

Extracting and Comparing PFAS from Literature and Patent Documents using Open Access Chemistry Toolkits

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Abstract

The extraction of chemical information from documents is a demanding task in cheminformatics due to the variety of text and image-based representations of chemistry. The present work describes the extraction of chemical compounds with unique chemical structures from the open access CORE (COncnecting REpositories) and Google Patents full text document repositories. The importance of structure normalization is demonstrated using three open access cheminformatics toolkits: CDK, RDKit and OpenChemLib. Each toolkit was used for structure parsing, normalization and subsequent substructure searching, using SMILES as structure representations of chemical molecules. Per- and polyfluoroalkyl substances (PFAS) were chosen as a case study to perform the substructure search, due to their high environmental relevance, their presence in both literature and patent corpuses, and the current lack of community consensus on their definition. Three different structural definitions of PFAS were chosen to highlight the implications of various definitions from a cheminformatics perspective. Since CDK, RDKit and OpenChemLib implement different criteria and methods for SMILES parsing and normalization, different numbers of parsed compounds were extracted, which were then evaluated using the three PFAS definitions. A comparison of these toolkits and definitions is provided, along with a discussion of the implications for PFAS screening and text mining efforts in cheminformatics. Finally, the extracted PFAS (~1.7 M PFAS from patents and ~27K from CORE) were compared against various existing PFAS lists and are provided in various formats for further community research efforts.

Introduction

Per- and polyfluoroalkyl substances (PFAS) are compounds of high public interest as there is increasing evidence that exposure to PFAS can lead to adverse human and environmental health effects^{1,2}. These concerns are accompanied by their documented accumulation in the environment (as so-called “forever chemicals”) due to their widespread use and stability³. Well-known PFAS include older PFAS such as PFOA (perfluorooctanoic acid) and PFOS (perfluorooctane sulfonic acid), as well as newer PFAS such as GenX (a replacement product for the older PFAS). There is strong regulatory debate about PFAS, including calls to regulate them as a class⁴ and for better approaches to detect PFAS in humans and in the environment. Since PFAS and replacement PFAS products are a fast-moving business, cheminformatics tools are gaining importance in identifying candidate PFAS compounds from within scientific and other text sources such as patent repositories, including in-house confidential business documentation.

Past efforts to identify and collect chemical structures of existing PFAS have resulted in several so-called “suspect” lists. The Organisation for Economic Co-operation and Development (OECD) released a PFAS list containing 4,729 PFAS entities in 2017^{5,6} (hereafter “OECDPFAS”). The United States Environmental Protection Agency (EPA) “PFASMASTER” list currently (December 2021) contains 12,048 PFAS entries⁷, merged from several PFAS lists on the EPA CompTox Chemicals Dashboard⁸. Of these two lists, PFASMASTER contains 10,785 entries that can be represented by an InChI (International Chemical Identifier), while the OECDPFAS list contains 3,741 entries with an InChI, using versions downloaded from the EPA website on 2021-12-11^{7,9} and available in the supplementary material¹⁰. The other entities in the lists are substances without a clear composition, or with known composition that cannot be represented fully with an InChI. Of the 3,741 OECD compounds with an InChI, 3,731 are also contained in the PFASMASTER list (by matching InChI).

These lists and more are used in environmental assessments to gauge the extent of the “PFAS knowledge gap”. Such lists serve additional purposes, e.g., to search for the respective compounds in analytical data of environmental samples¹¹. The majority of PFAS suspect lists are hand curated, painstakingly compiled by experts and thus limited both by access to relevant information and by the manual nature of the efforts. Since various definitions of PFAS exist with varying degrees of complexities, three different structural definitions of PFAS have been considered in the current work, clarified below and shown in *Figure 1*:

Definition A: Each compound that contains a CF_2 group is considered a PFAS. This definition has been proposed recently by the OECD^{12,13}. This definition will lead to a large amount of chemicals that are considered to be PFAS.

Definition B: Each compound that contains a $(\text{AH})(\text{AH})(\text{F})\text{C}-\text{C}(\text{AH})\text{F}_2$ group is considered a PFAS, where the AH groups could be hydrogen or any other atom and

the bond between both aliphatic carbon atoms is a single bond. This definition is used in this present work as a straightforward structural definition as a compromise between definitions A and C.

Definition C: Each compound that contains a $(R^1)(R^2)(F)C-C(R^3)F_2$ group is considered a PFAS, where the R groups are any atom except hydrogen and the bond between both aliphatic carbon atoms is a single bond. This is a new, very recent EPA definition^{14,15}. This definition will lead to the least amount of PFAS molecules.

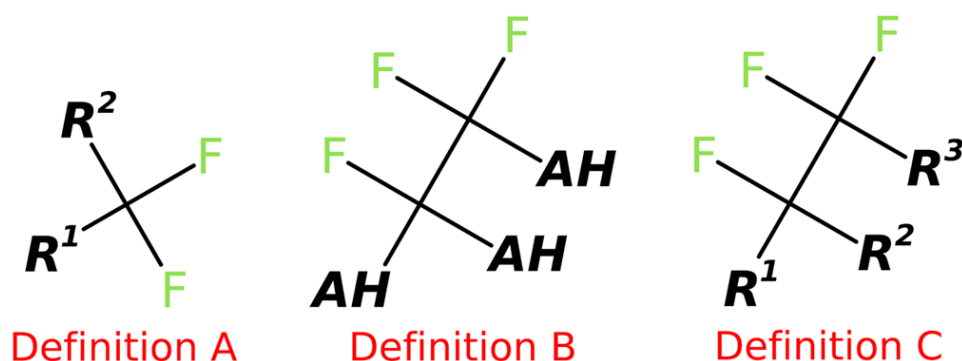


Figure 1: Schematic representation of the PFAS definitions A, B and C considered in this work. “ AH ” = hydrogen or any other atom; R^1 , R^2 , R^3 represent any atom other than hydrogen.

Extracting chemical information from text documents is a challenging task. Unlike other natural language terms, chemistry-related terms pose additional challenges, as the number of known chemical compounds with unique structures is not only very high (e.g. PubChem¹⁶ currently contains 110M unique compounds, which is only a tiny fraction of the estimated chemical space) but they may appear in text documents with a multiplicity of trivial names. Examples include [perfluorooctanesulfonic acid](#), (PFOS), International Union of Pure and Applied Chemistry (IUPAC) names (e.g. 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptafluorooctane-1-sulfonic acid), mixtures of trivial and IUPAC naming, enumerations of Markush¹⁷ structures, trade names and half formulas (e.g. Krytox oils, $F-(CF(CF_3)-CF_2-O)_n-CF_2CF_3$ where $n=10-60$), database identifiers such as Chemical Abstract Service (CAS) registry numbers (e.g. [1763-23-1](#)), PubChem Compound Identifiers (CIDs, e.g. [74483](#)), and even images that are referenced in the text with simple numeric labels. Advanced and flexible methods are required to capture all types of chemical information, with subsequent cheminformatic manipulation to ensure correct mapping to detailed structural information.

The automated analysis of the increasing number of accessible scientific documents may provide input to fuel scientific studies to identify novel molecules with potentially desired or undesired properties. OC|processor¹⁸ is a modular semantic annotation toolkit, based on Apache UIMA¹⁹. It is designed to annotate different document types such as PDF, images, HTML, XML, MS Office and plain text documents. It uses a range of established dictionaries and ontologies as well as rule-based algorithms to

annotate and index scientific named entities such as diseases, genes, species and chemistry. The properties of concept synonyms as well as the hierarchy of ontological concepts are taken into account to provide more accurate context sensitive annotation. For example, the term “sting” could be annotated as a known musician, a species, a disease or a protein. OC|processor disambiguates based on the term environment and the presence of related concepts, assigning the annotation / knowledge domain with the highest confidence value. For this study, the growing bodies of open access document repository CORE^{20,21} (COncecting REpositories) and patent full text documents in Google Patents²² were selected to demonstrate the automated capability of identifying and analyzing scientific entities, applied to the case study of potential PFAS in documents. OC|processor¹⁸ was used to automatically identify and extract mentions of chemical compounds from patents and other open access scientific documents such as scientific articles and university documents in CORE. The resulting collection of diverse chemical compounds was subsequently filtered for small molecule compounds for which a unique InChI²³ could be generated, thus removing incompletely-defined structures such as substances, polymers as well as mentions of chemical class terms and Markush-like¹⁷ structures. Of the three definitions presented above, Definition B was used for most of the detailed investigations in this study. The final PFAS lists are available for all 3 definition versions described above and have been made public, together with additional results, in various formats^{10,24} (see also data availability) for general assessment and as input for future studies.

Experimental

Semantic annotation and extraction of chemical compounds

OC|processor¹⁸ comprises various modules that take the different modalities of chemistry into account, aiming at a comprehensive annotation of chemistry terms in documents. This allows the identification of novel concepts and compounds that were not yet known at the time before annotating a given document. If new compounds are identified, these are registered in Google BigQuery²⁵ tables in the open access SciWalker-Open-Data project, giving access to >150 million small molecules with a unique standard InChI (version 1.3)²³. These unique InChIs were generated from connection tables generated from the SMILES^{26–28} representations of chemical structures. SMILES containing a wildcard entry (*i.e.* “*”) were considered as representing a scaffold containing an undefined substituent and were not registered. Thus, the current approach is limited by the expressivity of SMILES as well as the InChI rules. For example, standard InChI will represent different tautomers of a molecule as one unique structure, while neither SMILES nor InChI consider coordinate (dative) or hydrogen bonds. Since valence isomerism is not handled by either system, this would result in different structures for molecules exhibiting valence isomerism²⁹.

Hereafter, the use of “unique InChI” or InChI in this manuscript refers to a unique standard InChI (version 1.3).

Document sets

CORE Documents: A total of 71,963,421 de-duplicated documents were selected and downloaded from the CORE document set of open access documents²¹. These documents, when annotated with OC|processor, resulted in the annotation of 818,280 compounds with an unique InChI³⁰. The SMILES extracted from CORE are from the text only, images were not extracted.

Patent Documents: Google Patents contains over 120 million patent publications from 100+ patent offices worldwide, available for open access searching²². For the current work, a set of 111,730,728 Google Patent documents was semantically annotated with OC|processor using both the text and images found in these patents - the resulting annotations are made available in a BigQuery table³¹ dated May 13, 2021 (see Big Query³¹ *patents-public-data* in the *google_patents_research* dataset and table *annotations_202105*). In total, 51,928,230,588 annotations were found. Of those, 4,533,988,229 were compound annotations with associated SMILES and InChI. Of these 4.5 billion annotations, 18,032,261 had an unique InChI³² and respective Ontology Concept Identifier (OCID)³³ in the SciWalker-Open-Data project³⁴. As a next (pre-filtering) step, the 18,032,261 unique compounds from the chemistry annotations of patents were reduced to a dataset of 4,182,712 SMILES that contained an “F” character, resulting from a fluorine, iron or francium atom.

The quality of the chemistry-related annotations from the combined text and image patent data is lower than from the CORE set. Optical structure recognition and extraction from images often leads to erroneous structures such as compounds containing hypervalent atoms or wrong isotopes that arise from poor image quality.

Compound structure normalization

Normalization (or standardization) of compound structure representations is an important step in preparing compounds for further analysis, including reliable substructure searching. Thus, the various effects of parsing the SMILES strings from the steps above to create a molecule object, plus subsequent normalization, were investigated using three different open access chemistry toolkits: RDKit (version 2020.03.2)³⁵, the Chemistry Development Kit (CDK, version 2.4)^{36,37} and OpenChemLib (OCL, version 2021.11.3)³⁸. The approaches used were:

- RDKit: with the two available standardizers - molVS^{39,40} and rdMol.
- CDK: via SMILES parsing, normalizing the SMILES with the kekulize option.
- OCL: via SMILES parsing and MoleculeStandardizer, writing the SMILES in a kekulized form.

After parsing the input SMILES, the resulting molecule object was again represented as SMILES as an intermediate step before parsing it again and performing the substructure search to classify it as a PFAS or non-PFAS. This procedure has an effect on the parsing results as described below; in a production environment this additional SMILES generation step would probably not be performed.

PFAS substructure search with graph-based atom-by-atom-search (ABAS)

In-house Java code calling the respective CDK and OCL libraries and python scripts based on RDKit were used for the substructure calculations⁴¹. To ensure that the substructure atom-by-atom-search (ABAS) graph based subroutines were implemented correctly, the code was tested using the query and SMILES set mentioned in the RDKit manual. The SMILES structure used to test the implementation was “C1CC12C3 (C24CC4) CC3” (PubChem CID [141640](#); see *Figure 2A*). A correct implementation of the SMILES substructure search should return 4 for the SMARTS query “*1**1”.

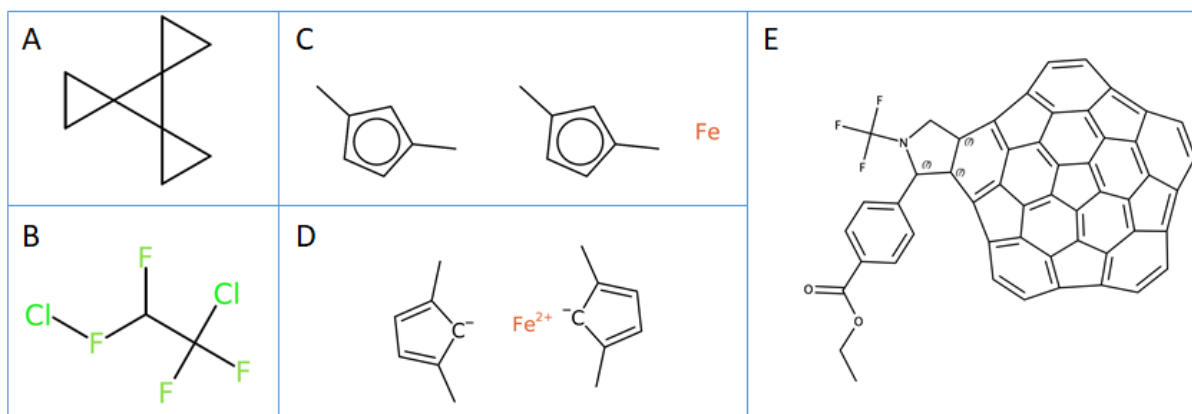


Figure 2: A: The structure to test the validity of substructure search algorithms. B: Erroneous SMILES, i.e. an incorrect representation of 1,2-dichlorotetrafluoroethane caught by RDKit. C: Invalid SMILES representations of ferrocene-like compounds, caught by CDK. D: “Correct” SMILES representation of ferrocene-like compounds, still demonstrating the limitation of SMILES in representing such compounds. E: The structure captured by CDK with ABAS only, but not FP+ABAS.

The PFAS SMARTS definitions $[#6](F)(F)$, $[#6](F)(F)[#6](F)$ and $[#6H0](F)(F)[#6H0](F)$ corresponding to PFAS Definitions A, B and C were used for RDKit and CDK, while the corresponding SMILES query definitions $C(F)(F)$, $C(F)(F)C(F)$ and $C(*) (F)(F)C(F) (*) (*)$ were used for OCL to perform the substructure search to define the number of unique PFAS compounds.

PFAS substructure search with fingerprint selection and ABAS

As a first step, molecular fingerprints were calculated for the extracted molecular structures to create a Lucene search index using Apache Lucene in the following manner. Fingerprints were calculated by the respective toolkit libraries as shown in Table 1. These fingerprints were then stored for each molecule as a “document” in a Lucene index, providing the necessary fingerprint index of the molecules. The fingerprint of the substructure query was then calculated in the same way, followed by searching the Lucene index for candidates. In a second step, the resulting candidate compounds were filtered by ABAS graph-based substructure search from above. Molecules passing both steps were considered as hits. This approach has recently been implemented in Schem⁴² storing fingerprint data in an experimental Lucene implementation ported to C. In this study, a standard Lucene implementation in Java 1.8 was used with fingerprint libraries pattern fingerprinter (RDKit), DescriptorHandlerLongFFP512 (OCL) and CDKFingerprinter (CDK). The pattern fingerprint of RDKit uses SMARTS pattern to generate topological fingerprints of molecules. The DescriptorHandlerLongFFP512 of OCL is a substructure fragment dictionary-based binary fingerprint similar to the Molecular Design Limited (MDL) keys. It relies on a dictionary of 512 predefined structure fragments. The CDKFingerprinter generates one-dimensional bit arrays, where bits are set according to the occurrence of a particular structural feature. The molecules were normalized using the options available in OCL and CDK, and the molVS standardizer for RDKit.

Results and Discussion

Compound structure normalization

Several instances of different cheminformatics toolkits producing different normalized SMILES expressions were found. These inconsistencies influence later results and are described below with specific examples.

Invalid SMILES Expressions: A particular SMILES may contain expressions that are not compliant with the official SMILES definitions, which should either be rejected or elicit a warning from a SMILES parser. For example, while C[N@@@H]C is not a syntactically proper SMILES, it is nevertheless accepted by the commercial toolkit ChemAxon⁴³ as well as CDK, which transform it to [#6;A][#7;AH1;@@@][#6;A] or C*C, respectively, which is likely something entirely different than what was originally intended. However, C[N@@@H]C is rejected by the RDKit and OCL parsers, which is likely a more reasonable behaviour.

Valence Rule Violations: While an extracted and parsed SMILES may be formally correct when generated by chemistry-recognizing annotation modules, such as the optical structure recognition software OSRA⁴⁴ for image-to-structure conversion, the resulting molecular structure may violate obvious valence bond order rules. For

example, the OSRA input SMILES (see *Figure 3A*) “CCc-1=n-c#c-n-1CC1OC(=O)C(C=2C=CC=CC=2)(C=2C=CC=CC=2)C1” is parsed by ChemAxon, OCL and RDKit, giving a parsed SMILES output shown in *Figure 3B* (ChemAxon, OCL) and *Figure 3C* (RDKit) below. The output SMILES are CCc1nccn1CC1CC(C(=O)O1)(c1ccccc1)c1ccccc1 (ChemAxon, OCL) and CCc1nc#cn1CC1CC(c2ccccc2)(c2ccccc2)C(=O)O1 (RDKit), respectively. However, it is rejected by CDK, as it can not assign a valid Kekulé structure to a 5-membered aromatic ring containing a triple bond - representing an abnormal valence. While this behaviour may be intended (or even desired), the end result is that it changes the input SMILES to a different output SMILES, which results in a different chemical structure and thus different InChI. In other words, it changes the meaning of the input to an assumed desired output. Ideally, such changes/corrections should be separated out into an optional module that can be switched on or off by the user of that toolkit, to enable better control over such behaviour depending on the use case.

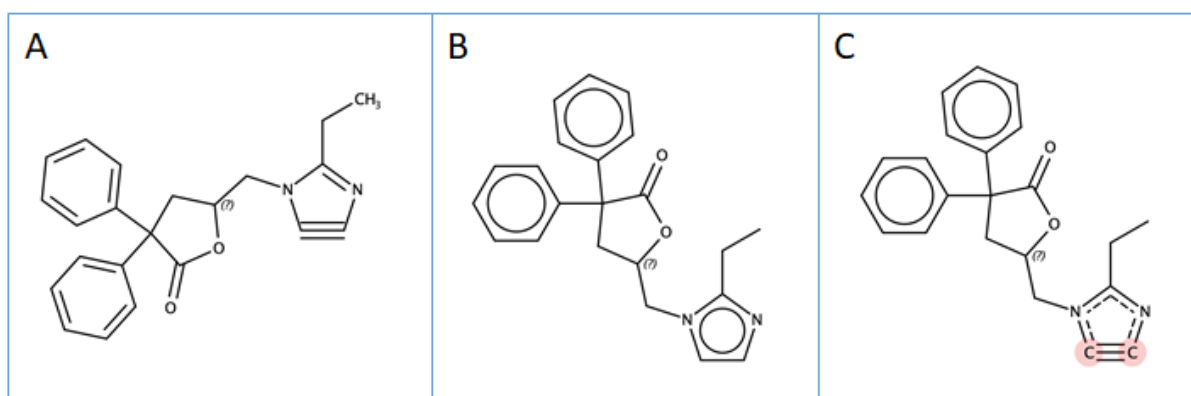


Figure 3: Interpretation of an input SMILES by different toolkits. **A:** The OSRA input: “CCc-1=n-c#c-n-1CC1OC(=O)C(C=2C=CC=CC=2)(C=2C=CC=CC=2)C1”. **B:** The interpretation by ChemAxon and OCL, with output SMILES “CCc1nccn1CC1CC(C(=O)O1)(c1ccccc1)c1ccccc1”. **C:** The RDKit interpretation, output: “CCc1nc#cn1CC1CC(c2ccccc2)(c2ccccc2)C(=O)O1”. CDK rejects the input SMILES.

The number of molecules rejected by parsing the SMILES with the different toolkits is quite different. A rejected SMILES cannot be used for subsequent substructure search, potentially reducing the number of identified PFAS molecules. Thus, the quality of the different SMILES parsers was checked by first parsing the input SMILES, then generating the corresponding InChI from the molecule object. In a second step, a normalized SMILES was written from the molecule object, parsed again and the InChI of these “reparsed” SMILES was calculated. Discrepancies between the InChIs from step one and step two in this procedure reveal issues in the quality of the parsing.

Normalization: For the purposes of further comparison, normalization or standardization of the SMILES input is needed, as the same molecule can be represented by different SMILES. While the terms “normalization” and

“standardization” can refer to different concepts in different contexts, they are used synonymously in this work. During normalization of SMILES, atomic charges and bond types may be changed. For example, a nitro group can be represented as either the charged form -[N+](=O)[O-] or the neutral form -N(=O)=O, both yielding different but valid SMILES strings with the same InChI, *i.e.*, InChI=1S/NO2/c2-1-3. Normalizing these two SMILES representations into a consensus SMILES facilitates further processing, *e.g.* for identity, similarity or substructure searching. Normalization of SMILES may flag alkali metals that are incorrectly connected to O or N, incorrect amide tautomers, and elements rendered as hypervalent or with abnormal valencies. For example, OCL flags and returns an error message when alkali metals are incorrectly covalently bonded to oxygen or nitrogen (*e.g.* NaO). The consensus representation is [Na+][O-]. Also, OCL flags and returns an error message when incorrect amide tautomers are parsed without a square bracket for the NH group. (*e.g.*, N=COH or HNC(=O) are incorrect representations of [NH]C(=O)). Since each chemistry toolkit uses somewhat different rules to normalize SMILES, this has an effect on the outcomes on the PFAS substructure search described below. Some normalization tasks may also be performed by specific “standardizer” modules of the toolkits that use rules (with varying degrees of available documentation) to transform SMILES into a normalized form.

PFAS substructure search (Definition B) and effect of prior normalization

The effect of normalization on the PFAS substructure search using Definition B (*Figure 1B*) on the CORE dataset is given in *Table 1*. The maximum number of unique PFAS compounds found by CDK and OCL using normalization is the same, *i.e.* 4,192 PFAS (according to Definition B). RDKit finds one structure less, which has a SMILES C1FC(F)C(F)(F)C1 (OCID190000011511). This compound structure is actually an incorrect representation of 1,2-dichlorotetrafluoroethane, containing a hypervalent fluorine (see *Figure 2B*). This structure was integrated into the OntoChem database of registered compounds when it was found in an early version of the Wikipedia Chemical infobox⁴⁵. Meanwhile, this entry has been corrected in Wikipedia Chemistry but still remains as a legacy in the OntoChem compound registry system, waiting for relinking to the correct structure and respective OCID190005899464.

In general, the number of SMILES that are not accepted by the different toolkits as valid SMILES are quite different (see “Invalid” entries in *Table 1*) and also depend on whether or not normalization is used. CDK seems to be more “forgiving” than RDKit and OCL, but only if normalization is used.

Table 1: Effect of normalization and toolkit selection on substructure search corresponding to PFAS Definition B in the 818,280 compound CORE dataset.

Toolkit	Normalizer	PFAS Definition B:			PFAS Definition B:		
		No normalization			With normalization		
		True	False	Invalid	True	False	Invalid
CDK	built-in	4,163	801,624	12,493	4,192	814,081	7
OCL	standardizer	4,192	813,829	259	4,192	813,834	254
RDKit	molVS	4,191	813,463	626	4,191	813,462	627
RDKit	rdMol	4,191	813,463	626	4,191	813,090	999

Of the 7 SMILES in CDK that are characterized as invalid SMILES representations with normalization, 6 are ferrocenes with coordinative bonds, such as [Fe].Cc1ccc(C)c1.Cc1ccc(C)c1 (OCID190071023137, see *Figure 2C*). A meaningful ferrocene SMILES should have an iron with 2 positive charges and two cyclopentadienes with a negative charge like for example [Fe++].CC1=CC=C(C)[C-]1.CC2=CC=C(C)[C-]2 (see *Figure 2D*), however this “correct” SMILES does not truly reflect the aromatic structure with a distributed negative charge and its coordinative bonding nature. This problem will be seen for all coordinative compounds, as the current SMILES syntax does not allow for coordinative or hydrogen bonds like they are available in the MDL MOL file version V3000 definitions⁴⁶. This is a serious deficiency of the current SMILES notation, excluding most metal complexes from the universe of SMILES and InChI descriptions, and is a topic under discussion within the InChI committee and IUPAC. The 7th invalid SMILES was generated by OSRA, with the hypervalent carbon atoms as shown and discussed in *Figure 3A* above (OCID190014261931).

For the 254 SMILES that were found to be invalid SMILES representations by OCL with normalization, all 254 contained an aromatic selenium atom “[se]” in a kekulized, non-aromatic SMILES string. In our opinion, this behaviour is correct, as there is no such thing as a single aromatic atom in a non-aromatic environment. However, this [se] is corrected to [Se] by the other toolkits at the normalization stage. In addition, the non-normalized OCL version finds 259 invalid SMILES - the 254 are as for the normalized OCL, while these 5 additional SMILES include atoms with excessive charges such as [As+8], [As+9], [O+8], [O+9], [I+9], which are corrected to their uncharged forms by the normalizer - a behaviour which likely undesirable. The invalid SMILES for CDK (7) and OCL (254) with normalization are the result of the initial SMILES parsing. The invalid SMILES from RDKit were not investigated further,

however, these are available in the supplementary material¹⁰ for further inspection. It is interesting to note that the number of PFAS compounds does not change when using OCL or RDKit, irrespective of whether normalization is applied or not. However, CDK clearly needs a structure normalization before performing substructure searching.

Mixed Toolkit Normalization and Substructure Searching on the CORE Dataset

Table 2 presents the results of using different combinations of toolkits for the normalization and subsequent substructure search engines. The first line per toolkit (two lines in the case of RDKit) repeats the results from *Table 1*, where the normalization and substructure search is performed by the same toolkit. As for *Table 1*, Definition B was used for parsing the PFAS query against the 818,280 CORE compound dataset.

Table 2: Effect of different normalization procedures prior to substructure search (SSS) with various combinations of CDK, OCL and RDKit normalizers and subsequent substructure searches using PFAS definition B. Kekulization in CDK is turned off for non-CDK standardizers. The top row for each toolkit (shaded in light yellow; two rows for RDKit) are as given in *Table 1*.

SSS	Standardizer	True	False	Invalid
CDK	CDK Normalizer	4,192	814,081	7
CDK	OCL Standardizer	4,192	813,834	256
CDK	RDKit Standardizer molVS	3,018	266,657	548,605
CDK	RDKit Standardizer rdMol	3,018	266,862	548,400
OCL	OCL Standardizer	4,192	813,834	254
OCL	CDK Normalizer	4,192	814,072	16
OCL	RDKit Standardizer molVS	4,191	813,220	869
OCL	RDKit Standardizer rdMol	4,191	813,220	869
RDKit	RDKit Standardizer molVS	4,191	813,462	627
RDKit	RDKit Standardizer rdMol	4,191	813,090	999
RDKit	OCL Standardizer	4,191	813,051	1038
RDKit	CDK Normalizer	4,191	813,453	636

For the CDK, while the combination of RDKit normalization and CDK substructure search does not appear to work well together, the CDK substructure search works well with its own CDK as well as with OCL normalization. For the OCL results, it is interesting to note that the syntactically wrong SMILES with aromatic selenium mentioned above are corrected to non-aromatic by CDK, therefore reducing the number of invalid SMILES for the CDK+OCL combination. For the RDKit results, while the number of identified PFAS molecules was not influenced by the normalization used, the least invalid SMILES were found when using RDKit for both normalization and substructure search. Since the molVS model from RDKit returned fewer invalid entries but the same number of PFAS, this was used subsequently. Not surprisingly, *Table 2* shows that it seems to be meaningful to take normalization and substructure search from the same toolkit.

PFAS substructure search (Definition B) on the Patent Dataset

Using the insights gained from *Table 2*, the larger, more heterogeneous SMILES data set of 4,182,712 SMILES from the patent extraction was investigated. The results of normalization and PFAS substructure search using the CDK, OCL and RDKit toolkits are shown in *Table 3*.

Inspecting the invalid 36 SMILES obtained for the CDK results revealed that all structures are ferrocene type compounds as already observed with the CORE dataset. Of the 263 invalid OCL SMILES, 237 were the already known problematic aromatic selenium compounds within a non-aromatic SMILES, 25 had problems with the assignment of aromatic bonds, while one SMILES contained an incorrect nitrogen notation “[N-13]”. Again, it is interesting to note that the results from OCL and CDK are very close to each other. The invalid RDKit SMILES were too numerous for (detailed) further inspection, but are available in the supplementary material¹⁰.

Table 3: Extracted PFAS from the 4,182,712 patent compound dataset using CDK, OCL and RDKit with PFAS Definition B.

SSS	Standardizer	True	False	Invalid
CDK	CDK Normalizer	78,412	4,104,264	36
OCL	OCL Standardizer	78,411	4,104,038	263
RDKit	molVS	75,762	3,988,584	118,366

PFAS substructure search and effect of prior fingerprint selection

Tools that implement substructure searching for large chemical databases perform this task typically in two steps - first, fingerprints are generated and searched for a list of candidate molecules for step two, a full graph-based search also known as atom-by-atom search (ABAS). The reason for this is that ABAS is a NP complete problem and such searches can take quite some time, depending on the query structure. Thus, to achieve reasonable search results in a short time, the number of ABAS searches needs to be reduced to a minimum, which is achieved by a fast fingerprint compound pre-selection step. Thus, fingerprints should deliver a superset of compound candidates, which are then narrowed down by ABAS to the set of compounds that truly contain that substructure. The smaller the difference between this initial fingerprint list and the number of final compounds, the better and thus the more efficient the applied fingerprint algorithm. As a consequence, many fingerprint algorithms have been developed and optimized for pre-selection.

It is not the goal of this work to qualify and compare different fingerprint algorithms, since the described substructure search results were obtained with an ABAS on all compounds of interest (not only on a subset), as accurate results were the prime interest and search time was not an issue. However, a combined compound normalization + fingerprinting + substructure search process was also used to identify PFAS compounds from the extracted structures, as this method would probably be used in the future by typical chemistry database users to identify PFAS compounds. *Table 4* shows the effect of fingerprint screening in substructure search for PFAS Definitions A, B and C across the two compound datasets (CORE and Patents). It is interesting to note that the combined use of fingerprint selection and subsequent substructure search on the selected list resulted in quite comparable results for all the chemistry toolkits when using the higher quality CORE dataset. The number of identified PFAS is the same for CDK and OCL, slightly lower for RDKit. The CDK fingerprint selection appears to be more efficient than using the OCL or RDKit fingerprints for PFAS Definition A and B. For the more strict Definition C, OCL fingerprints are most selective. Not surprising is the lower number of identified PFAS for the more heterogeneous patent SMILES dataset, since more molecules are sorted out by the RDKit parser as shown in *Table 4*.

The results of PFAS selection with the combined use of fingerprints and subsequent ABAS selection correspond exactly to the results when using ABAS on all input molecules - with one exception of CDK for Definition A where the direct ABAS search finds one structure in addition to the fingerprint+ABAS process, which is OCID190080191030 (PubChem CID [117959248](#)) with a very extensive polycyclic aromatic structure, shown in *Figure 2E*.

Table 4: Efficacy of different fingerprints in pre-selection for substructure searching.

Definition A	PFAS hits from the 818,280 compound (CORE) dataset		PFAS hits from the 4,182,712 compound (patent) dataset	
	FP	FP + ABAS	FP	FP + ABAS
OCL	58,132	27,287	4,044,452	1,844,193
CDK	45,632	27,287	2,658,045	1,844,254
RDKit	300,848	27,282	4,047,047	1,792,598
Definition B				
OCL	23,830	4,192	2,225,142	78,411
CDK	16,922	4,192	1,335,409	78,412
RDKit	299,969	4,191	4,041,432	75,762
Definition C				
OCL	9,043	3,507	4,72,731	62,553
CDK	16,922	3,507	1,335,409	62,561
RDKit	215,514	3,502	3,502,138	60,426

Finalized PFAS CORE and Patent Lists via OCL

Since compound structures may be described by syntactically correct SMILES strings but these may represent non-existing compounds, for example if they contain hypervalent atoms or non-existing isotopes (as discussed above), a final cleaning step was implemented based on the results above. Both input sets from CORE and patents from above were used, along with the following procedure to derive a dataset of both valid normalized and standardized SMILES of PFAS classified molecules according to the three definitions using the OCL toolkit:

- Parsing the input SMILES and eliminating erroneous wrong compound structures with hypervalent atoms or wrong isotopes
- Calculating the standard InChI of the input SMILES (“InChI-1”)
- Standardizing the parsed SMILES molecule object, writing a standardized SMILES and calculating the standard InChI of the standardized SMILES (“InChI-2”)
- De-duplicating structures based on “InChI-2”
- Running a ABAS substructure query on the standardized SMILES for PFAS Definition A, B and C.

In the CORE set 974 structures were found with a wrong SMILES and 25,627 structures with a changed InChI after normalization using OCL - these were removed from the datasets. In the patent set, 108,492 structures had incorrect SMILES and 81,272 structures had a changed InChI after normalization with OCL.

The results of the normalized structures classified as PFAS are shown in *Table 5* and compared with the existing PFASMASTER and OECDPFAS lists (mentioned in the introduction) by InChIKey. The number of entries missing from PubChem was determined by matching InChIKeys in each PFAS dataset and the OCID-PubChem dataset in sciwalker: *sciwalker-open-data.chemistry_compounds.ocid_pubchem_cid*.

Table 5: Finalized PFAS compound lists for the CORE and Patent datasets according to Definitions A, B and C, compared with the PFASMASTER and OECDPFAS (2021-12-11 versions). IKFB=InChIKey first block (structural skeleton).

	Total	Not found in PFASMASTER (10,782 InChI)	Found in PFASMASTER (10,782 InChI)	Found in OECDPFAS (3,741 InChI)	Not found in PubChem
CORE Definition A	27,058	25,446	1,612 (1686 IKFB)	944 (988 IKFB)	7,119
CORE Definition B	4,139	2,652	1,487	939	1,175
CORE Definition C	3,457	2,095	1,362	931	915
Patents Definition A	1,783,651	1,780,041	3,610	1,529	216,777
Patents Definition B	75,108	71,818	3,290	1,520	10,809
Patents Definition C	34,197	32,564	1,633	847	4,882

The overlaps between the lists extracted here and the existing PFAS lists were much less than expected. Likewise more entries were missing from PubChem than originally expected, especially for the CORE database. The results were reality checked - here documented with an example for the CORE set using the stringent definition C (915 compounds not in PubChem). One of these 915 compounds includes OCID190080091261 (InChIKey LZICQIXBOVBGMV-UHFFFAOYSA-N), shown in Figure 4. This was published in a PhD thesis⁴⁷ in Chemistry and extracted from the document section IV. Experimental Part 240 16.8.2 via name to structure from "Trimethyl({4'-[(7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododecyl)oxy]-1,1'-

biphenyl-4-yl}ethynyl)silane”, which has been interpreted correctly. This shows the potential for literature mining to capture structures that are real and worthy of further investigation, but not yet known to PFAS researchers or to large open databases such as PubChem.

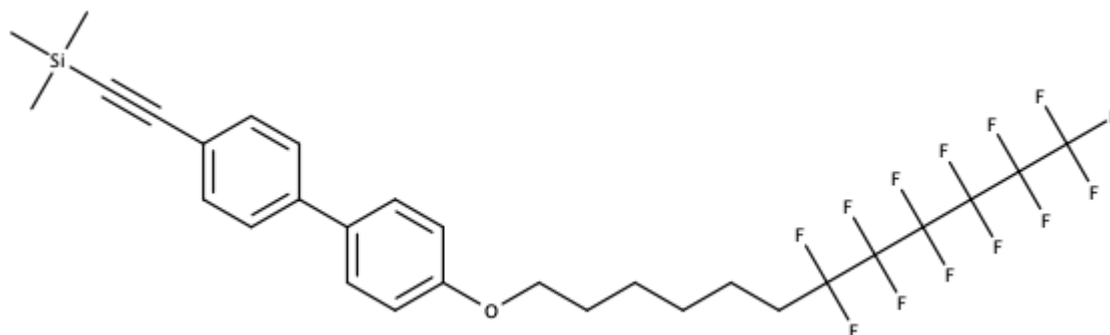


Figure 4: A PFAS classified compound (all definitions) that was indexed in a CORE publication but is not in PubChem (OCID190080091261).

To enhance the discovery of these PFAS in environmental samples, both datasets have been made available as CSV files²⁴ for use in mass spectrometry-based screening approaches, such as MetFrag⁴⁸ and patRoom⁴⁹. Two separate files have been created, for the CORE and Patent datasets respectively - with each entry tagged according to the PFAS definition that the given structure satisfies. The CORE dataset additionally includes the number of references in which the structure was found, which can be used for prioritization of candidate matches. The files were formatted as a MetFrag localCSV, where all entries that cause MetFrag to fail (formulas with digits preceding the carbon; certain unusual elements as removed in PubChemLite⁵⁰) were removed. Where available, names and CIDs were filled in via PubChem, otherwise the OCID was assigned as a name. The resulting files contained 26,695 entries for CORE (of which 5903 entries are without CIDs and 363 entries were removed from the original CORE list) and 1,778,470 entries for Patents (of which 85,277 are without CIDs and 5,181 entries were removed). The number of PubChem CIDs is higher than above due to the different style of querying; here a combination of FTP files (InChIKey to CID mapping) and REST API (SMILES to CID mapping for remaining entries without CIDs) was used, as the REST API offers the SMILES standardization to match with the final version in PubChem. For the original lists, 5937 CIDs were missing in the CORE set of 27,058 SMILES (21.9 %), while 85,472 CIDs were missing in the Patents set of 1,783,651 SMILES (4.8 %). The ratio of missing CIDs was very similar in the final MetFrag files. Both datasets were deposited to PubChem (Feb. 12, 2022, submissions 112615 and 112624) to fill these gaps. The MetFrag CSV files are available on Zenodo²⁴ for use in all mass spectrometry workflows, and are also available in the dropdown menu of the MetFrag Web interface (<https://msbi.ipb-halle.de/MetFrag/>).

Comparison of CORE with OECDPFAS Classification

Finally, the PFAS structures extracted from the CORE database were investigated using the OECDPFAS classification system via the PubChem Classification Browser⁵¹ to determine whether particular PFAS classes were under or over-represented in the extracted data sets compared with the entire OECDPFAS list. The CORE set of 27,058 InChIKeys was uploaded to the PubChem ID Exchange⁵², which returned 20,907 matches via Entrez History. This was then used to browse the NORMAN SLE Classification tree in PubChem⁵¹. Since the influence of searching via InChIKey first block (structural skeleton) versus full InChIKey was not dramatic (only an additional 44 entries found, see row 1 of Table 5), this analysis was kept at the InChIKey level for consistency with the rest of this article. The OECDPFAS list is split into many categories; of primary interest for data extraction is the “Structure Category”, which covers 8 major PFAS categories (denoted 100 through 800), with several subcategories in each. The major categories and the number of matches in CORE are shown in Table 6.

Table 6: OECDPFAS list overlap with CORE according to Structure Category via the S25 OECDPFAS⁶ list in the PubChem Classification Browser⁵¹.

OECD Structure Category	Total	In CORE	Ratio
S25 OECDPFAS List of PFAS from the OECD	3677	940	26%
100 Perfluoroalkyl carbonyl compounds	490	126	26%
200 Perfluoroalkane sulfonyl compounds	458	193	42%
300 Perfluoroalkyl phosphate compounds	16	7	44%
400 Fluorotelomer-related compounds	1392	350	25%
500 Per- and polyfluoroalkyl ether-based compounds	322	52	16%
600 Other PFAA precursors or related - perfluoroalkyl	282	129	46%
700 Other PFAA precursors or related - semifluorinated	716	83	12%
800 Fluoropolymers*	1	0	0%

*neither mapping captures polymers, due to use of InChIKeys. PFAA = perfluoroalkyl acids.

Table 6 shows that PFAS in the categories 200, 300 and 600 are found quite well in the CORE documents (approx 40 % coverage). In contrast, categories 500 (per- and polyfluoroalkyl ether-based compounds) and 700 (semifluorinated perfluoroalkyl acid (PFAA) precursors), are underrepresented (16 and 12%, respectively). Even within categories, different subcategories were underrepresented, for instance very few entries were found from subcategory 103 “other perfluoroalkyl carbonyl-based nonpolymers” (only 13 of 168 entries in OECDPFAS, *i.e.* 8%). Likewise, only 3 of 127 (2%) of subcategory 701.2 “Semi-fluorinated alkanes (SFAs) and derivatives (n>=4)”

were found, and only 26 of 405 (6%) of 705 “side-chain fluorinated aromatics”. It would be interesting future work to investigate whether the CORE and Patent datasets could capture additional knowledge to add more PFAS to these categories, for instance by expanding the “splitPFAS” work at categorizing PFAS⁵³ (prototyped so far on only 4 of the OECDPFAS categories) for this context.

Conclusions

This article details methods to extract mentions of potential PFAS compounds and their structures as SMILES strings from scientific documents and patents, along with the use of three open access chemistry toolkits to identify PFAS structures in these compound lists by parsing, removing wrong structures, normalizing, standardizing and substructure searching these SMILES. The resulting PFAS lists have been compiled, together with their references and chemical structures using three different structural definitions of PFAS (A, B and C). While A is a very broad definition, B is a narrower definition and a subset of A, while C is a subset of B. Of the extracted mentions, FCC(F)(F)F [1,1,1,2-tetrafluoroethane] was the most frequently detected compound - overall 6323 times in the CORE dataset.

The resulting PFAS lists have been compared with two of the largest publicly available lists of PFAS molecules, PFASMASTER from the US EPA and the OECDPFAS list, released by the OECD. The overlap between the lists and the data extracted from scientific documents and patents is lower than expected, showing that many molecules on these lists are not found in the scientific documents and patents investigated, while also many molecules from the document extraction are not found in the published PFAS lists. Several thousand were also not in PubChem, but have since been deposited. The CORE and Patents datasets have been provided as CSV files on Zenodo²⁴ for mass spectral screening. This information will add to the number of known potential PFAS substances and hopefully help contribute to alleviating the “PFAS knowledge gap”. The provision of public datasets will allow the integration of this information into various non-target mass spectrometry workflows, such as the open workflows MetFrag⁴⁸ and patRoom⁴⁹, thus enabling other researchers to investigate the potential occurrence of the identified PFAS compounds in humans and the environment in future studies.

Author Contributions

SJB: Investigation, Software, Data curation; TB: Software; SB: Conceptualization, Data curation; MI: Software; CR: Software; TK: Software, Data curation; ELS: Conceptualization, Data curation, Writing – original draft, Writing – review & editing; LW: Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Conflicts of Interest

SJB, TB, SB, MI, CR, LW declare that they are involved in the creation of the commercial products OC|processor and Google Patents discussed in this paper.

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Data Availability Statement

All input files and results are on FigShare (DOI: [10.6084/m9.figshare.17168960.v1](https://doi.org/10.6084/m9.figshare.17168960.v1)), the final CSV lists are also available on Zeondo (DOI: [10.5281/zenodo.6034586](https://doi.org/10.5281/zenodo.6034586)) and available in MetFrag online (<https://msbi.ipb-halle.de/MetFrag/>). The code associated with this work is on GitHub (<https://github.com/ontochem/PFAS>). Finally, the [patent annotations](#) and the unique compounds from [patents](#) and [CORE](#) can be accessed via the embedded URLs (also given in the reference section, references 30-32).

Supplementary materials

Due to the size of the supplementary materials, these have been provided in various ways as described in the main text, including [annotations in patent documents](#)³¹, the list of 18,032,261 unique compounds (by InChI) [extracted from Google Patents documents](#)³², the 818,280 compounds extracted from [CORE documents](#)³⁰, all supporting data including input files and results for each table on FigShare¹⁰ (DOI: [10.6084/m9.figshare.17168960.v1](https://doi.org/10.6084/m9.figshare.17168960.v1)), CSV files of the final CORE and Patents lists (all definitions) for further use in MetFrag, patRoön and other software on Zenodo²⁴ as well as in the drop down menu in MetFrag online (<https://msbi.ipb-halle.de/MetFrag/>). Finally, code associated with this processing is available on GitHub⁴¹ (<https://github.com/ontochem/PFAS>).

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