removal efficiencies: carbamazepine, diclofenac, hydrochlorothiazide, irbesartan, sotalol, telmisartan and losartan.

APIs in hospital effluents

in Sweden (Linköping and Norrköping), Germany (Wismar) and Estonia (Pärnu)

- Sum concentration: 75–1200 µg/L. Gabapentin, metformin and paracetamol were found at highest concentrations.
- The sum concentration (**µg/L**) was generally higher in hospital effluents compared to the sum concentrations in the influents of the connected WWTPs.
- The total load (**g/day**) in the effluents from hospitals were only up to 3 % of the overall load to the connected WWTPs.
- Hospitals have less contribution to the **total load** of APIs to the WWTPs compare to the households.

APIs in effluents of a manufacturing facility in Latvia (after pre-treatment)

- 10 of the analysed APIs were listed as products of the manufacturer.
- Effluents contained high levels of certain APIs, especially paracetamol.
- The total load of the detected APIs in effluents was at maximum 5 % of the overall API load to the connected WWTP.

API	API group	Concentration, µg/L		Dosage and product form produced by the manufacturer
		Sampling time 07.12.2017.	Sampling time 28.05.2018.	
Atenolol	other cardiovascular medicines	<LOQ	<LOQ	50 mg /100 mg film-coated tablets
Diclofenac	NSAIDs and analgesics	0.042	0.022	20 mg/g ointment
Ibuprofen	NSAIDs and analgesics	<LOQ	N/A	not specified
Ketoprofen	NSAIDs and analgesics	0.86	N/A	2.5% gel
Paracetamol	NSAIDs and analgesics	4.5	16	500 mg tablets
Risperidone	psychopharmaceuticals	<LOQ	0.072	2 mg, 4 mg film-coated tablets
Simvastatin	metabolic disease medications	<LOQ	<LOQ	2 mg, 4 mg film-coated tablets
Sulfadiazine	antibiotics	0.58	<LOQ	10 mg/g ointment
Venlafaxine	psychopharmaceuticals	0.25	N/A	37.5 mg / 75 mg tablets
Warfarin	other cardiovascular medicines	2.0	0.068	2.5 mg / 3 mg / 5 mg tablets

Landfill leachates in Finnish case study area

- Landfill leachates were analysed before and after treatment at the landfill's WWTP. The untreated leachate contained:
  - 26 out of 74 analysed APIs
  - sum conc: 3.5–172 µg/L
  - max conc: paracetamol and hydrochlorothiazide (up to 80 µg/L)

- API levels decreased after treatment by 35–76%.

- Low water volume ➡ the total load of APIs (g/day) from the landfill WWTP was low compared to the API load from municipal WWTPs.

- Many landfills have no treatment at all.

APIs in surface waters and sediments at Finnish and Estonian fish farms

- Temporarily elevated concentrations in water were found for the antibiotic trimethoprim near one of the fish farms after a medication event.
- The concentration of trimethoprim was lower than the PNEC.
- Otherwise, the number of detected APIs and their sum concentration was about the same or lower in the fish farm waters compared to other studied surface waters.

APIs in watercourses downstream livestock farms in Latvia

- The watercourses downstream a pig farm and a poultry farm in Latvia contained 7–21 of 59 analysed APIs.
- The sum concentration of detected APIs was 0.18–0.62 µg/L, which is within the range found in other surface water samples.
- The concentrations of the veterinary medicines tiamulin and toltrazuril were higher downstream the pig farm than in other surface water samples.

Conclusions – sources of APIs

- The major source of APIs are the medicines consumed in households.
- Hospitals and API manufacturing facilities are minor sources compared to households.
- APIs are spread to the Baltic Sea environment mainly via WWTPs.
- Many APIs are incompletely removed at conventional WWTPs.
- Most cost-efficient solution is to install advanced treatment technologies at the WWTPs to reduce the total load of APIs.
- APIs are leaking from landfills.
- Livestock farms may be significant sources of APIs used for veterinary purposes.

8 recommendations

1. Measurements of environmentally risky APIs should be included in: - regular environmental monitoring programmes, - effluents from WWTPs.

2. The analytical methods should be further developed to make comprehensive estimates of APIs in the environment, including metabolites.

3. The statistics on the use of medicines should be improved, by making data publicly available in DDD format (defined daily dose) and in mass units (kg).

4. Further studies should be performed on the use of veterinary medicines and their dispersal in the environment. Restrict unnecessary use of APIs.

8 recommendations

5. Further studies should be performed on the environmental levels and risks of antibiotics, including the spread of antibiotic resistance genes.

6. More ecotoxicological data are needed on:
- single APIs and their metabolites, - mixture toxicity,
- different trophic levels and matrixes, - chronic effects.

7. Emissions of APIs from landfill leachates should be further analysed, especially where household waste is or has been disposed of at landfills.

8. The emissions of environmentally risky APIs should be reduced by improved wastewater treatment and upstream measures.

Data compiled by 9 organisations from 6 countries. WP2 report recently published.

Ek Henning, H., Putna.Nimane, I., Kalinowski, R., Perkola, N., Bogusz, A., Kublina, A., Haiba, E., Barda, I., Karkovska, I., Schütz, J., Mehtonen, J., Siimes, K., Nyhlén, K., Dzintare, L., Äystö, L., Sinics, L., Laht, M., Lehtonen, M., Stapf, M., Stridh, P., Poikāne, R., Hoppe, S., Lehtinen, T., Kõrgma, V., Junttila, V., Leisk, Ü. (2020). Pharmaceuticals in the Baltic Sea Region – emissions, consumption and environmental risks. Report no. 2020:28, Länsstyrelsen Östergötland, Linköping. Available at: https://www.lansstyrelsen.se/4.f2dbbcc175974692d268b9.html

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fimea Finnish Medicines Agency






Thank you!

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