Report summary medicinal products (active pharmaceutical ingredients, diagnostics, anesthetics and intermediates)

Contents

Preface

The scope of this report summary is to present the results of a quick scan on PFAS use in the medical sector, more specific in medicinal products. This report does not contain the PFAS production stage (like for the manufacturing of PTFE, PFOA etc.) nor the end of life/waste stage. As a consequence, the manufacturing of the active pharmaceutical ingredients (API) and medical products, hence reagents or solvents is not addressed here.

Medical devices is described in a separate summary.

It should be noted that the tonnages APIs are currently based on the molecular weight of the API and not on the fluorinated part only. Anesthetics and contrast media in this report are reported individually, so not directly into medicinal products. They are both named in the medicinal products summary and medical applications summary. The lists presented in this document reflect non exhaustive lists.

1. Uses / Applications

The following main uses can be distinguished.

- Medicinal Products (APIs, diagnostics, anesthetics)
- Medicinal Products and Medical Technology production ingredients (e.g., intermediates,)

2. APIs with PFAS like moieties

Starting point of the selection of fluoro-containing medicinal products was a recent paper (Inoue, Sumii et al. 2020), who listed 340 of such compounds that are present in the database of the WHO Collaborating Centre for Drug Statistics Methodology hosted by the Norwegian Institute of Public Health[1], not necessarily all in use in EU.

68 APIs with one or more CF_2 or CF_3 group were found with a market registration for human use in the EU or in one or more of its member states. The substances cover a broad and diverse application range with a large variety mode of actions. They are distributed over 56 chemical-therapeutical-pharmacological groups according the WHO-ATC system and are presented in table 1.

Table 1 Overview of registered PFAS-APIs with 1 or 2 CF_2 groups are indicated by asterix, the other APIs contain at least one CF_3-group.

API	CASNR	ATC
alpelisib	1217486-61-7	L01XX
apalutamide	956104-40-8	L02BB
aprepitant	170729-80-3	A04AD
bendroflumethiazide	78-48-3	C03AA C03AB C03EA
benfluorex	23602-78-0	A10BX
bicalutamide	90357-06-5	L02BB
cangrelor	163706-06-7	B01AC
celecoxib	169590-42-5	C08CA L01XX M01AH
cinacalcet	226256-56-0	H05BX
delamanid	681492-22-8	J04AK
desflurane	57041-67-5	N01AB
dexfenfluramine	3239-44-9	A08AA
doravirine	1338225-97-0	J05AG
dutasteride	164656-23-9	G04CA G04CB
efavirenz	154598-52-4	J05AG
eflornithine*	70052-12-9	D11AX
elexacaftor	2216712-66-0	R07AX[a]
enzalutamide	915087-33-1	L02BB
fenfluramine	458-24-2	A08AA
flecainide	54143-55-4	C01BC
fluoxetine	54910-89-3	N06AB
flunixin	38677-85-9	QM01AG
fluphenazine	69-23-8	N05AB

[1] https://www.whocc.no/atc_ddd_index/

API	CASNR	ATC
fluvoxamine	54739-18-3	N06AB
fosaprepitant	172673-20-0	A04AD[b]
fosnetupitant	1703748-89-3	A04AD[b]
fulvestrant	129453-61-8	L02BA
gemcitabine*	95058-81-4	L01BC
glecaprevir*	1365970-03-1	J05AP
isoflurane	26675-46-7	N01AB
ivosidenib*	1448347-49-6	L01XX
lansoprazole	103577-45-3	A02BC A02BD
ledipasvir*	1256388-51-8	J05AP
leflunomide	75706-12-6	L04AA
letermovir	917389-32-3	J05AX
lomitapide	182431-12-5	C10AX
lumacaftor*	936727-05-8	R07AX
maraviroc*	376348-65-1	J05AX
mefloquine	53230-10-7	P01BC P01BF
netupitant	290297-26-6	A04AD[b]
nilotinib	641571-10-0	L01XE
nilutamide	63612-50-0	L02BB
nitisinone	104206-65-7	A16AX
pantoprazole*	102625-70-7	A02BC A02BD
penfluridol	26864-56-2	N05AG
perflutren	76-19-7	V08DA
ponatinib	943319-70-8	L01XE
pretomanid	187235-37-6	unknown
regorafenib	755037-03-7	L01XE
riluzole	1744-22-5	N07XX
roflumilast*	162401-32-3	R03DX
rolapitant	552292-08-7	A04AD
sevoflurane	28523-86-6	N01AB
silodosin	160970-54-7	G04CA
siponimod	1230487-00-9	L04AA
sitagliptin	486460-32-6	A10BH
sonidegib	956697-53-3	L01XX
sorafenib	284461-73-0	L01XE
tafluprost*	209860-87-7	S01EE
telotristat	1033805-22-9	A16AX
teriflunomide	163451-81-8	L04AA
tezacaftor*	1152311-62-0	R07AX
tipranavir	174484-41-4	J05AE
travoprost	157283-68-6	S01EE
trifluoperazine	117-89-5	N05AB
upadacitinib	1310726-60-3	L04AA
vinflunine*	162652-95-1	L01CA
voxilaprevir*	1535212-07-7	J05AP

[a] no ATC code available, based on similarity with tezacaftor and ivacaftor we tentatively assigned the code R07AX

[b] no ATC code available, based on similarity with aprepitant and rolapitant we tentatively assigns the code A04AD

3. Tonnage band

Pharmaceutical prescriptions

Data on pharmaceutical prescriptions were collected from the Dutch GIP Databank.[2] This databank amongst others shows a ranking of the top 500 pharmaceuticals in the Netherlands based on total number of DDD (daily defined dosage) delivered to patients in the years 2015-2019. This enables calculation of a mass (tonnage) of PFAS pharmaceuticals, using the following formula:

$$Use = DDD_{NL} \times dosage \times \frac{Population_{EU27}}{Population_{NL}} \times 10^{-9} \quad (^{ton}/_{year})$$

where:

- DDD = daily defined dosage (#)
- dosage = typical mass of a DDD (mg)
- Population = total population in EU (#)
- 10^{-9} = conversion factor for mg to ton

Amounts of medicinal products used in the Netherlands (population 17,407,575 at 1-1-2020) have been extrapolated to the EU27 by correction for the population (447,706,200 at 1-1-2020)[3]. The typical dosage of one DDD was retrieved from the WHO ATC/DDD website[4]. Prescription of pharmaceuticals is registered by insurance companies in the Netherlands. Since health insurance is obligatory in the Netherlands, the data present a accurate view of prescribed medicinal products. Although, OTC[5] medicinal products are not included, this will probably not largely influence the total tonnage since not many PFAS containing APIs are present in over the counter drugs.

The use of prescribed APIs with at least one CF2 or CF3 group in the EU in 2019 is, based on the above, estimated to be 400-500 tonnes per year and the use seems to increase with 3.4% per year. Therefore, we further report a use of >500 tonnes medical products per year. See figure 1. Please note that tonnages for medicinal products and intermediates are given based on the total molecular weight of the molecule, rather than on the fluorinated part of the molecule only.

[2] Top 500 van geneesmiddelen o.b.v. het aantal DDD's in 2019 | GIPdatabank.nl
[3] https://ec.europa.eu/eurostat/documents/2995521/11081093/3-10072020-AP-EN.pdf/d2f799bf-4412-05cc-a357-7b49b93615f1
[4] WHOCC - ATC/DDD Index
[5] OTC medicinal products: over the counter medicinal products

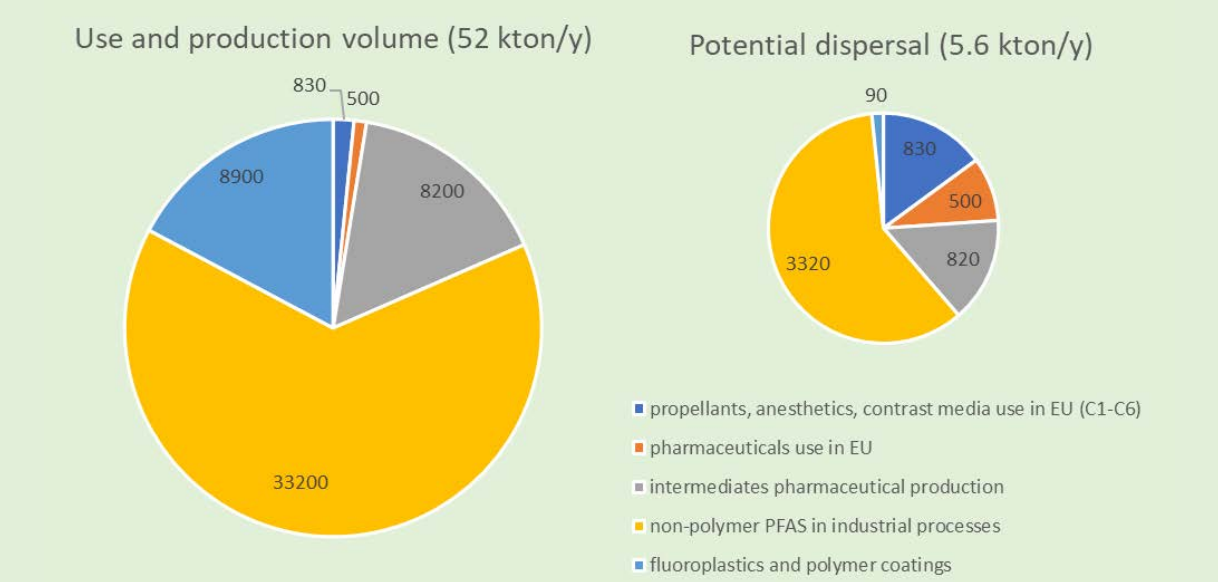

Figure 1 Overview of estimated usage of PFAS used in medicinal products and the manufacturing thereof and their potential environmental dispersal. Midpoint of the uncertainty range in ton/y. See orange for medicinal products.
Note: Medical devices are also mentioned a.o. for comparing with medicinal products (and intermediates).

PFAS non-polymers

Next to the above consultation & calculation a list of 80 PFAS non-polymers and their medical use is obtained from two sources:

1) The ECHA database
2) Response to the Call for evidence (summer 2020)

An overview of tonnages and number of non-polymers (excluding APIs) has been constructed (table 2). It shows that the ECHA database gives approximately 4 times higher tonnages than the Response to the Call for Evidence (CfE) in 2020. A possible explanation is that only a selection of companies has responded to the CfE and that companies have not recognized their use as a medical use. Also no response has been received with respect to pharmaceutical production, whereas in the ECHA data Pharmaceutical production there is a separate category with substantial amount of data.[6]

Table 2 Tonnage range (ton/year) of non-polymer PFAS based on two data-sources.

	C1-C6 PFAS			C7-C26 PFAS			Total		
Data source	#	range	midpoint	#	range	midpoint	#	range	midpoint
All substances									
Response CfE (2020)	36	1,100 – 2,200	**1,600**	17	610 -790	**400**	53	5,400 – 17,000	**11,000**
ECHA	11	26,000 – 47,000	**36,000**	33	225 – 11,000	**5,400**	44	26,000 – 57,000	**42,000**
Intermediates only									
Response CfE (2020)	8	26 – 210	**120**	1	50	**50**	9	78 – 270	**170**
ECHA	6	2,100 – 6,000	**3,000**	19	170 – 8,200	**4,200**	25	2,200 – 14,000	**8,200**

Many non-polymer PFAS and their medical use are used for multiple purposes. One category is relatively unique and these are the intermediates, mostly for pharmaceutical products. The volumes of intermediates are reported separately.

[6] The database was searched for PFAS substances via P29 (an ECHA code for Pharmaceutical industry) and any record from other production categories that contained “medical”, “drug”, “pharmaceutical” or “API”.

Approximately 8,200 ton/y PFAS pharmaceutical intermediates have been calculated based on the ECHA data. This is much larger than the calculated volume of 400-500 ton human medicinal products per year that has been estimated earlier in this report.

Metered Dose Inhalers (MDI)

Metered-Dose Inhalers (MDIs), typically used for the treatment of asthma and other respiratory conditions, use hydrofluorocarbons as propellants. The volume of F-gases for metered dose inhalers has been estimated in four different ways:

1) Production based on stakeholder information;
   Based on communication with the trade organisation an amount of 5,000-6,000 ton propellants /year propellants is produced in the EU. This includes production for export.
2) Production based on ECHA database;
   Total F-gases in relation to metered dose inhalers is 15,000 to >30,000 ton/y
3) Use based on MDI sales;
   Based on average F-gas content and sold cannisters extrapolated to the EU, a volume of approximately 160 up to 1.8 million ton F-gases used on the EU market is estimated. The amount reflects the use by patients in the EU.
4) Use derivation from the report of Health Care Without Harm (HCWH 2019);
   As with anesthesia, global data on emissions from MDIs is not available, however, UNFCCC Annex 1 nations report data on emissions from this source. For UNFCCC Annex 1 nations, emissions from MDI use totaled 6.9Mt CO2 equivalents. The full global emissions from MDIs can be expected to be substantially greater than this figure (HCWH 2019). For the EU this equals approximately 400 ton F-gas propellants. The amount reflects the use by patients in the EU.

The emission factor of propellants by MDI use is set at 100% whereas the emission factor of propellants during production is much lower, probably < 10% (see ECHA's environmental release categories in Appendix 1, Table 5). The approaches for volume estimation are summarized in Table 3.

Table 3 Annual production, use and emissions of F-gases from metered dose inhalers in the European Union to the atmosphere. Worst case emission factors were used for a preliminary assessment of atmospheric release.

	Volume	**Emission factor**	**Atmospheric emissions (ton/y)**
Use	160-400	100%	160-400

4. Manufacturing & Market data

The use of prescribed PFAS-pharmaceuticals in the EU in 2019 is estimated to be > 500 tonnes per year and the use seems to increase with 3.4% per year (see figure 2). In table 3 the market data/tonnages of the main PFAS moieties containing APIs in the period 2015-2019 are displayed.

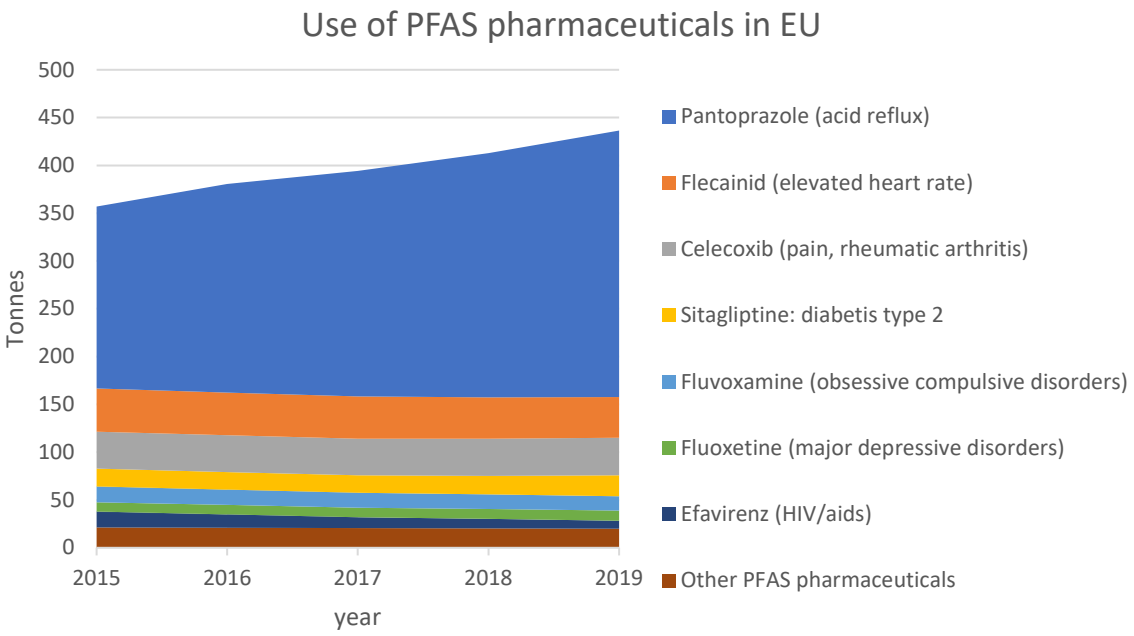

Figure 2: Estimated trend in the use of PFAS-pharmaceuticals and their major field of application in the European Union. Note: Pantoprazole has a CF2-unit but formally is outside the chemical scope of the restriction preparation.

Table 3: Total mass of main PFAS containing API 2015-2019.

		Tonnage (EU)						Percentage					
	ATC-code	**2.015**	**2.016**	**2.017**	**2.018**	**2.019**	Change (ton per year)	**2.015**	**2.016**	**2.017**	**2.018**	**2.019**	Change % per year
A02BC02	Pantoprazol	190,4	218,0	235,9	255,6	278,6	21,4	68%	78%	85%	92%	100%	8%
C01BC04	Flecainide	45,0	44,7	44,2	43,2	42,7	-0,6	105%	105%	104%	101%	100%	-1%
M01AH01	Celecoxib	38,7	38,5	38,3	39,0	39,2	0,2	99%	98%	98%	100%	100%	0%
A10BD07+A10BH01	Sitagliptine (sum)	18,8	18,4	18,4	19,3	22,0	0,7	86%	83%	84%	88%	100%	3%
N06AB08	Fluvoxamine	16,6	16,1	15,6	15,3	14,9	-0,4	111%	108%	104%	102%	100%	-3%
N06AB03	Fluoxetine	9,7	9,9	9,9	10,4	10,7	0,3	91%	92%	93%	97%	100%	2%
J05AR06	Efavirenz (+emtricitabine+tenofov	16,61	13,97	11,34	9,94	8,49	-2,0	196%	165%	134%	117%	100%	-24%
	sum others:	*21,2*	*21,0*	*20,6*	*20,2*	*19,8*	*-0,4*	*107%*	*106%*	*104%*	*102%*	*100%*	*-2%*
	others:												
S01EE04	Travoprost	7,0	6,9	6,6	6,2	5,9	*-0,3*	119%	117%	112%	106%	100%	-5%
L02BB03	Bicalutamide	5,1	4,8	4,6	4,5	4,3	*-0,2*	119%	112%	109%	105%	100%	-4%
S01EE05	Tafluprost	3,2	3,2	3,1	3,1	3,1	*0,0*	101%	103%	99%	99%	100%	-1%
A02BC03	Lansoprazol	3,1	3,0	2,8	2,7	2,6	*-0,1*	118%	114%	109%	104%	100%	-5%
H05BX01	Cinacalcet	1,4	1,5	1,6	1,6	1,7	*0,1*	84%	92%	96%	98%	100%	4%
L04AA13	Leflunomide	0,7	0,8	0,8	0,9	0,9	*0,0*	79%	86%	90%	94%	100%	5%
G04CA04	Silodosine	0,3	0,3	0,4	0,4	0,5	*0,0*	59%	71%	83%	91%	100%	10%
N05AG03	Penfluridol	0,1	0,1	0,2	0,2	0,2	*0,0*	41%	43%	65%	92%	100%	17%
L02BA03	Fulvestrant	0,1	0,1	0,2	0,2	0,2	*0,0*	36%	45%	65%	85%	100%	17%
L04AA31	Teriflunomide	0,1	0,1	0,1	0,1	0,2	*0,0*	32%	57%	74%	87%	100%	16%
N05AF01	Flupentixol	0,1	0,1	0,1	0,1	0,1	*0,0*	94%	96%	99%	98%	100%	1%
G04CB02	Dutasteride	0,1	0,1	0,1	0,1	0,1	*0,0*	117%	117%	106%	102%	100%	-5%
	Total mass	378,1	401,4	415,0	433,2	436,4	14,8	87%	92%	95%	99%	100%	3%

No. of production sites:

79 companies indicated in the Call for Evidence (2020) that they produce, import or distribute PFAS substances for medicines. Most likely the actual number may be much higher.

5. Emissions

Emission factors used were, in general, 90% for pharmaceuticals, propellants, anesthetics and contrast media used by patients (consumers) or physicians. A factor of 10% for non-polymer PFAS in industrial processes (heat transfer agents, specialty cleaners, formulation and processing aids, intermediates and end-products) was applied. This range finding approach could be refined for individual substances or substances group using EUSES environmental release categories[7] and OECD emissions scenarios.

Table 4: Overview of PFAS volumes in the medical sector (both medicinal products and medical devices) and provisional estimation of their potential dispersal. H(igh)= dispersal to water, air or soil through PFAS excretion by humans or animals; M(edium) = PFAS may be disposed of as waste, recovered after the production processes or treated in industrial waste treatment plants; L(ow)= PFAS in products that are collected as waste.

	Use	**source**	**volume distribution over molecular size (based on midpoint of uncertainty range)**				**dispersal potential**
	ton/year		**C1-C6**	**C7-C25**	**>C25**	**total**	
non-polymers	**27,000-58,000**	**approx. 160**					
Medicinal products (use)							
human	>500	68		>500			High (90-100%) >1,300 ton/y
veterinary	unknown	3		M			
anesthetics (use)	2-1000*	5	500				
contrast media (use)	2-100	1	50				
propellants (use)	160-400**	3	280				
intermediates	2,200-14,000	27	4,000	4,200			Medium (10%) 4,200 ton/y
Industrial processes including F-gases production	24,000-43,000	54	32,000	1,200			
polymers	**3,700-14,000**				8,900		Low (1%) 90 t/y
Total	**31,000-71,000**		**37,000**	**>5,900**	**8,900**	**52,000**	5,600
			71%	**12%**	**17%**		

*: Might be an overestimation as HCWH 2019 is looking broader than needed here
**: Might be an underestimation as Dutch (extrapolated) data will lead to roughly doubling of the range.

6. Exposure

Although the medicines may be beneficial for patients with certain diseases, the exposure of non-target individuals and ecosystems may lead to negative side-effects. Medicines are excreted unchanged or as metabolites in hours to days after they have entered the body. The fluorinated parts of the molecules are likely conserved in the excreta. Depending on the chemical properties of the medicines they end up in air or in sewage system.

No further information was available.

[7] What is Environmental Release Category (ERC) and How It is Used for Environmental Risk Assessment (chemsafetypro.com)

7. General discussion on emission and exposure

Reported volumes are compared with estimations that we have based on statistics from other sources and databases (for instance EMA, WHO, Eurostat and ECHA). In the ECHA database there is information about non-polymers only, so for polymer volumes we used information from the Call for Evidence (CfE).

Depending on the chemical properties of the medicinal products they end up in air or in sewage systems. Persistent medicinal products will ultimately reach the surface water system, which has already been demonstrated for several medicinal products. Veterinary medicinal products will also reach the soil, through spreading of manure.

8. Alternatives

For medicinal products non-PFAS alternatives are available. It is outside the scope of this document to go into detail about actual alternatives.

9. Economic impacts in case of a full PFAS ban

No information has been provided.

10 Methods used & uncertainties

Data research was mainly based on Call for Evidence information (2020)., literature and (extrapolated) insurance data from the Netherlands. Uncertainties of the volume estimates are considerable, therefore midpoint estimations have been given.

References

HCWH (2019). Health care's climate footprint. How the health sector contributes to the global climate crisis and opporrtunities for action**:** 48

Inoue, M., Y. Sumii and N. Shibata (2020). "Contribution of organofluorine compunds to pharmaceuticals." ACS Omega **5**: 10633-10640.

Annex

For the medicines (human), medicines (veterinary) and pharmaceutical intermediates, tonnages, market trend and emissions are presented below.

Sub-use	**Tonnage PFAS/y in EEA**	**Expected tonnage trend (--/-/0/+/++)***	**Emission/y EEA (tonnes PFAS)**
Medicines (human medicinal products)	> 500**	+	>500**
Medicines (veterinary medicinal products)	No data	No data	No data
Pharmaceutical** intermediates	8,200 (ECHA)	No data	No data

*--=strong decrease, -=decrease, +-=increase, ++=strong increase, 0=neutral

**: Molecular weight of API is used in this calculation, not the fluorinated part only