

Pan-European Risk of in-use Pharmaceuticals to the Environment

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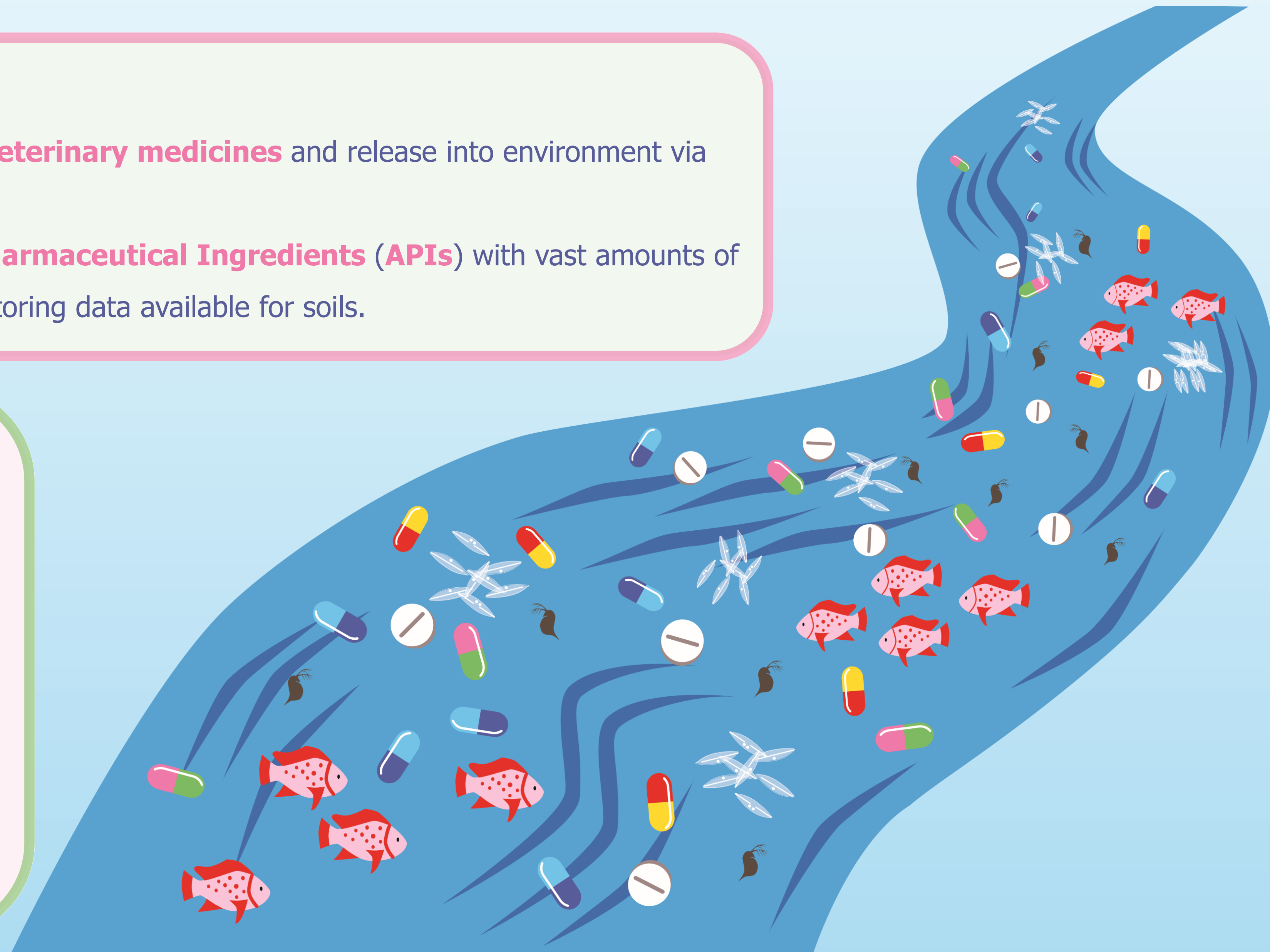
Pharmaceutical pollution and existing data

- Rising concern of pharmaceutical pollution with **increasing use** of **human** and **veterinary medicines** and release into environment via excretion, improper disposal and manufacturing.
- Growing scientific interest on **environmental occurrence** and fate of **Active Pharmaceutical Ingredients (APIs)** with vast amounts of monitoring data available across European surface waters, and more limited monitoring data available for soils.

Risk Ranking Approach

- Construct **database** of European **API monitoring** data
- Identify **in-use APIs** (parent & transformation products) posing greatest **risk** to **species** using:
 - Worst-case **95th %-ile** concentrations ^[1-6]
 - Hazardous concentration** to **50%** of species (**HC₅₀**) derived from **Species Sensitivity Distributions (SSDs)** ^[7]
- APIs ordered based on **Hazard Quotient (HQ)** & **Detection Frequency (DF)**

$$HQ \text{ Rank} * DF \text{ Rank} = \text{Risk Rank}^{[8]}$$



Worst-case Risk Ranking of detected in-use Pharmaceuticals in European Freshwaters (FW) and Soils

Figure 1: Hazard Quotient (HQ) of top 30 APIs in FWs

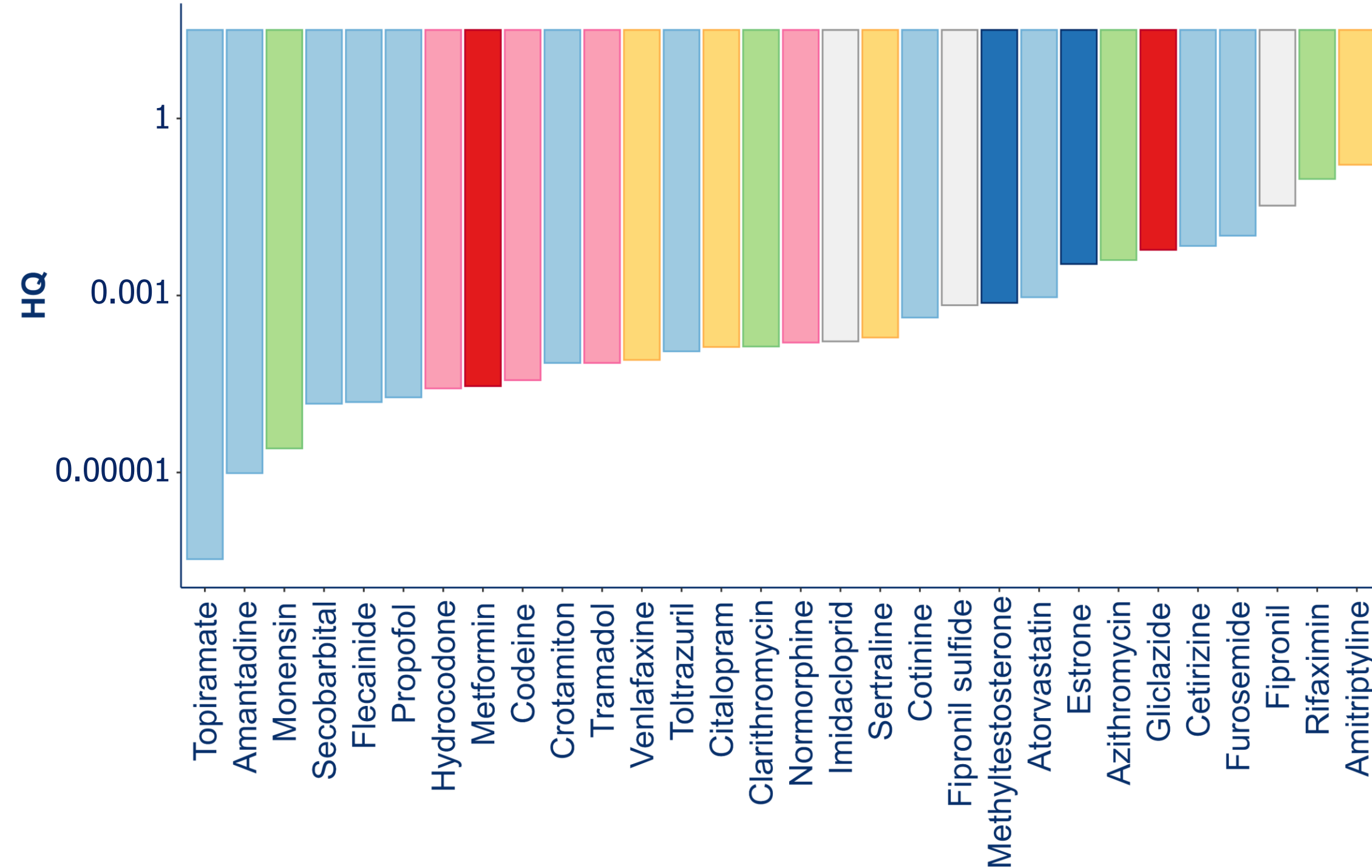


Figure 2: Therapeutic class of top 30 APIs in FWs

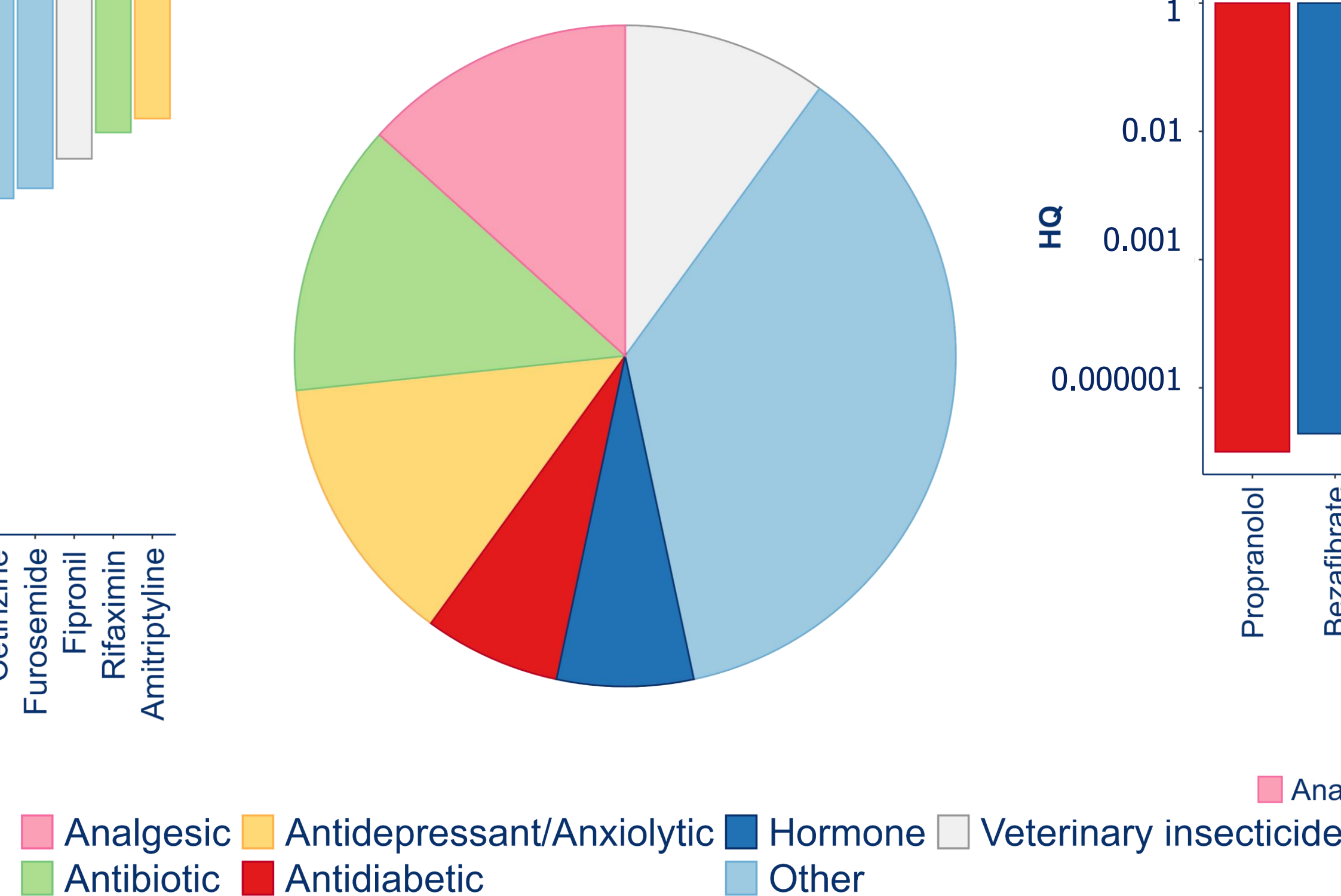
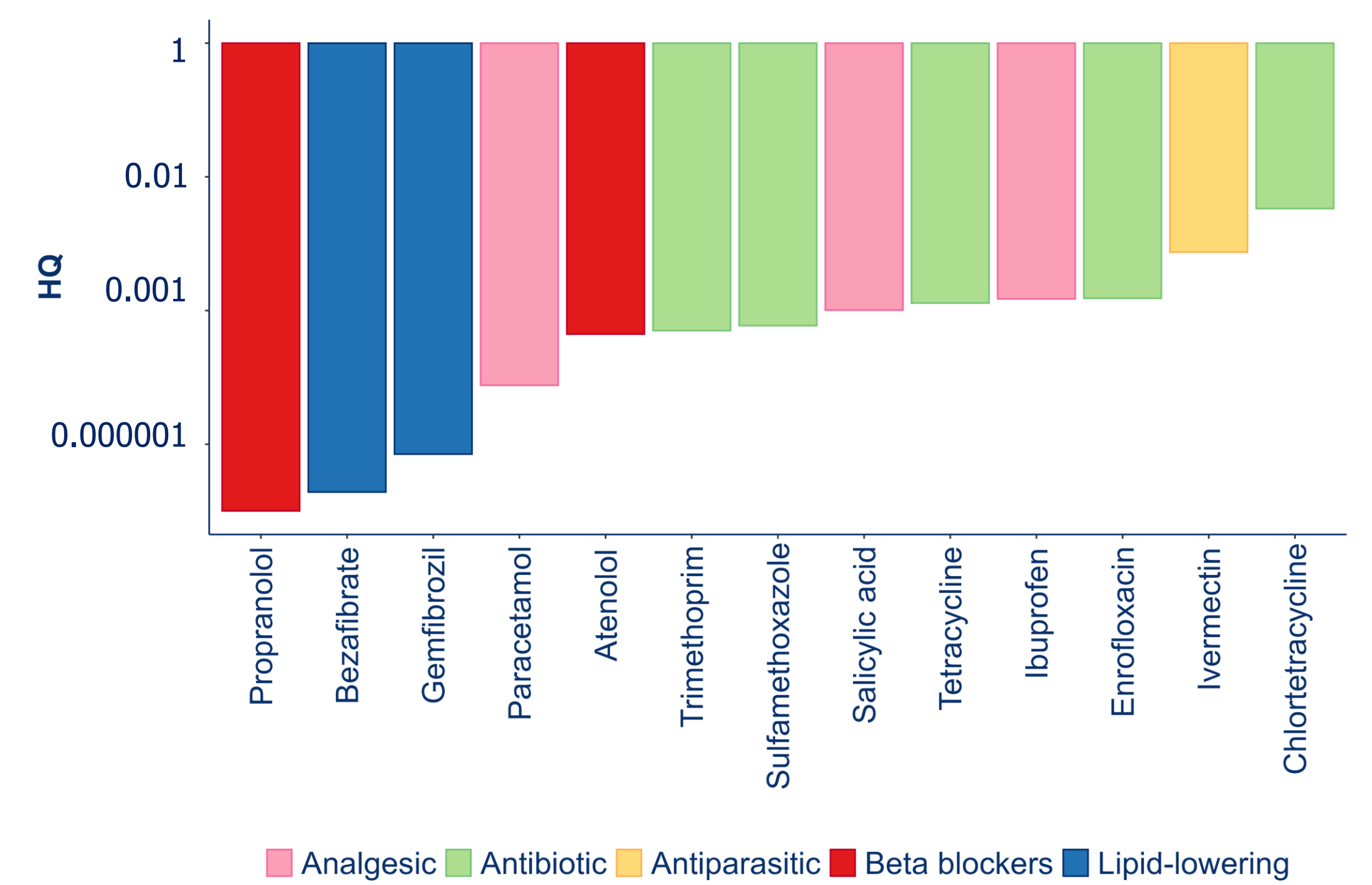


Figure 3: Hazard Quotient (HQ) of APIs in soils



European countries (n=33): Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland, Ukraine and United Kingdom.

Risk to Surface Waters

- 692 **APIs** (~220,000 measurements), 59% of APIs (n=405) **detected often** (≥ 10 times) and 55% of APIs (**n=225**) with community-based **SSD HC₅₀** values.
- APIs (n=225) have **HQs < 1** indicating concentrations **below hazard thresholds** for **affecting 50% of species** (Figure 1).
- Amongst **relative risk** of 225 APIs **top 30 APIs** include Analgesic, Antibiotic, Antidepressant/Anxiolytic, Antidiabetic, Hormone and Veterinary insecticide medications (Figure 2 & Table 1).
- Top 5 APIs **posing greatest risk** to **aquatic species** are Rifampicin (Antibiotic), Fipronil (Veterinary insecticide), Propofol (Anesthetic), Secobarbital (Barbiturate) and Monensin (Antibiotic) (Table 1).

Risk to Soils

- 93 **APIs** (~600 measurements) and 2% of APIs (**n=13**) with **EC₅₀** values for *Eisenia*.
- HQs < 1** indicating concentrations **below hazard thresholds** (Figure 3).
- Top 5 APIs posing greatest risk to soil species include Antibiotic, Analgesic, Beta blocker and Lipid-lowering medications (Table 1).

Table 1: Risk Rank for top 30 APIs in Freshwaters and APIs in soils

Risk Rank	API	Therapeutic class	Risk Rank	API	Therapeutic class
1	Rifampicin [‡]	Antibiotic	1	Chlortetracycline [‡]	Antibiotic
2	Fipronil [†]	Veterinary insecticide	2	Salicylic acid [‡]	Analgesic
3	Fipronil sulfide [*]	Fipronil metabolite	3	Atenolol	Beta blockers
4	Propofol [‡]	Anesthetic	4	Gemfibrozil	Lipid-lowering
5	Secobarbital [‡]	Barbiturate	5	Bezafrate	Lipid-lowering
6	Monensin [‡]	Antibiotic	6	Ivermectin [‡]	Antiparasitic
7	Amantadine	Antidyskinetic	7	Ibuprofen	Analgesic
8	Topiramate	Anticonvulsant	8	Enrofloxacin [‡]	Antibiotic
9	Amitriptyline [‡]	Antidepressant/Anxiolytic	9	Tetracycline [‡]	Antibiotic
10	Cetirizine [‡]	Antihistamine	10	Trimethoprim [‡]	Antibiotic
11	Gliclazide	Antidiabetic	11	Paracetamol	Analgesic
12	Cotinine [‡]	Nicotine metabolite	12	Sulfamethoxazole [‡]	Antibiotic
13	Furosemide [‡]	Diuretic	13	Propranolol	Beta blockers
14	Imidacloprid [‡]	Veterinary insecticide			
15	Methyltestosterone	Testosterone			
16	Sertraline [‡]	Antidepressant/Anxiolytic			
17	Azithromycin [‡]	Antibiotic			
19	Hydrocodone [‡]	Analgesic			
19	Metformin	Antidiabetic			
20	Atorvastatin	Anticholesterol			
21	Crotamiton [‡]	Antipruritic			
22	Tramadol [‡]	Analgesic			
23	Venlafaxine [‡]	Antidepressant/Anxiolytic			
24	Codeine	Analgesic			
25	Normorphine [‡]	Morphine metabolite			
26	Flecainide [‡]	Antiarrhythmic			
27	Estrone	Oestrogen			
28	Citalopram [‡]	Antidepressant/Anxiolytic			
29	Clarithromycin [‡]	Antibiotic			
30	Toltrazuril [†]	Antiparasitic			

* API transformation products, ‡ APIs for human & veterinary use and † APIs for veterinary use
Includes APIs with FW measurements from UK monitoring programs or ≥ 3 databases ^[1-6]

References: ^[1] EA WIMS, LC-MS & GC-MS datasets; ^[2] NAIADES database; ^[3] NORMAN database; ^[4] PHARMS-UBA database; ^[5] UKWIR CIP database; ^[6] Wilkinson *et al* 2023 PNAS 119; ^[7] Posthuma *et al* 2019 ET&C 38; ^[8] Spurgeon *et al* 2022 STOTEN 835