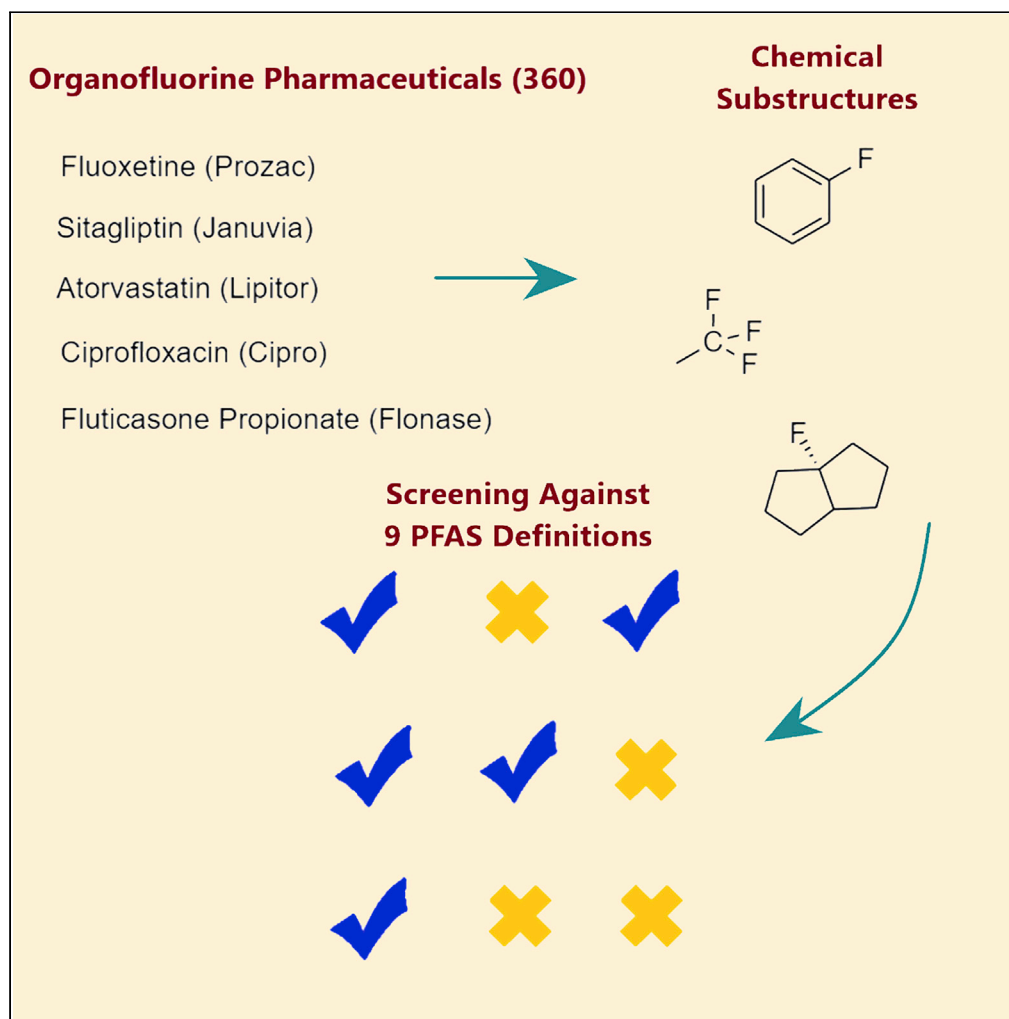


Article

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Highlights

Nine PFAS definitions were evaluated and used to screen 360 organofluorine drugs

Broad definitions include many top prescribed pharmaceuticals, e.g., Prozac and Lipitor

Implications for fluorinated pharmaceuticals depend on intended use of the definition

Findings necessitate discussion of possible exemptions for pharmaceuticals

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Article

Implications of PFAS definitions using fluorinated pharmaceuticals

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SUMMARY

There are 9,000+ per- and polyfluoroalkyl substances (PFAS) in existence, which makes studying and regulating PFAS individually, or even as small mixtures, infeasible. Multiple PFAS definitions based on structure have been proposed, yet these definitions do not consider the implications for the full suite of organofluorine chemicals. For example, organofluorine pharmaceuticals, whose use may be essential and are found in human serum and wastewater, are not uniformly identified across all definitions. Using nine definitions prepared by various stakeholders, we screened the 360 organofluorine pharmaceuticals approved and used globally between 1954 and 2021. Definitions ranged in their inclusion of organofluorine pharmaceuticals (1%–100%). The most inclusive definitions include several top prescribed pharmaceuticals, e.g., Prozac and Lipitor. This analysis provides a framework against which organizations can make decisions about how best to proceed when defining PFAS.

INTRODUCTION

Since manufacturing began in the 1940s, per- and poly-fluoroalkyl substances (PFAS) have been widely used in textile manufacturing, food packaging, cookware, pesticide applicators, medical equipment, and other commercial products (Glüge et al., 2020). To date, upward of 9,000 PFAS have been identified (USEPA, 2021a). Many are toxic, persistent, and widely detected in the environment and human serum, prompting global discussion around their cost and benefits (Cordner et al., 2021), essential uses (Cousins et al., 2019), and effective strategies for regulation.

The large number of PFAS and the substitution of legacy compounds such as PFOA and PFOS by newer compounds—about which less is known although they may turn out to be just as problematic—has prompted movement away from the traditional chemical-by-chemical regulation toward regulation of these compounds as a class in both the U.S. (116th Congress, 2019; Kwiatkowski et al., 2020; Bălan et al., 2021) and Europe (ECHA, 2021). Several agencies, non-governmental organizations, and other groups have adopted class-based PFAS definitions for regulatory and non-regulatory purposes (Tables 1 and 2). Notably, the U.S. National Defense Authorization Act (NDAA) includes the PFAS Act of 2019, which adopts a structural definition classifying PFAS as any compound with at least “one fully fluorinated carbon” (116th Congress, 2019). The act authorizes funding for Department of Defense (DoD) initiatives related to PFAS remediation in areas impacted by military activities and sets restrictions on the use of PFAS in firefighting foam, personal protective equipment for firefighters, and food packaging used in military meals. Importantly, the act also sets requirements for environmental monitoring for PFAS in surface and groundwater and biomonitoring for PFAS among military personnel.

Recent work describes the advantages and disadvantages of different grouping strategies of PFAS based on their persistence and toxicity (Cousins et al., 2020; Wallington et al., 2021), yet relatively little work has been done to understand the differences between specific PFAS definitions and what set of compounds they will include. We focus here on organofluorine pharmaceuticals: they present an opportunity to assess the implications of PFAS definitions for a diverse but well-defined set of chemicals used globally. Organic fluorine was first introduced to the pharmaceutical industry in 1954 and is useful in altering the physicochemical properties of a drug to achieve a desired pharmacological effect (Inoue et al., 2020). Pharmaceuticals represent a class of regulated chemicals whose use might be deemed at least partially “essential” for medical purposes. They are also of interest to environmental scientists for a number of reasons. For example, pharmaceutical waste enters the wastewater treatment systems (Kolpin et al., 2002), where metabolites are

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Table 1. Organizations, proposed and adopted definitions of PFAS, listed by year, evaluated in this analysis

Organization	Year	Regulatory?	Intended purpose
Buck et al.	2011	No	Establish clarity around the nomenclature of PFAS, including classifications based on molecular structure
OECD	2018, 2021	No	Characterize the universe of PFAS based on structural similarities between compounds containing fully fluorinated methyl or methylene moieties
Glüge et al.	2020	No	Understand major use areas; support work being done to address essentiality and feasibility of PFAS-free replacements
TURA Program, Massachusetts	2021a, 2021b	Yes	Establish new toxic substance category on toxic use inventory list in Massachusetts
U.S. EPA OPPT	2021	Yes	Lists chemicals for review under the Toxic Substances Control Act (TSCA) to evaluate risks to human health and the environment
NDAAs, WA, CA, VT, ME ^a “≥ 1 Fully Fluorinated Carbon”	2019, 2020, 2021	Yes	Applications vary across agencies; reporting of PFAS in media impacted by military activities, ban of PFAS used in firefighting foam and equipment, and biomonitoring of PFAS in military personnel (NDAA); reporting and eventual ban of PFAS used in firefighting foam and firefighting equipment (CA); firefighting foam and food contact materials (WA); firefighting foam and products used in rugs/carpets/food packaging/ski wax (VT); any product containing intentionally added PFAS (ME).
NGOs ^b “All Organofluorine”	2021	No	Environmental advocacy; reflects organizations' broader mandates to protect constituents and the environment

^aAuthorities whose legislation defines PFAS as a class of fluorinated organic chemicals containing at least one fully fluorinated carbon atom.

^bNGOs that advocate for broader definitions of PFAS to include all organofluorines.

either discharged back into the receiving waters, or are found in the biosolids after treatment (Massey and Waldron, 2011). While the degradation products of many pharmaceuticals remain unknown, active pharmaceutical ingredients and their metabolites are measurable in wastewater effluent (Yu et al., 2006). Models to predict biodegradability suggest some organofluorine pharmaceuticals may degrade into metabolites with trifluoromethyl groups and thus are likely to persist in the environment given the strength and durability of the CF₃-R functional group (Neuwoehner et al., 2009).

Definitions of PFAS are developed for multiple purposes, also referred to as “working scopes” (OECD, 2021), and can be both regulatory and non-regulatory. Regardless of its intended purpose, a useful definition requires clear, unambiguous language that is interpretable by stakeholders. In this analysis, we describe nine definitions of PFAS and examine some potential ambiguities in their language. We use each definition to screen a comprehensive list of organofluorine pharmaceuticals to determine which pharmaceuticals are included. Finally, we discuss some implications of these definitions given their intended purpose for use in regulatory or non-regulatory initiatives. Similar analyses could be performed for other groups of compounds.

RESULTS

Definitions of PFAS and their intended uses

Tables 1 and 2 show the nine PFAS definitions and their intended purpose. These include definitions developed by Buck et al. (2011), the Organisation for Economic Co-operation and Development (OECD), Glüge et al. (2020), the Toxic Use Reduction Act (TURA) Program of Massachusetts, U.S. EPA Office of Pollution Prevention and Toxics (U.S. EPA OPPT) (USEPA, 2021b), the NDAA (116th Congress, 2019) and laws from the states of Washington (2021), Vermont (2021), Maine (2021), and California (2020), and several non-governmental environmental advocacy organizations (e.g., Sierra Club of Massachusetts)

Table 2. Definitions of PFAS included in analysis

Definition	Formal definition verbatim from organization	Informal interpretation
Buck et al. (2011)	"Aliphatic substances containing one or more C atoms on which all the H substituents present in the nonfluorinated analogues from which they are notionally derived have been replaced by F atoms, in such a manner that PFASs contain the perfluoroalkyl moiety C_nF_{2n+1} ."	Compounds that contain at least one carbon atom that is bound to three fluorine atoms ($-CF_3$). The structure must be saturated with no double or triple bonds (the only definition with this restriction).
OECD (2018)	"PFASs, including perfluorocarbons, that contain a perfluoroalkyl moiety with three or more carbons (i.e. $-C_nF_{2n-}$, $n \geq 3$) or a perfluoroalkylether moiety with two or more carbons (i.e. $-C_nF_{2n}OC_mF_{2m-}$, n and $m \geq 1$)."	Compounds with at least three carbons on which all of the hydrogens have been replaced by a fluorine atom, so as to form a three-carbon unit with the subunits of ($-CF_2-$). It also includes compounds with an oxygen placed between two carbon atoms on which all of the hydrogens have been replaced by a fluorine atom, so as to form a carbon-oxygen-carbon unit with the subunits ($-CF_2OCF_2-$)
OECD (2021)	"PFASs are defined as fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), i.e. with a few noted exceptions, any chemical with at least a perfluorinated methyl group ($-CF_3$) or a perfluorinated methylene group ($-CF_2-$) is a PFAS."	Compounds containing at least one carbon that has three fluorine atoms attached ($-CF_3$). Also includes compounds that have at least one carbon attached to two fluorine atoms ($-CF_2-$). In both cases, the carbon atom cannot be attached to a hydrogen, chlorine, or bromine atom. It still includes compounds whose carbon-fluorine units are attached together by an oxygen ($-CF_2OCF_2-$). These structures can contain rings or be arranged in a chain
Glüge et al. (2020)	In addition to substances containing C_nF_{2n+1} , where $n \geq 1$, it also "includes (i) substances where a perfluorocarbon chain is connected with functional groups on both ends, (ii) aromatic substances that have perfluoroalkyl moieties on the side chains, and (iii) fluorinated cycloaliphatic substances. Additionally, "polymeric PFAS with the $-CF_2-$ moiety and non-polymeric PFAS with the $-CF_2-CF_2-$ moiety ... [excluding] non-polymeric substances that only contain a $-CF_3$ or $-CF_2-$ moiety, with the exception of perfluoroalkylethers and per- and polyfluoroalkylether-based substances. For these two PFAS groups, substances with a $-CF_2OCF_2-$ or $-CF_2OCFHCF_2-$ moiety are also included."	Does not include compounds with a single $-CF_2-$ or $-CF_3$, but can include compounds with two or more $-CF_2-$ or $-CF_3$ groups. Compounds can contain rings or be arranged in a chain. Also includes compounds that contain two carbon atoms next to each other, each containing at least two fluorine atoms ($-CF_2-CF_2-$). The two fluorinated carbons can be attached together by an oxygen atom ($-CF_2OCF_2-$ or $-CF_2OCFHCF_2-$).
TURA (2021a)	"Those PFAS that contain a perfluoroalkyl moiety with three or more carbons (e.g., $-C_nF_{2n-}$, $n \geq 3$; or $CF_3-C_nF_{2n-}$, $n \geq 2$) or a perfluoroalkylether moiety with two or more carbons (e.g., $-C_nF_{2n}OC_mF_{2m-}$ or $-C_nF_{2n}OC_mF_{m-}$, n and $m \geq 1$)."	Key to this definition is that the compound must contain a string of at least three carbon atoms, each containing two or more fluorine atoms. Perfluoroalkylethers are compounds that contain two $-CF_2-$ groups connected by an oxygen. Includes linear, branched, cyclic compounds and aromatic rings
TURA (2021b)	"Certain PFAS not otherwise listed includes those PFAS that contain a perfluoroalkyl moiety with three or more carbons (e.g., $-C_nF_{2n-}$, $n \geq 3$; or $CF_3-C_nF_{2n-}$, $n \geq 2$) or a perfluoroalkylether moiety with two or more carbons (e.g., $-C_nF_{2n}OC_mF_{2m-}$ or $-C_nF_{2n}OC_mF_{m-}$, n and $m \geq 1$), wherein for the example structures shown the dash (-) is not a bond to a hydrogen and may represent a straight or branched structure, that are not otherwise listed."	Clarifies that in TURA 2021a the (-) does not include a bond to hydrogen
U.S. EPA OPPT (2021)	"... a structure that contains the unit $R-CF_2-CF(R')$ (R''), where R, R', and R'' do not equal "H" and the carbon-carbon bond is saturated (note: branching, heteroatoms, and cyclic structures are included)."	Compounds that contain a string of two adjacent carbon atoms, with one of them containing at least two fluorine atoms and the other containing at least one fluorine atom, and neither carbon bound to a hydrogen

(Continued on next page)

Table 2. Continued

Definition	Formal definition verbatim from organization	Informal interpretation
≥ 1 Fully Fluorinated Carbon ^a	Organic chemicals containing “at least one fully fluorinated carbon atom.”	A compound with at least one carbon on which all of the hydrogen atoms have been replaced by fluorine atoms. The number of bonds on the carbon is not specified
All Organofluorine ^b	All organic compounds containing at least one fluorine atom should be classified as PFAS.	Any compound whose structure contains a carbon attached to a fluorine atom

^aAuthorities whose legislation defines PFAS as a class of fluorinated organic chemicals containing at least one fully fluorinated carbon atom (WA, VT, ME, CA, NDAA).

^bNGOs that advocate for broader definitions of PFAS to include all organofluorines.

(Massachusetts Executive Office of Energy and Environmental Affairs, 2021). We consider two definitions proposed by the OECD, one from 2018 (OECD, 2018) and the update in 2021 (OECD, 2021). We also evaluated two definitions proposed by the TURA Program Administrative Council to the Massachusetts Department of Environmental Protection (MassDEP): the original definition developed by the TURA Science Advisory Board, represented as TURA (2021a) (Administrative Council on Toxics Use Reduction, 2021a), and an amended version clarifying the definition, represented by TURA 2021b (Administrative Council on Toxics Use Reduction, 2021b).

Screening organofluorine pharmaceuticals

Using the publicly available KEGG drug database (KEGG, 2021), 363 pharmaceuticals approved in the U.S., Japan, and Europe are identified including two over-the-counter drugs. Three compounds were excluded from analysis: the insecticide novaluron, the veterinary pharmaceutical dirilotapide, and sulfur hexafluoride (Lumason) which does not contain organically bound fluorine. The remaining 360 pharmaceuticals were included in the analysis: the complete list of chemical structures, therapeutic use areas, chemical identifiers, and numbers of prescriptions (where available) are provided in the supplemental information (Data S1).

Organofluorine pharmaceuticals can be organized by substructures within the compound. Figure 1 presents the frequency of substructures identified among the 360 fluorinated pharmaceuticals; 50% of organofluorine pharmaceuticals contain a single fluorine; 35% contain a single aromatic fluorine; 10% contain more than three fluorine atoms. Only four pharmaceuticals were fully or nearly fully fluorinated aliphatic compounds. There were 88 compounds containing at least one trifluoromethyl moiety (R-CF₃) where R is not hydrogen, 15 of which contained two trifluoromethyl moieties.

Table 3 summarizes the proportion of organofluorine pharmaceuticals that meet each of the nine structural definitions, disregarding for now their intended applications. The most inclusive is the “all-organofluorine” definition, including 100% of organofluorine pharmaceuticals. The revised TURA 2021b definition is least inclusive and captures the fewest (1.1%). We will now discuss each PFAS definition in roughly in the order in which they were proposed.

PFAS identified by Buck et al.

Buck et al. (2011) provided one of the earliest and most widely used of the PFAS definitions, replacing earlier terminology. According to Buck et al., PFAS are “aliphatic substances containing one or more C atoms on which all the H substituents present in the nonfluorinated analogs from which they are notionally derived have been replaced by F atoms, in such a manner that PFASs contain the perfluoroalkyl moiety C_nF_{2n+1}–.” A restatement in less technical language is given in Table 2. Importantly, this definition excludes aromatic compounds (structures containing unsaturated hydrocarbon rings with double and single bonds). Based on this definition, 8 (2.2%) fluorinated pharmaceuticals would be classified as PFAS. An example of a fluorinated pharmaceutical compound meeting the definition outlined by Buck et al. is perflubron, a contrast imaging agent previously used in magnetic resonance imaging (MRI) scans which is now being investigated as liquid oxygen used to stabilize hemorrhage during major surgery (Figure 2A). While the Buck et al. definition is not regulatory, it has been adopted by the California Biomonitoring Program (OEHHA, 2021).

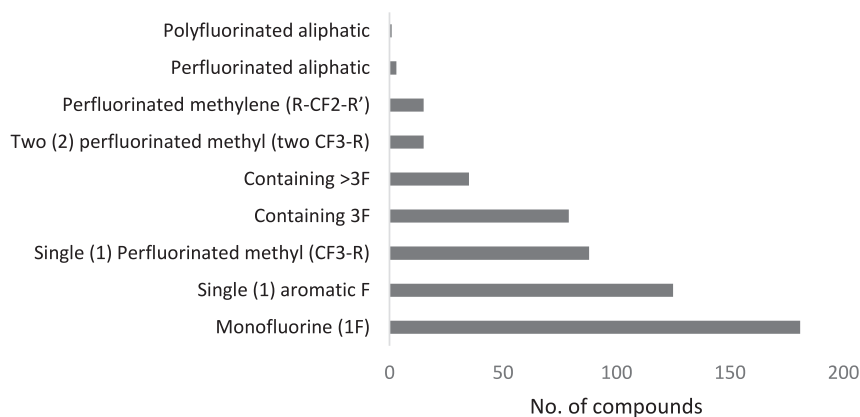


Figure 1. Substructures identified among organofluorine pharmaceuticals

PFAS identified by the Organisation for Economic Co-operation and Development (OECD)

The OECD originally defined PFAS as structures “that contain a perfluoroalkyl moiety with three or more carbons (i.e. $-C_nF_{2n-}$, $n \geq 3$) or a perfluoroalkylether moiety with two or more carbons (i.e. $-C_nF_{2n}OC_mF_{2m-}$, n and $m \geq 1$)” (OECD, 2018). Unlike Buck et al., this definition includes aromatic compounds. The OECD released a revised definition in 2021 including “fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), i.e. with a few noted exceptions, any chemical with at least a perfluorinated methyl group ($-CF_3$) or a perfluorinated methylene group ($-CF_2-$)” (OECD, 2021). The revised definition reduced the number of carbons that must contain fluorine, but is clearer about the other atoms to which those carbons can be bonded. The 2018 OECD definition includes 5 (1.4%) organofluorine pharmaceuticals; the revised 2021 OECD definition includes 107 (30%) organofluorine pharmaceuticals. An example of a substance captured by the 2018 OECD definition but not Buck et al. is enflurane (Figure 2B). Included in the 2021 OECD definition but not Buck et al. are the cancer drug alpelisib (Figure 2C) and the widely used antidepressant fluoxetine (Prozac) (Figure 2G): the perfluorinated methyl groups warrant inclusion under the 2021 OECD definition, but the aromatic ring excludes them from Buck et al.

PFAS identified by Glüge et al.

The definition of Glüge et al. (2020) is broader than Buck et al., but narrower than the revised OECD 2021 definition (see Table 2 for the precise definition). Glüge et al. include aromatic compounds, similar to the OECD definition, yet does not include compounds with a single $-CF_3$ or $-CF_2-$, providing contrast to Buck et al. The antidiabetic medication gemigliptin meets the Glüge et al. definition because it is an aromatic substance that contains two perfluoroalkyl moieties on the side chains (Figure 2D). The Glüge et al. definition includes 22 (6.1%) organofluorine pharmaceuticals.

PFAS identified by the TURA Program of Massachusetts

The TURA Program originally defined PFAS as a compound containing “a perfluoroalkyl moiety with three or more carbons (e.g., $-C_nF_{2n-}$, $n \geq 3$; or $CF_3-C_nF_{2n-}$, $n \geq 2$) or a perfluoroalkylether moiety with two or more carbons (e.g., $-C_nF_{2n}OC_mF_{2m-}$ or $-C_nF_{2n}OC_mF_{m-}$, n and $m \geq 1$)” (Administrative Council on Toxics Use Reduction, 2021a). The slightly revised definition (Table 2) clarifies that the “-” excludes bonding to hydrogen. The original definition was ambiguous about this point and could be interpreted to include enflurane (Figure 2B) while the revised definition would not. Both would include perflorane (Figure 2E). The TURA 2021a definition includes six (1.7%) organofluorine pharmaceuticals while the revised definition includes four (1.1%).

PFAS identified by the U.S. EPA Office of Pollution Prevention and Toxics (OPPT)

The U.S. EPA OPPT defines PFAS as “... a structure that contains the unit $R-CF_2-CF(R')$ (R''), where R , R' , and R'' do not equal “H” and the carbon-carbon bond is saturated” (USEPA, 2021b). It also indicates that branched structures, heteroatoms, and cyclic structures are included. This definition is unambiguous, recognizing five (1.4%) organofluorine pharmaceuticals as PFAS. There were no compounds included

Table 3. Number of pharmaceuticals included under different definitions of PFAS (% of 360)

Definition	Number (%) organofluorine pharmaceuticals
Buck et al. (2011)	8 (2.2)
OECD (2018)	5 (1.4)
OECD (2021)	107 (30)
Glüge et al. (2020)	22 (6.1)
TURA (2021a)	6 (1.7)
TURA (2021b)	4 (1.1)
U.S. EPA OPPT (2021)	5 (1.4)
≥ 1 Fully Fluorinated Carbon ^a	337 (94)
All Organofluorine ^b	360 (100)

^aAuthorities whose legislation defines PFAS as a class of fluorinated organic chemicals containing at least one fully fluorinated carbon atom (NDAA, WA, ME, VT, CA).

^bNGOs that advocate for broader definitions of PFAS to include all organofluorines.

under the OPPT definition that were not also captured by the 2021 OECD definition. Perflutren (Optison) is a contrast agent used in MRI and positron emission tomography (PET) imaging technology (Figure 2F). Perflutren meets all nine PFAS definitions examined as it is an aliphatic structure with three fully fluorinated carbon atoms (two perfluorinated methyl moieties and a perfluorinated methylene moiety).

PFAS identified by authorities as including at least one fully fluorinated carbon

The U.S. NDAA defines PFAS as any substance containing “at least one fully fluorinated carbon” as do certain laws of the states of Washington, Vermont, Maine, and California (specific applications are discussed below). The NDAA defines a fully fluorinated carbon as “a carbon atom on which all of the hydrogen substituents have been replaced by fluorine” (116th Congress, 2019). However, the definition does not specify whether the fully fluorinated carbon is saturated or unsaturated (saturated compounds only contain single bonds). We therefore interpreted it to mean that the carbon could have single, double, or even triple bonds. This interpretation includes compounds containing a single fluorine atom attached to a benzene ring. As written, this definition captures 337 (94%) organofluorine pharmaceuticals. It includes the cholesterol-lowering medication atorvastatin (Lipitor), the top prescribed drug in the U.S. (Figure 2H) with 112,104,359 annual prescriptions (Table 4), as well as ciprofloxacin, a critical antibiotic (See Data S1). The ambiguity of the term “fully fluorinated carbon” is worth further consideration. If it had instead been interpreted to mean a trifluoromethyl group (R-CF₃) where R is not hydrogen, similar to Buck et al. (but without the latter definition’s restriction to aliphatic compounds), neither Lipitor nor ciprofloxacin would be included, but Prozac (Figure 2G) would.

PFAS identified by non-governmental organizations: “all-organofluorine”

Some NGOs (Table 1) advocate for a broader definition of PFAS as any substance containing organofluorine. This definition is unambiguous and includes all 360 (100%) organofluorine pharmaceuticals, including widely used cancer chemotherapy drugs as well as Prozac and Lipitor discussed earlier.

DISCUSSION

The large number of PFAS listed by U.S. EPA and OECD suggests that research and regulation on a compound-by-compound basis is not practical. Multiple groups have devised definitions of PFAS to facilitate research into the prevalence, usage, and health effects of these substances, as well as serve as the basis for regulatory actions. Our analysis shows that the definitions have a very large range in the percent of organofluorine pharmaceuticals included. For this group of compounds, the definitions offer different and often conflicting views of what is and is not “PFAS”. The framework we used is consistent with the systematic approach described in the OECD report (OECD, 2021) that provides practical guidance on characterizing PFAS based on molecular structure, and is similarly in line with the strategies described by (Wang et al., 2021) to facilitate unambiguous communication around PFAS. The cited examples serve to illustrate why PFAS definitions must be clear and that seemingly straightforward language—e.g., “fully fluorinated carbon”—can have multiple interpretations. Without specifying saturation (i.e., saturated compounds contain only single bonds), the fully fluorinated carbon definition can be interpreted to include any compound with

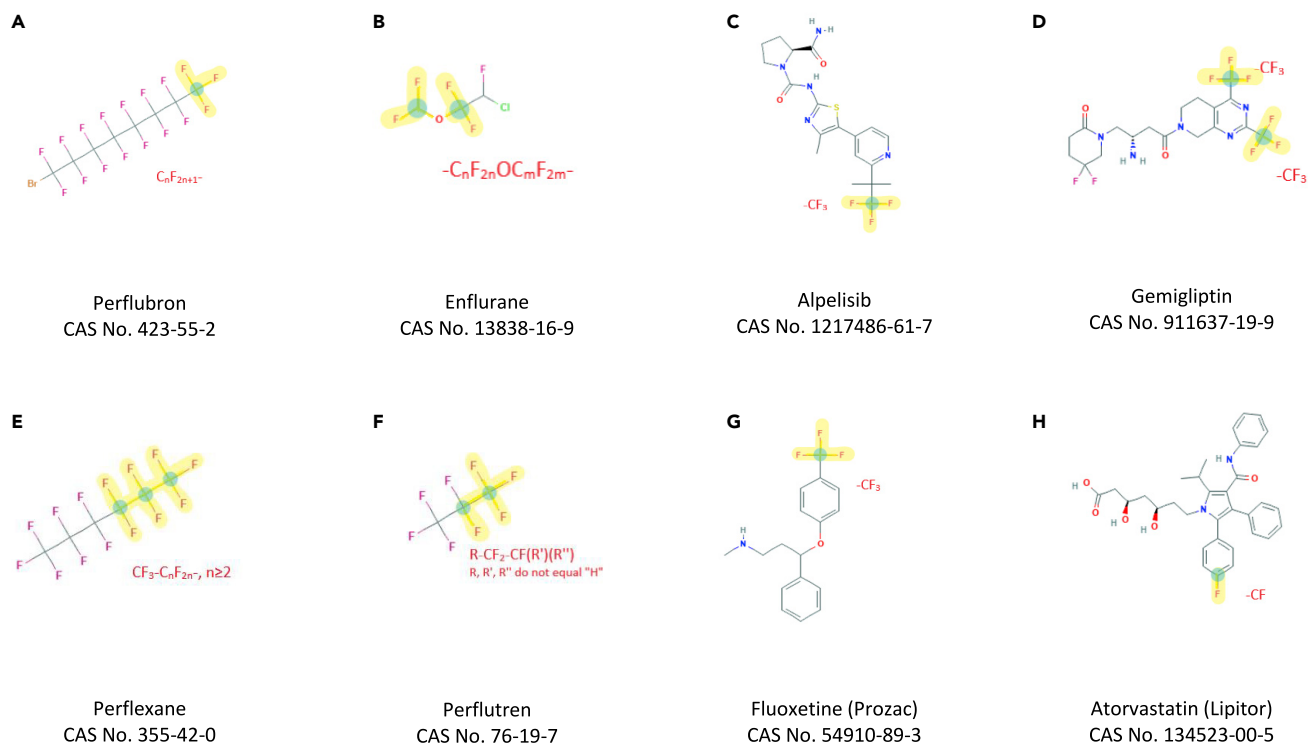


Figure 2. Examples of organofluorine pharmaceuticals that meet the nine PFAS definitions

(A) Buck et al. includes the contrast agent, perflubron (CAS No. 423-55-2).

(B) 2018 OECD and TURA 2021a both include the general anesthetic enflurane (CAS No. 13838-16-9).

(C) The 2021 OECD definition includes the antineoplastic alpelisib (CAS No.: 1217486-61-7).

(D) Glüge et al. includes the antidiabetic medication gemigliptin (CAS No. 911637-19-9).

(E) The TURA 2021b definition includes the cardiac ultrasound imaging agent perflexane (CAS No. 355-42-0).

(F) U.S. EPA OPPT includes the ultrasound contrast agent Perflutren (CAS No. 76-19-7).

(G) The ≥ 1 fully fluorinated carbon definition includes the antidepressant fluoxetine (Prozac) (CAS No. 54910-89-3).

(H) The “all-organofluorine” and ≥ 1 fully fluorinated carbon definitions include the cholesterol lowering medication atorvastatin (Lipitor) (CAS No. 134523-00-5).

a single aromatic fluorine, as well as other cases. While the definition was presumably intended to be clear and easy to interpret by stakeholders, it illustrates the importance of using specific and non-ambiguous language and being explicit in describing the context for which a definition shall be used.

To avoid confusion, it would ideally be useful to have a clear, universally agreed upon definition of PFAS. However, the appropriateness of a PFAS definition, or the possible need for exceptions in certain applications, may depend on the mandate of the group using the definition and its purpose. Of the nine definitions we have reviewed, five—Buck et al., OECD 2018 and 2021, Glüge et al., and “all organofluorines”—are non-regulatory at this time. The OECD, while not a regulatory institution, developed its own PFAS definition which may have regulatory implications if it is adopted by regulatory organizations, like the Registration, Evaluation, and Authorization of Chemicals (REACH) in the EU (European Commission, 2020). Five European countries (Germany, Netherlands, Denmark, Norway, and Sweden) announced their intention to develop a REACH restriction proposal for the European Commission that would cover all non-essential uses of PFAS in the EU (European Commission, 2020). Though not yet established at the time of this writing, this definition, if similar to the OECD, 2021 definition, may present important regulatory implications for the pharmaceutical industry and other producers of organofluorine chemicals.

Biomonitoring and environmental monitoring (e.g., of air and water) are critical surveillance aspects of environmental health. For example, biomonitoring of environmental chemicals is important for examining time trends (effectiveness of interventions, emerging problems, etc.) as well as geographical and demographic disparities and more. The definition used for PFAS has a potentially important role for biomonitoring, providing problem scoping, although there are practical limitations such as sample sizes, cost, availability of standards,

Table 4. Classification of organofluorine pharmaceuticals that rank in the top 500 U.S. prescribed drugs from 2019 and global sales in USD

Drug name	Brand name	Therapeutic class	Total Rx (2019) ^a	Drug rank ^b	Global sales 2018 (millions) ^c	All-organofluorine	≥ 1 Fully fluorinated carbon	OECD (2021)	TURA (2021a)	TURA (2021b)	Gluge et al	Buck et al	OECD (2018)	U.S. EPA OPPT
Flecainide	Tambacor	Tachyarrhythmia	2,318,516	215	296	X	X	X	X	X	X			
Fluoxetine	Prozac, Sarafem	antidepressant	27,110,302	20	945	X	X	X						
Celecoxib	Celebrex	NSAID; arthritis	6,595,235	102	3,980	X	X	X						
Levofloxacin	Iquix, Levaquin	Antibiotic	3,202,649	182	432	X	X	X						
Dexlansoprazole	Dexilant	proton pump inhibitor	2,290,526	218	3,831	X	X	X						
Leflunomide	Arava	rheumatoid arthritis	1,057,644	324	420	X	X	X						
Sulindac	Clinoril	NSAID	318,884	408	30	X	X	X						
Atorvastatin	Lipitor	cholesterol lowering agent	112,104,359	1	7,414	X	X							
Pantoprazole	Protonix	proton pump inhibitor	28,880,217	16	569	X	X							
Fluticasone propionate	Flonase	glucocorticoid (OTC)	27,893,102	18	791	X	X							
Escitalopram	Lexapro	antidepressant	27,510,958	19	1,282	X	X							
Rosuvastatin	Crestor	cholesterol lowering agent	27,041,319	21	n/a	X	X							
Citalopram	Celexa	antidepressant	21,546,700	30	n/a	X	X							
Sitagliptin	Januvia	antidiabetic	8,866,811	88	24,250	X	X							
Triamcinolone	Aristocort; Trianex	corticosteroid	6,320,751	107	n/a	X	X							
Ezetimibe	Zetia	cholesterol lowering agent	6,221,674	108	8,865	X	X							
Ciprofloxacin	Cipro	Antibiotic	5,878,441	113	488	X	X							
Fluconazole	Diflucan	antifungal	5,149,547	133	371	X	X							
Risperidone	Perseris Kit, Risperdal	antipsychotic	4,285,907	149	2,795	X	X							
Clobetasol	Clobex	corticosteroid	3,226,423	180	1,485	X	X							
Nebivolol	Bystolic	antihypertensive agent	3,061,887	191	2,800	X	X							
Ticagrelor	Brilinta	anticoagulant	2,299,436	216	3,007	X	X							
Ofloxacin	Floxin	antibiotic	2,051,823	232	153	X	X							

(Continued on next page)

Table 4. Continued

Drug name	Brand name	Therapeutic class	Total Rx (2019) ^a	Drug rank ^b	Global sales 2018 (millions) ^c	All-organofluorine	≥ 1 Fully fluorinated carbon	OECD (2021)	TURA (2021a)	TURA (2021b)	Gluge et al	Buck et al	OECD (2018)	U.S. EPA OPPT
Canagliflozin	Invokana	antidiabetic	1,373,540	290	4,327	X	X							
Betamethasone	Celestone, Alphatrex	corticosteroid	1,311,106	296	n/a	X	X							
Betamethasone dipropionate		corticosteroid	1,311,106	296	498	X	X							
Fluocinonide	Lidex	corticosteroid	1,290,749	300	555	X	X							
Travoprost	Izba, Travatan	glaucoma	1,264,924	303	2,722	X	X							
Difluprednate	Durezol	corticosteroid	717,461	356	587	X	X							
Dexamethasone	Decaderm, Decadron	corticosteroid	711,271	359	381	X	X							
Moxifloxacin	Avelox	antibiotic	666,288	363	n/a	X	X							
Fluorouracil	Adrucil, Carac, Efudex	antineoplastic	642,441	364	447	X	X							
Fluorometholone	Oxylone, Flarex	corticosteroid	434,531	389	161	X	X							
Fluocinolone acetonide	Flucinolone, Capex	corticosteroid	313,715	410	153	X	X							
Flurbiprofen	Ansaid	NSAID	21,338	477	6	X	X							
Emtricitabine	Emtriva	antiretroviral	3,632	501	5,457	X	X							
Paroxetine	Paxil	antidepressant	9,783,755	78	741	X								
Lansoprazole	Prevacid	proton pump inhibitor	2,772,218	200	963	X								
Diflunisal	Dolobid	NSAID	116,622	441	20	X								

^aAnnual prescription data for organofluorine pharmaceuticals are available from ClinCalc DrugStats database for the top 500 prescribed drugs in the U.S. for 2019.

^bDrug Rank represents the rank order by frequency prescribed within a calendar year in the U.S.; data were compiled from the ClinCalc DrugStats database.

^cGlobal sales data reported by PharmaCompass include prescriptions covered under Medicaid.

detection limits, etc. Biomonitoring programs may not be interested in organofluorine pharmaceuticals (e.g., the widely used Lipitor) themselves, except perhaps to try to close some of the gap between currently measured PFAS in serum vs. extractable organic fluorine (Yeung et al., 2008). Instead, biomonitoring programs would be more likely to examine the trends of known PFAS and add emerging compounds as they are discovered. California Biomonitoring currently uses the Buck et al. definition of PFAS (which would include very few organofluorine pharmaceuticals) (OEHHA, 2021). As discussed earlier, the PFAS definition included in the NDAA—which requires biomonitoring for PFAS among all military firefighters during their annual exam—uses the very broad and ambiguous “fully fluorinated carbon” definition, which includes over 90% of organofluorine drugs. Both of these applications may consider exempting such compounds.

On the other hand, monitoring of surface water, wastewater, biosolids, and other environmental media may be more interested in organofluorine pharmaceuticals as well as more traditional PFAS. Here, the definition of PFAS could well have regulatory implications and the choice of definition and possible exceptions would need to be carefully considered. For example, the NDAA applies the “fully fluorinated carbon” definition to environmental monitoring of PFAS in surface and groundwater by the United States Geological Survey (116th Congress, 2019). Recent efforts to measure total organic fluorine (TOF) in surface water (Ruyle et al., 2021) and in animal serum (Yeung et al., 2009) show that only a fraction of extractable organic fluorine (EOF) can be explained by known (targeted) PFAS, leaving a substantial portion of unidentified fluorine from other sources. Given the fate of organofluorine pharmaceuticals in wastewater, it is likely that these compounds would contribute to EOF measured in wastewater, and authorities that use the “fully fluorinated carbon” definition to measure or regulate PFAS will need to consider the implications for organofluorine pharmaceuticals. Alternatively, if the U.S. EPA OPPT definition were used, only a handful of organofluorine pharmaceuticals would be included. As a result, most pharmaceutical compounds, for which very little is understood on the biodegradability and recombination of breakdown products, would not be measured.

Four of the definitions we have considered—TURA 2021a/b, U.S. EPA OPPT, and the “fully fluorinated carbon” definition used by several states and the NDAA—have regulatory implications. There are important challenges around clarity and feasibility of regulating substances as a class. Ambiguities in how a definition is interpreted and applied can lead to misinterpretations by stakeholders, raising the likelihood of legal ramifications and ultimately slowing the process, potentially defeating the original goal of accelerating regulation through assessing PFAS on the basis of classes rather than individual chemicals. Earlier, we discussed the ambiguity in the “fully fluorinated carbon” definition and how it dramatically increased the number of organofluorine pharmaceuticals included. This would likely be true of other groups of organofluorine compounds not classified as PFAS under many of the other definitions.

Legislation in Washington, Vermont, California, and Maine (as well as the NDAA discussed above) each define PFAS as any compound containing at least one fully fluorinated carbon, but the applications differ. In California, the fully fluorinated carbon definition applies specifically to PFAS used in firefighting equipment and aqueous film forming foam (AFFF) (California, 2020). In Washington, this definition is applied to AFFF and food contact materials (Washington, 2021). Vermont applies the definition to AFFF as well as products added to rugs, food packaging, and ski wax (Vermont, 2021). When applied in these cases, the definition would not include organofluorine pharmaceuticals. Maine applies the fully fluorinated carbon definition in its legislation banning the selling or importing of any product containing intentionally added PFAS (Maine, 2021). The language of this legislation recognizes product categories in which the use of PFAS is currently unavoidable, which may include pharmaceuticals. Without this recognition, this law would include 94% of organofluorine pharmaceuticals.

The Massachusetts Toxic Use Reduction legislation provides an interesting example of exceptions. Certain industrial sectors are exempt from reporting toxic substances (MassDEP, 2018), including hospitals that may generate waste containing fluorinated contrast agents or other organofluorine pharmaceuticals used during hospital-based activities (e.g., surgical procedures, ventilation, etc.). Another approach to exceptions relevant to organofluorine pharmaceuticals is whether such products are deemed essential (Cousins et al., 2019).

Importantly, the list of organofluorine pharmaceuticals is dynamic and new drugs containing fluorine are developed each year. In fact, five organofluorine pharmaceuticals were approved during the final months of 2021, including Pfizer’s new drug Paxlovid, the first protease inhibitor for treatment of SARS-CoV-2

(Pfizer, 2021). Pfizer signed a licensing agreement in November 2021 that will enable qualified manufacturers to produce and distribute the drug globally in order to reach a wider range of the global population (Pfizer, 2021). Paxlovid is an organofluorine pharmaceutical that meets the criteria of the revised OECD definition, the all-organofluorine definition, as well as the fully fluorinated carbon definition.

Moving forward with a useful framework

The definitions may be characterized by three attributes: clarity, inclusion, and specificity. Clarity may be interpreted as the degree to which a particular definition is open to conflicting decisions on whether a given PFAS structure meets the stated definition. Next, inclusion may be interpreted as the extent to which a definition would label any organofluorine compound as "PFAS", which we have illustrated here with pharmaceuticals. By specificity, we mean usefulness for its intended purpose. Specificity may be of particular importance to monitoring and regulatory bodies, which may need to consider exemptions for certain types of organofluorines if broad PFAS definitions are used. While consideration of these factors is important as we move forward, the real danger is not adopting any definition, for fear of not having a perfect definition, and the consequential delay in decision making.

Limitations of the study

This analysis considers nine available definitions of PFAS, yet new definitions may be developed for unique purposes, and previously established definitions may be revised in the future. Only those definitions available in the public space were included in this analysis. We include a comprehensive list of organofluorine pharmaceuticals approved between 1954 through June 1, 2021, including compounds that have been withdrawn. New therapeutics containing organofluorine approved after June 1, 2021 are not included. Our analysis is limited to human pharmaceuticals and does not include pharmaceuticals used in animals. Finally, available data on annual prescriptions are limited to the most widely prescribed drugs.

GLOSSARY

Aliphatic: saturated organic compounds in which the carbon atoms may form an open chain or closed rings

Alkyl group: a portion of a compound made up by carbon and hydrogen atoms arranged in a chain and whose structure follows the formula C_nH_{2n+1}

Aromatic: organic compounds containing a planar unsaturated ring of atoms that is stabilized by an interaction of the bonds forming the ring. Such compounds are typified by benzene and its derivatives

Ether: organic functional group typified by an oxygen atom connected to two carbon atoms, which may be aliphatic, olefinic, or aromatic.

Methyl group: a small molecule consisting of one carbon and three hydrogen atoms $-CH_3$

Methylene group: a small molecule consisting of one carbon attached to two hydrogen atoms $-CH_2-$

Moiety: a portion of a molecule with its own functional group

Olefinic: unsaturated organic compounds in which the carbon atoms may form an open chain or closed rings, including carbons that are double or triple bonded to another carbon.

Perfluorinated: a term to describe a hydrocarbon chain in which all of the hydrogen atoms are replaced by fluorine atoms

PFAS: per- and poly-fluoroalkyl substance

Polyfluorinated: a hydrocarbon chain in which multiple but not all hydrogen atoms are replaced by fluorine atoms

Polymer/polymeric: a class of compounds composed of macromolecules, usually consisting of multiple, repeating units called monomers

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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 - Organofluorine pharmaceutical database
 - Quantitative and qualitative analysis

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.isci.2022.104020>.

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AUTHOR CONTRIBUTIONS

Conceptualization, E.H., T.W., and W.H-B.; Methodology, E.H., T.W., R.G., and W.H-B.; Writing, E.H., T.W., W.H-B., and R.G.

DECLARATION OF INTERESTS

W.H-B and R.G. are members of the Toxic Use Reduction Institute Science Advisory Board in Massachusetts. The authors declare no other competing interests.

INCLUSION AND DIVERSITY

One or more of the authors of this paper self-identifies as a member of the LGBTQ+ community. One or more of the authors of this paper received support from a program designed to increase minority representation in science.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Other		
Chemical Structures and identifiers	National Library of Medicine PubChem Database	https://pubchem.ncbi.nlm.nih.gov/
Drug Database	KEGG Drug Database: Krypto Encyclopedia of Genes and Genomes	https://www.genome.jp/kegg/drug/
Prescription Drug Data	ClinCalc DrugStats Database	https://clincalc.com/
Global Sales Data	PharmaCompass Database	https://www.pharmacompass.com/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the [lead contact](#), Emily Hammel (eghammel@bu.edu).

Materials availability

This study did not generate new materials.

Data and code availability

This paper analyzes existing, publicly available data. The data generated in this manuscript are supplied in a supplemental table. Any additional information required to reanalyze the data reported in this paper is available from the [lead contact](#) upon request. This paper does not report original code.

METHOD DETAILS

Identifying PFAS definitions

We selected and reviewed nine adopted definitions of PFAS that were available at the time of writing developed by both regulatory and non-regulatory organizations, presented in [Table 1](#). Selection was based on the availability of a PFAS definition and a traceable description of the purpose for the development of the definition as it fits into the organizations' mandates or working scope. We present the organizations chronologically based on when the definition of PFAS was developed. For the purposes of direct comparison, we present the updated definitions for two of the organizations together with the originally developed definition.

Organofluorine pharmaceutical database

To establish a comprehensive list of organofluorine pharmaceuticals registered globally to date, we extended the work by [Inoue et al. \(2020\)](#), which included pharmaceuticals approved between 1954 and 2019, by querying the KEGG Drug database (Release version 99.1) for new organofluorine drugs approved between January 1, 2020 and June 1, 2021 ([KEGG, 2021](#)). KEGG Drug Database is a publicly available repository of approved drugs in the U.S., Europe and Japan, their chemical properties, and molecular structure, and other identifiers for prescription and over-the-counter (OTC) pharmaceuticals, including organofluorine pharmaceuticals that have been withdrawn either due to lack of demand or risk to patients.

The organofluorine pharmaceuticals identified from the KEGG Drug Database were queried using PubChem for the drug names, available synonyms, CAS registry number, molecular structure, chemical formula, InChI key, and therapeutic use area ([Kim et al., 2019](#)). Drug name refers to the generic pharmaceutical name; available brand names the pharmaceutical is sold under are listed separately as synonyms. Where available, the most recently collected data from 2019 on the number of U.S. prescriptions and the rank order by frequency prescribed within a calendar year were compiled from the ClinCalc DrugStats database ([ClinCalc DrugStats Database, 2019](#)) and are presented in [Table 4](#) in addition to being made available in an Excel worksheet ([Data S1](#)). Drug utilization data from ClinCalc DrugStats was generated via the Agency for Healthcare Research and Quality's most recent Medical Expenditure Panel Survey (MEPS) from 2019, accessed in January 2022 ([Agency for Healthcare Research and Quality, 2019](#)). MEPS is a large-scale nationally

representative survey of households and medical care providers across the U.S. and includes information on household-reported prescription drug use.

We also compile data on global sales and revenues from PharmaCompass, where available, on the organofluorine pharmaceuticals that rank in the top 500 prescribed drugs (PharmaCompass, 2021). “Blockbuster” drugs are defined as those whose global sales exceed \$1B annually. Revenues can change from year to year based on whether a drug’s patent is expired, and the availability of generics. It is more useful and consistent with the available data to compare the total number of prescriptions in a calendar year as a measure of how widely a drug is used. The pharmaceutical name and CAS registry number refers to the non-ionic form of the drug, unless the ionic equivalent is necessary for identification in which case both forms are included. Ionic equivalents are presented primarily for corticosteroids in which case multiple ionic forms of the compounds have distinct clinical uses. For example, fluoxetine hydrochloride is presented simply as fluoxetine whereas fluticasone propionate and fluticasone furoate are presented separately since they are different drugs with unique pharmacological activity.

Quantitative and qualitative analysis

Each of the identified organofluorine pharmaceutical structures were reviewed against the nine definitions. The definitions were ranked from most to least inclusive with the most inclusive definition containing the largest number of compounds. We describe ambiguities in some definitions with examples.