PFAS: Environmental Chemistry Investigations, Contamination Source Identification, Toxicology and TERQ Risk Assessments, including FTOH

PFAS : Chimie Environnementale, Diagnostics & Identification des Sources de Pollution, Toxicologie et Evaluation des Risques (EQRS), incluent les FTOH

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1. Introduction

PFAS: Per- & Polyfluoro-Alkyl Substances have gradually become since the 1960s a major environmental problem, also for Public Health, due to their multiple and vast application (historical and still current). This environmental and public health threat has started to be taken into account little by little since the 2010s and strongly in 2022 & 2023. Consequently, PFAS are now found in soils, groundwater, food and water. drinking water as well as in soil gases and ambient air for a family of volatile PFAS, the FTOHs: Fluorotelomer-Alcohols. Between 9,000 and 12,000 synthetic PFAS pollutants have been produced.

PFAS polymers of the "Teflon" type (or PFTE) etc. do not have good bioavailability and are therefore much less toxic than monomeric PFAS. These PFAS monomers are the subject of the work presented herewith. PFAS are known in particular for their toxicological effects of endocrine disruptors, hepatotoxicity, immunotoxicity, their effects on fetal development and for some, carcinogenicity (e.g. PFOA) [1 - 84].

An important characteristic of PFAS is their behavior in Environmental Chemistry, because only polyfluorinated PFAS are modified by microbiological bio-transformation into perfluorinated PFAS, which remain totally stable and non-degradable, or even bioaccumulable.

The sources of pollution by PFAS are multiple and particularly present on industrial sites, which have used these products, sites of former fires or firefighting training, where firefighting foams (AFFF: Anti Fire Fighting Foams, eg at airports) were used. Agricultural land is also a source of PFAS pollution, due to the input of sludge from STEP: Wastewater Treatment Plants which contain accumulated PFAS.

The following (historical) activities can cause PFAS pollution: Entrainements anti-incendie,

- Airport or air base military site,
- Fire site and use of AFFF,
- Electrochemical galvanizing,
- Production of "waxed" paper or cardboard,
- Production of Waterproof Textiles,
- Sprays, paints, waterproofing lacquers,
- Production and application of Teflons (PTFE, etc.),
- Petroleum and chemical industry sites and/or production and application of paints, dyes, inks, pigments, chemical waxes and polishing products,
- Solvent applications (garages, dry cleaners, laundries, etc.,
- Landfills and former municipal landfills, etc. (ISDD, ISDND, ISDD, etc.),
- Dyeings & Tanneries,
- Carpets, rugs, fabrics and plastics with flame retardants,
- Production of objects and furniture containing surfaces,
- Production of cleaning products,
- Photographic chemistry (laboratories, and production of papers and films, etc.),
- Production of electronic elements,
- Production and applications of pesticides and biocides,
- Production of cosmetic products,
- Sites having received Sludge from STEP.

2. <u>Environnemental Chemistry</u>

The environmental chemistry of PFAS is particularly important and complicated. There is no group of pollutants showing more complex environmental chemistry than PFAS. In particular, it should be noted that there are more than 9,000 PFAS substances, divided into 33 substance categories. The best known are Perfluoroalkane-sulfonic acids (PFASs), Perfluoroalkyl-carboxylic acids (PFCA), Perfluoroalkyl-phosphates & their esters, Fluorotelomer-alcohols (FTOH), etc. (including more than 32 other groups…). Some of them, eg. PFOA: Perfluoro-octanoic acid and PFOS: Perfluoro-octane-sulfonate (see Fig. 1) are banned (and prohibited in the EC and USA & Canada) by the Stockholm Convention in the category of POPs: Persistent Organic Pollutants. PFOA is carcinogenic. Commercial products mainly contain mixtures.

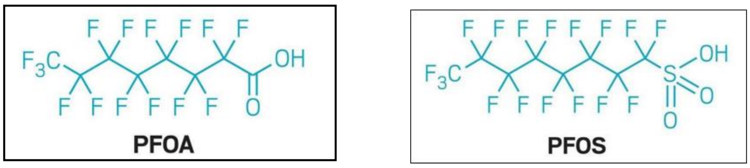

Fig. 1: Structural formulas of PFOA and PFOS

The reason for the high water solubility associated with lipophilia is based on the fact that there are PFAS:

- Anionics (e.g. sulfonates, sulfates, carboxylates and phosphates),
- Cationic (e.g. quaternary ammonium),
- Amphoteres (e.g. betaines and sulfo-betaines): base + acid and
- Non-ionic (eg polyethylene glycols, acrylamide oligomers).

It is very important to emphasize, that not fully fluorinated poly-fluorinated PFAS (“Precursors”) can be converted by bio-transformation into persistent and fully fluorinated chemicals, the per-fluorinated PFAS [87 – 94]. Complete microbiological degradation of PFAS has not yet been demonstrated.

The following diagram shows an example of the biotransformation of polyfluorinated alkyl phosphates (PAP) in soils and groundwater to volatile fluorotelomer alcohols (FTOH) which subsequently migrate into soil gases and into the ambient air. Subsequently, the FTOHs are transformed microbiologically into stable per-fluorinated PFAS. For example ; 6:2-FTOH is biotransformed into PFHxA and PFPeA and 8:2-FTOH into PFOA, PFHpA, PFHxA and 2H-PFOA (see the following Figs).

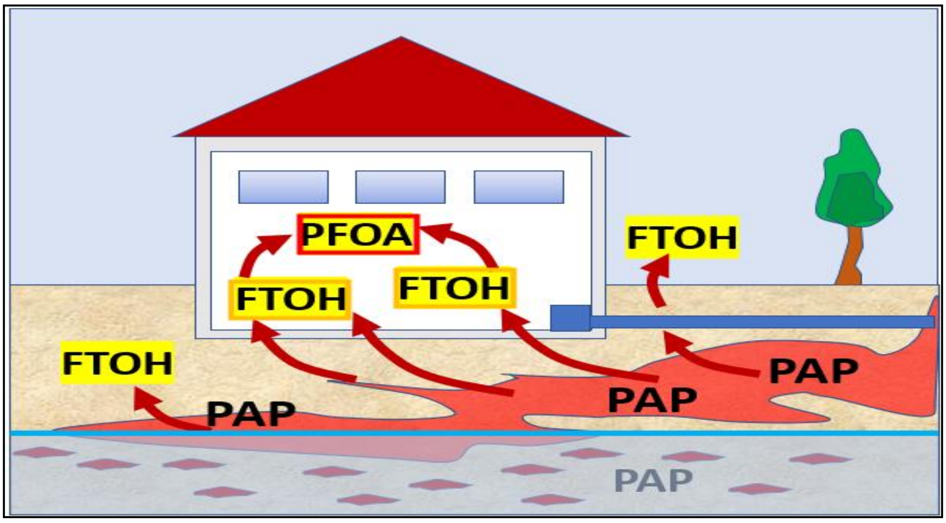

Fig. 2: Example of biotransformation of polyfluorinated alkyl phosphates (PAP) in soils and groundwater to volatile fluorotelomer alcohols (FTOH) and stable per-fluorinated PFAS, such as e.g. carcinogenic PFOA L. KOPF / HPC, 2017 and F. KARG, 2021 & 2022.

The following diagram shows an example of the biotransformation of 8:2-FTOH ($F(CF_2)_8CH_2CH_2OH$) via intermediate products to stable perfluorinated PFAS, such as PFPA (Perfluoro-pentanonic acid), PFHxA (Perfluoro-pentanonic acid), hexanonic), PFHpA (Perfluoro-heptanonic acid), 2H-PFOA, Acid 7:3 and carcinogenic PFOA (Perfluoro-octanonic acid).

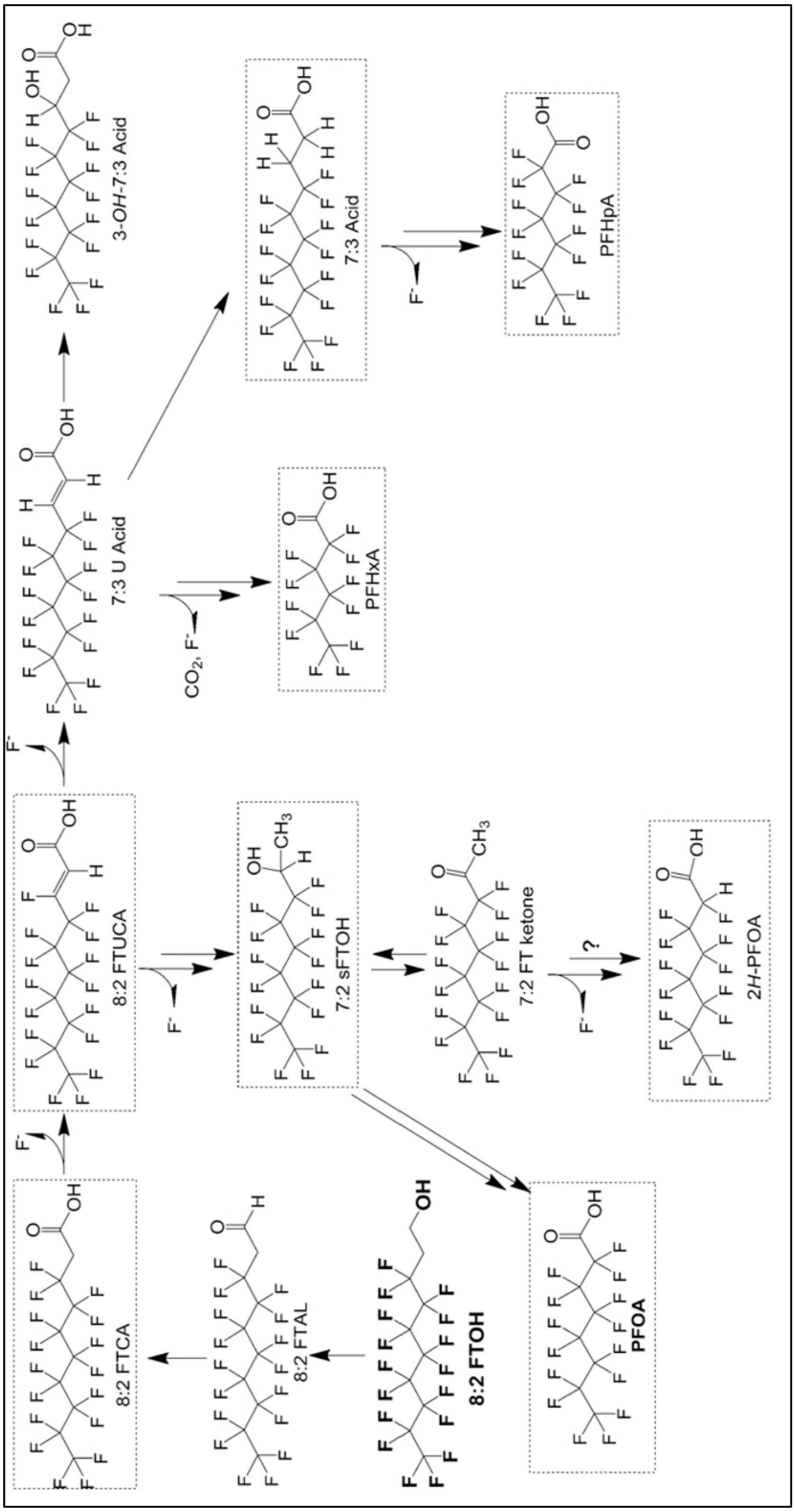

Fig. 3: Example of aerobic biotransformation of 8:2 FTOH ($F(CF_2)_8CH_2CH_2OH$) in soils. Double arrows indicate the formation of stable per-fluorinated substances (Wang et al. 2009, modified).

In the event of a change in pH, some PFAS could become more or less soluble, which also has an impact on the emanations of volatile fluorinated telomeres like FTOH, etc. in soil gases. Some precursors could modify their solubilities (and their extractabilities during chemical analysis procedures). Eg. the intrusion of seawater into the aquifer could lead to an increase in the basic pH and therefore the solubility of Capstone B. This was observed in 2022 in the port area of Hamburg / Germany following flooding by water from sea and groundwater intrusion, cf. Fig. next. These effects could result in concentrations more than 10 times higher in groundwater than before seawater intrusion into soils and groundwater.

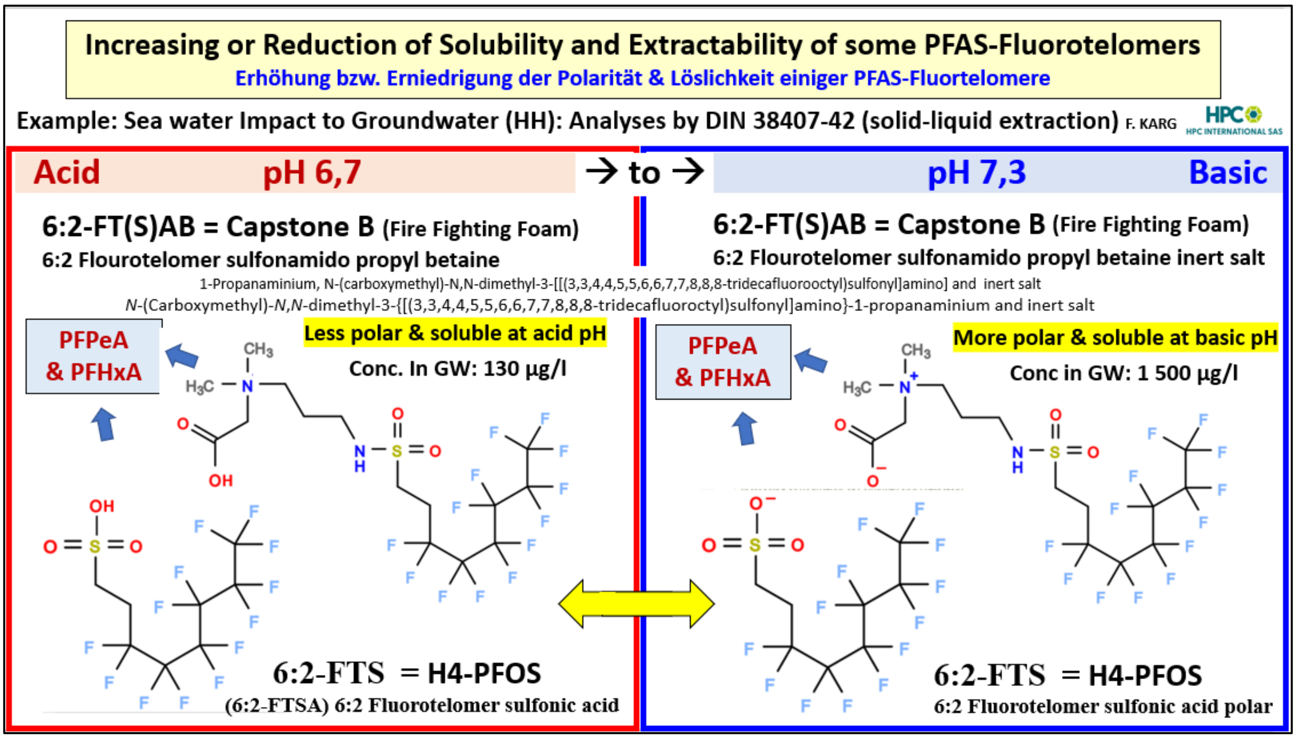

Fig. 4: PFAS solubilities according to pH (example: before and after seawater intrusion into an aquifer

3. Identification of PFAS Pollution Sources

Pollution of soil, groundwater and surface water by PFAS are frequently mixtures at the origin of several sources of commercial products and sources of pollution. It is possible to carry out complete screening of individual PFAS substances in order to identify between 9,000 and 12,000 molecules, but in the daily management of pollution in the environment this is not applicable due to the technical-economic feasibility limit.

For this reason it is necessary to reduce the number of PFAS compounds to be analyzed during environmental diagnostics thanks to the chemical signature of the commercial products suspected of being the source of the contamination. Indeed, PFAS being a family of more than 9,000 compounds, it would be impossible to quantify them all. Nevertheless, it is necessary to seek the identity of the commercial product(s) likely to be the source of contamination of the subsoil, on the basis of the PFAS contents measured in the soil or water (underground, surface or sanitation).

The solution for identifying commercial products suspected of being the source of PFAS pollution, via a chemical signature, has already been developed by HPC with US-American and Swiss partners. This is Fingerprinting by analysis of “PFAS Clusters” (Karg et al. & Monti 2022 & 2023) |85 – 86 & 95 - 97]. It follows from this work that it is sufficient to analyze 8 to 30 individual PFAS in order to identify, via the relationships between the individual PFAS, the products and sources of the original pollution.

It has thus been possible to identify (using the results of chemical analyzes from several analysis laboratories), among almost 60,000 Analyzes of PFAS in ground and surface waters in North-East Italy, 24 sources of pollution at the origin of a very large PFAS pollution plume. In comparison of the relationships of only 8 PFAS between them, the commercial products and activities at the origin could be identified, thanks to the databases (USA & Europe) concerning the PFAS Clusters. These sources are e.g. Textile impregnations, fire-fighting foams, galvanizing, production of electronic boards, surface treatments of paper, cardboard, wood, etc.

The origins of PFAS pollution can be identified by analyzes of PFAS Clusters (Fingerprinting) (Fig. 5). We have developed this application with partners in Switzerland and the USA. This mainly concerns the distribution of 8-30 stable perfluorinated PFAS, in order to identify the original products (fire-fighting foams, textile impregnation products, lacquers, fluorinated polymers (Teflon, PTFE, PVDF, etc.) .), foams from galvanic processes, etc. We can integrate up to 500 individual PFAS in this Cluster analysis, but the limitation to 20 – 30 individual PFAS is less expensive and in most cases sufficient. to dissociate in the North-East of Italy several different origins of large pollution plumes by PFAS mixed in groundwater and surface water (Fig. 6).

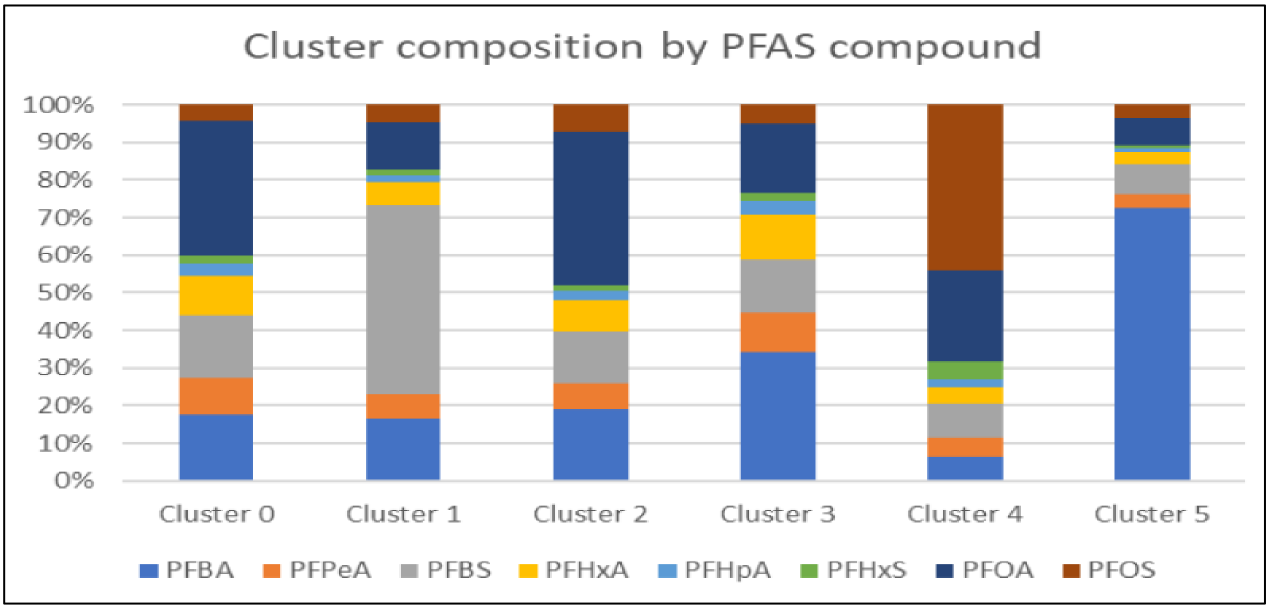

Fig. 5 : PFAS Clusters depending on commercial products

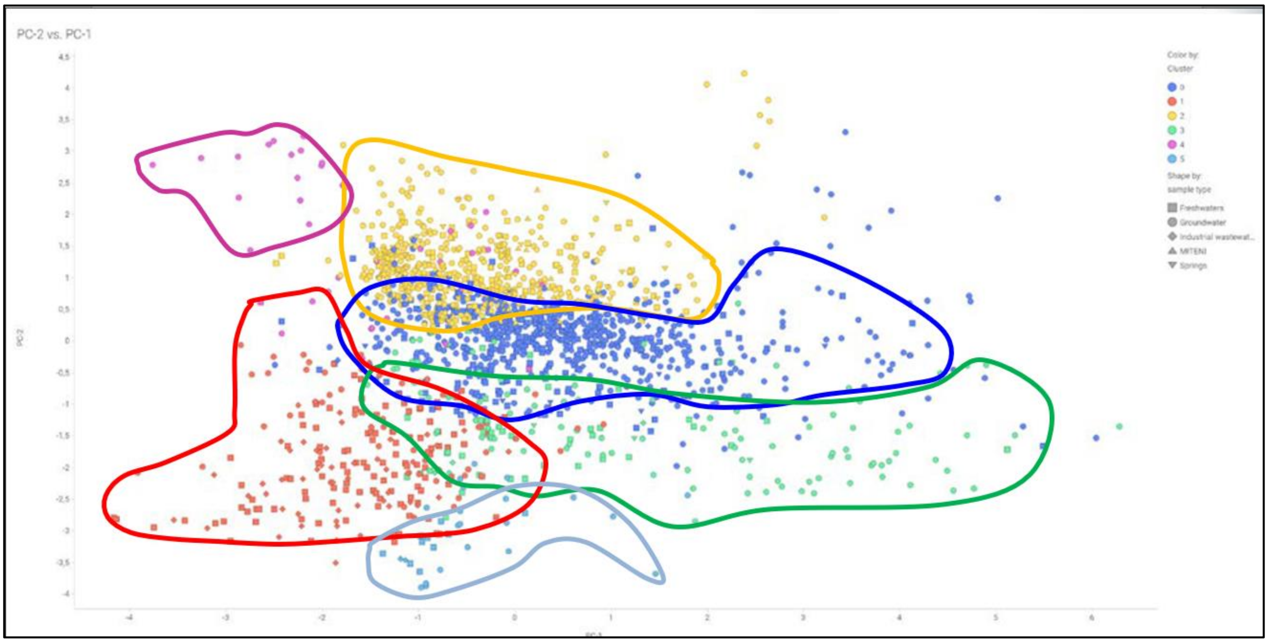

Fig. 6: Identification of 6 products of origin via analyzes of the PFAS Clusters (area of 761 ha and 472 analyzes of groundwater and surface water in the North-East of Italy) 85 - 86].

Finding the identity of the commercial product(s) likely to be the source of subsoil contamination, based on PFAS levels measured by a reduced number of PFAS (signature PFAS list) in the soil or waters (ground, surface or sewage), will be based on prior recordings of individual PFAS spectra (Extended PFAS List), in comparison with the percentages of individual PFAS in relation to total PFAS (TOF: Total Organo Fluorite), cf. Fig. 7.

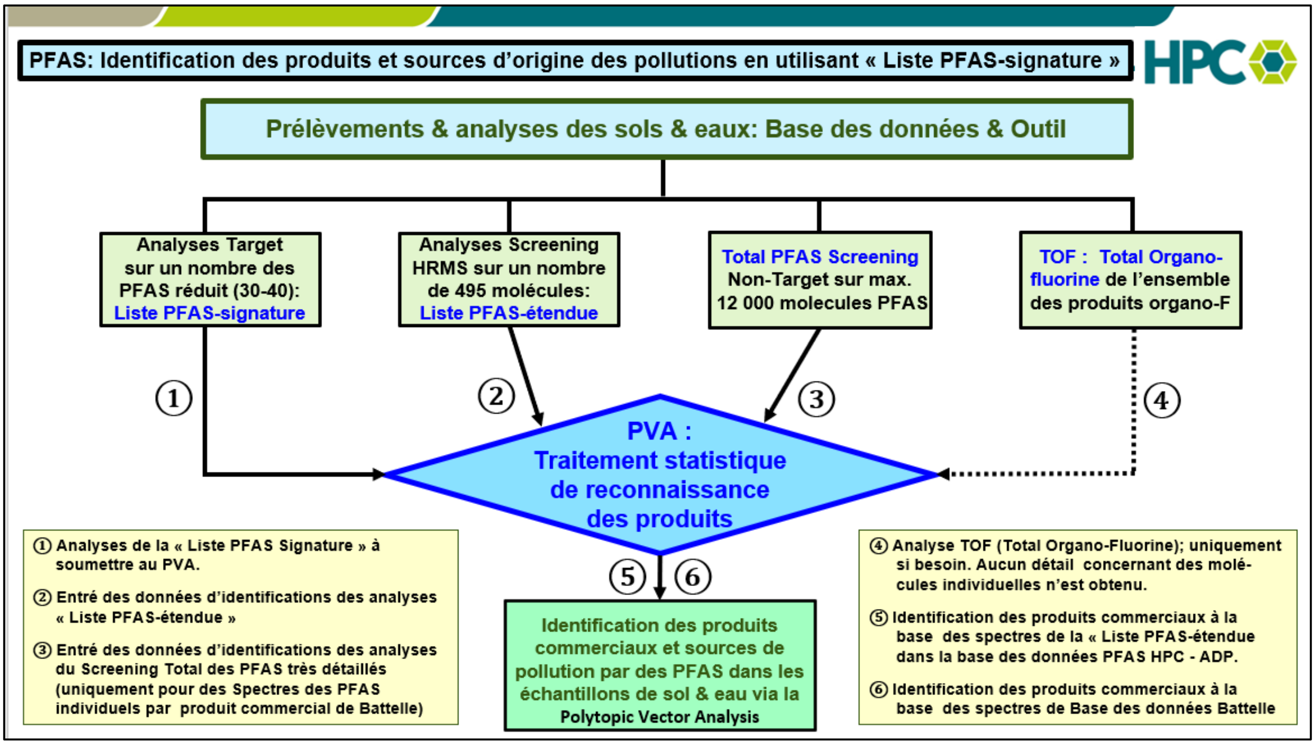

Fig. 7: Principles of development and operation of the PFAS HPC Database

The identification of commercial products containing PFAS also requires historical studies of applications of commercial PFAS products (as also provided for in the Ministerial Order of 2023 concerning the monitoring of PFAS emissions, e.g. in wastewater from ICPEs :

- **Bibliographic research;**
- **Visits to the (potentially) polluted sites concerned;**
- **Interviews with various witnesses.**

The following data will be sought in particular:

- **The nature of the products used;**
- **The period of use of the products;**
- **The places of use / storage of the products;**
- **The frequency of use of the products;**
- **The annual quantities consumed;**
- **Any identified incidents (accidental spillage, fire, etc.);**
- **The possible carrying out of depollution or development work on potentially exposed sites.**

In order to define individual PFAS spectra of commercial products and sources of PFAS pollution, the chemical characterization analyzes are as follows:

- Quantitative "Non-target analyses" on approximately 500 individual PFAS molecules by Liquid Chromatography High Resolution Mass Spectrometry (LC-HR-MS or HRMS) to identify a "PFAS-signature List" from a "PFAS-Extended List" (up to 500 individual PFAS).

- Constitution of a chemical signature sufficiently representative of the commercial products analyzed by non-targeted analyses. Total PFAS analyzes (hereinafter referred to as "Total PFAS") can be carried out either by a "Total Organo-Fluorine (TOF: Total Organofluorine) which does not provide any information on individual molecules of PFAS, or by a total screening in order to identify up to 12,000 PFAS molecules (these analyzes have a very high cost and are therefore not systematically considered).

The construction of the database of individual spectra of commercial PFAS products is carried out as follows (cf. Fig. 8):

- An "HPC Database" of spectra of molecules of commercial PFAS products from Microsoft Access (or Excel).

- For Commercial Products sampled at sites or obtained from suppliers of commercial PFAS products and further analyzed, approximately 500 individual PFAS molecules ("PFAS-Extended List") will be recorded in the HPC PFAS Database.

- For the spectra of the analyzes of degraded commercial PFAS Products (aging of Poly-fluorinated by biotransformations) in lysimeters equipped with biotransformation bacteria), their spectra on a maximum of 500 individual PFAS molecules ("Extended PFAS List") will also be recorded in the HPC PFAS Database.

- Chromatograms of analyzed and recorded Commercial Products and Products subject to aging are digitally transformed and stored in the "HPC Database" on Microsoft Access.

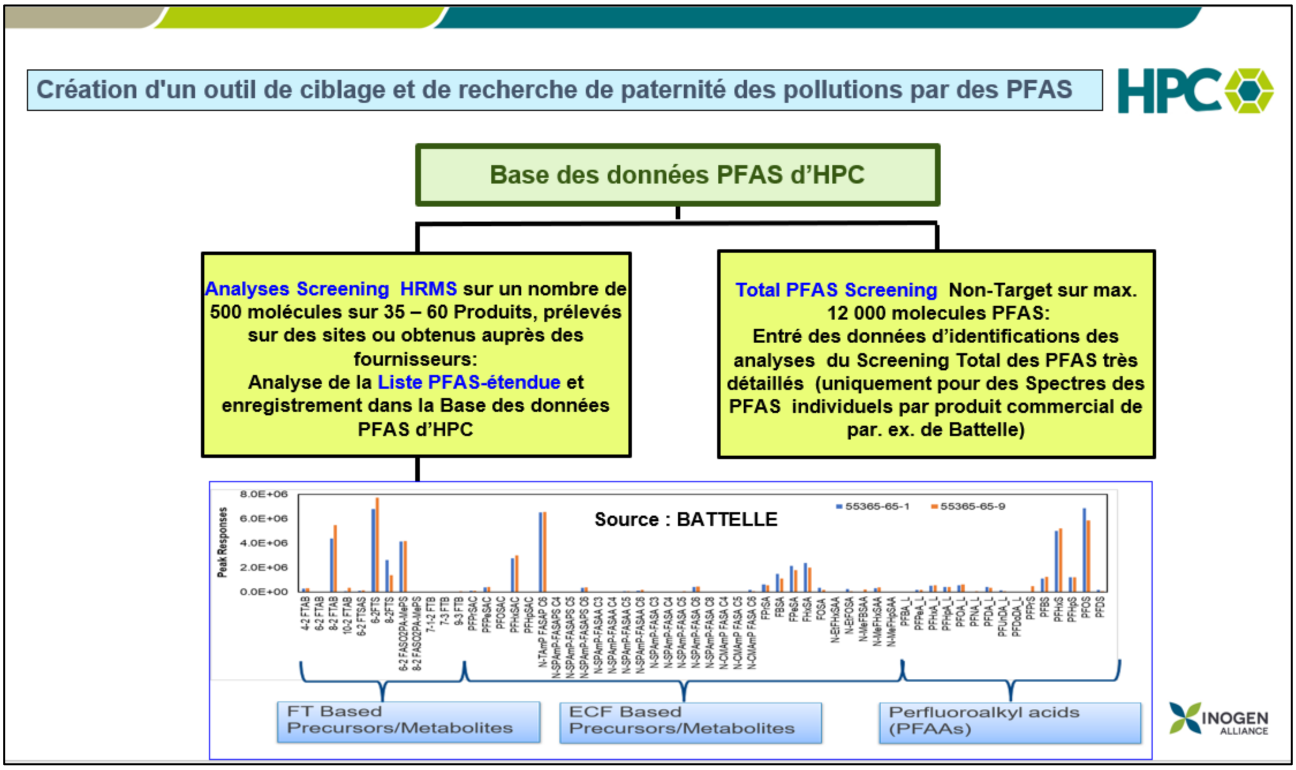

Fig. 8: HPC database of molecular spectra of commercial HPC PFAS products

 The "PFAS HPC Database" on Microsoft Access is superior to that of other Databanks, because it integrates, in addition to the known spectra (PFAS Chromatograms), those of Commercial Products subjected to aging by Lysimeters and Bacteriological Biotransformation polyfluorinated PFAS).

 A list of Queries (Possible Queries or Identification Parameters, e.g. the recognition of commercial products from the relationships of the individual PFASs of the "PFAS-signature list") will be created to identify the commercial products from the standard list of reduced PFAS analyzes (30 – 40 individual substances = “PFAS-signature list”).

The principles of identifying commercial products and sources of PFAS pollution at the origin are demonstrated in Figs. 9 – 11.

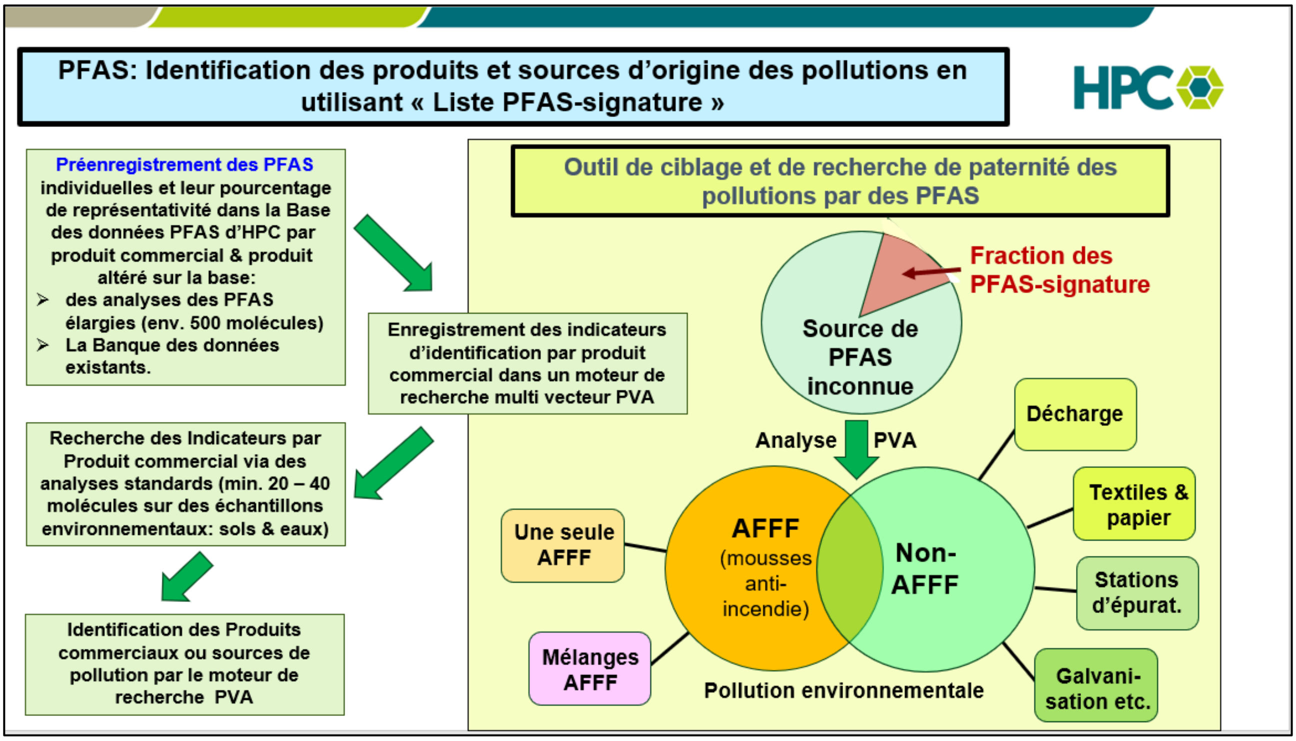

Fig. 9: Identification of initial PFAS products in mixtures of commercial products causing pollution (1/3)

The identification program concerning the origin of commercial products: The identification program makes it possible to search for the origin of commercial products on the basis of a reduced number of individual PFAS in the analyzes of environmental samples (soil and water) from the "PFAS database of HPC" on Microsoft Access (or Excel). This includes:

- ➢ The expected concentration distribution research results will be expressed as a % of the total expected concentration in soils or in groundwater, surface water or sewerage (Function A).
- ➢ Search for the identity of the commercial product(s) likely to be the source of contamination of the basement.
- ➢ The identification program indicates (in the form of a table) the probability of origin of pollution in the soil or in groundwater, surface water or sanitation compared to the commercial Products listed in the "Database PFAS of HPC".
- ➢ As part of the probabilistic identifications of the origins of PFAS contamination, the Spectra (chromatographic distributions of PFAS) of commercial Products altered and recorded in the "HPC PFAS Database" are included.
- ➢ The identification program on the "PFAS HPC Database" will be superior to those existing, because it uses, in addition to the existing spectra, also spectra (Chromatograms of PFAS) of Commercial Products subjected to aging by Lysimeters and of the Bacteriological biotransformation of polyfluorinated PFAS, etc.).

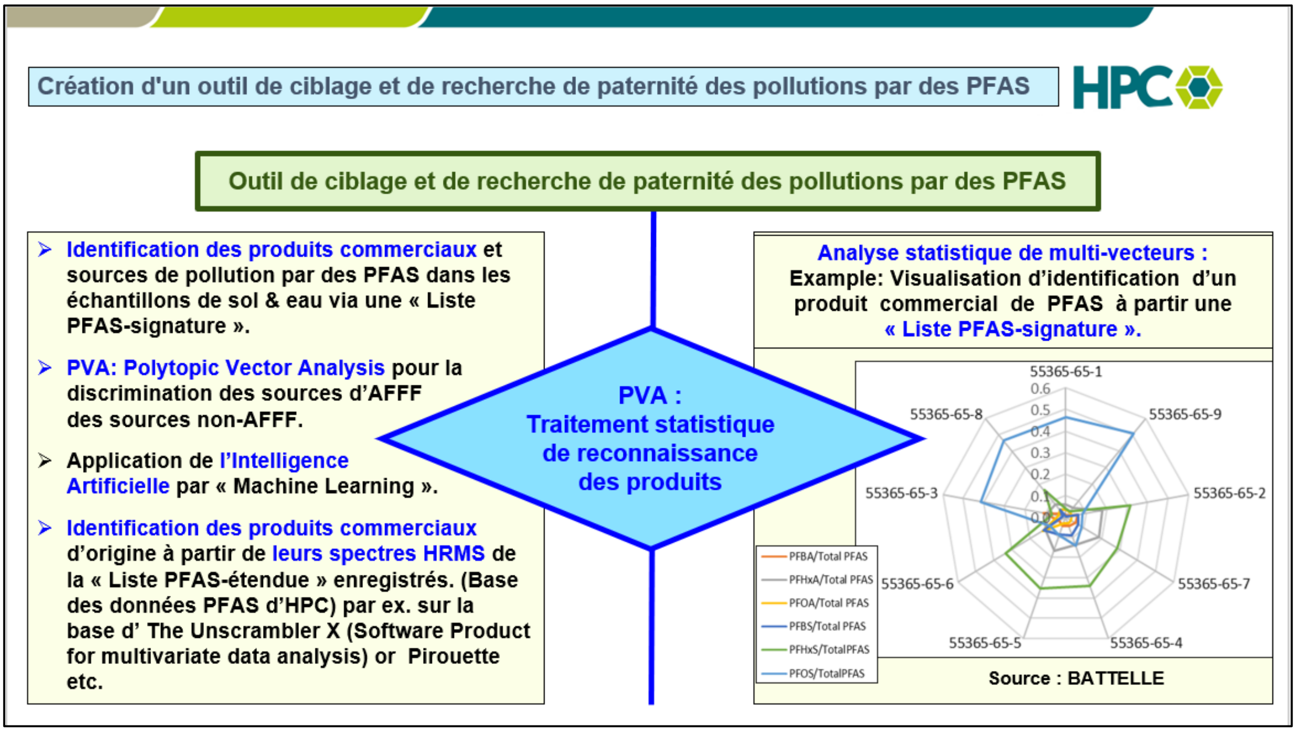

Fig. 10: Identification of initial PFAS products in mixtures of commercial products causing pollution (2/3)

- The commercial product identification program will be a statistical classification model like the one originally developed by Batelle for the detection of AFFF (and other products) in mixtures of different PFAS sources. This model will also be based on Artificial Intelligence and, in particular, on the Machine Learning approach.

- The application of the Tool will be based on the presence and quantification in the samples analyzed of restricted PFAS compounds that are extremely stable under environmental conditions, and which characterize the footprint of AFFF or other sources of additional PFAS existing identification programs on stable perfluorinated PFAS formed by the biotransformation of the weathering of commercial products.

- The results of applying the Tool are the probabilities that the mixture of PFAS found in a sample is related to certain commercial products (or pollution sources).

- Using the statistical method called PVA (Polytopic Vector Analysis), it is possible to assign a percentage of statistical membership (or resemblance) of environmental samples to each Commercial Product (or source of Pollution).

- The software used for the development of the Tool are R, Mathematica®, The Unscrambler® and Pirouette®.

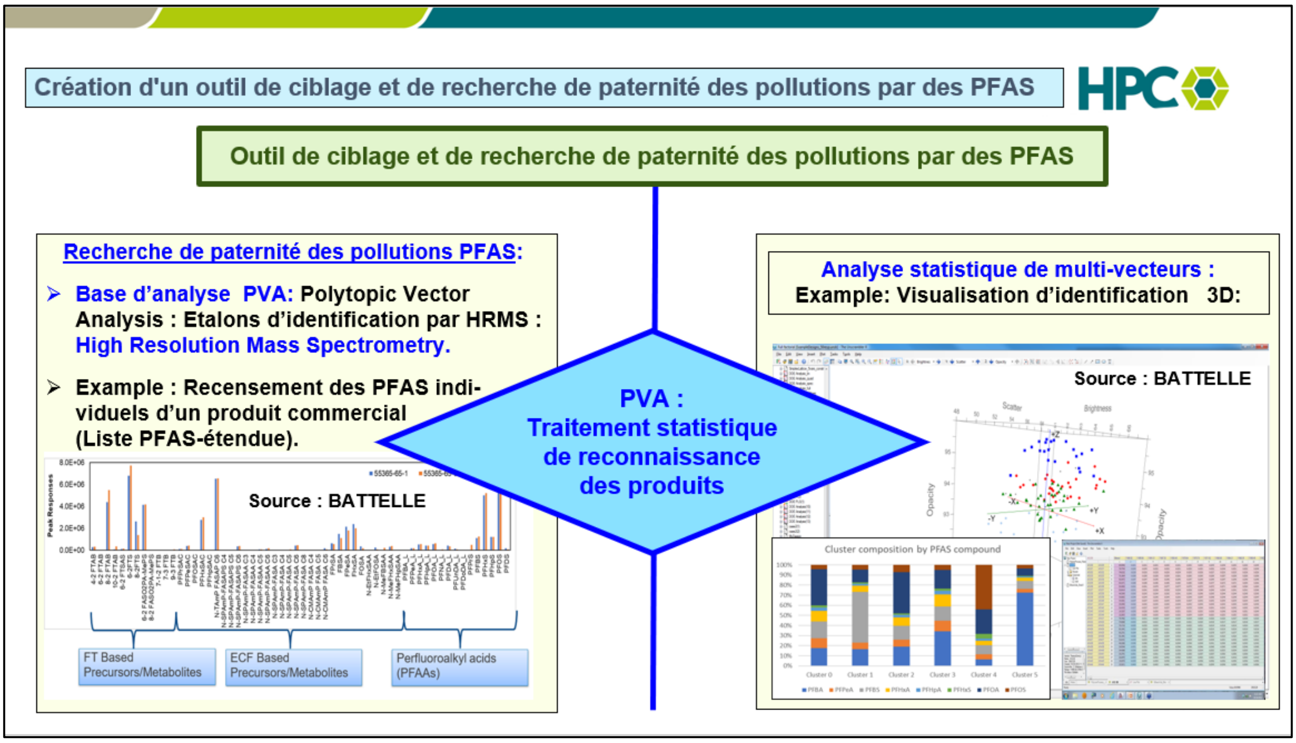

Fig. 11: Identification of initial PFAS products in mixtures of commercial products causing pollution (3/3)

The existing difficulty are the spectra (chromatograms) of the commercial products degraded by biotransformation from poly-fluorinated to per-fluorinated, because these individual PFAS spectra are different from the "fresh" products and also from those integrated into the HPC database at from existing databanks.

To overcome this difficulty of identifying altered commercial products in environmental samples (soil & water, analyzed for a reduced number of PFAS), the "PFAS-HPC Database" will contain expanded Chromatograms on 500 individual PFAS, representing PFAS spectra of commercial Products subjected to aging tests in Lysimeters These tests will be carried out via a reputable bacteriological consortium of the bio-transformation in question (of the type Acidimicrobium sp. Strain A6 (Huang & Jaffé 2019) and/or Pseudomonas strain SYC and /or Rhodococcus jostii RHA1 and/or Pseudomonas oleovorans (Ying Shi, 2018).

This is how standards representative of commercial mixtures of PFAS will be obtained by simulating aging for several years. As a general rule, it is recommended to include in the diagnosis of contamination by PFAS at least the following pollutants:

N°	Polluant PFAS de base	Synonyme	VTRs existantes
1	Acide perfluoro-butanoïque	PFBA	Oui
2	Acide perfluoro-pentanoïque	PFPeA	Oui
3	Acide perfluoro-hexanoïque	PFHxA	Oui
4	Acide perfluoro-heptanoïque	PFHpA	Oui
5	Acide perfluoro-octanoïque	PFOA	Oui
6	Acide perfluoro-nonanoïque	PFNA	Oui
7	Acide perfluoro-decanoïque	PFDA	Oui
8	Acide perfluoro-butane-sulfonique	PFBS	Oui
9	Acide perfluoro-hexane-sulfonique	PFHxS	Oui
10	Acide perfluoro-heptane-sulfonique	PFHpS	Oui
11	Perfluoro-octane-sulfonate	PFOS	Oui
12	Acide H4-polyfluoro-octane-sulfonique	H4-PFOSA	associé au PFOS
N°	Polluant PFAS de base	Synonyme	VTRs existantes
13	Perfluoro-octane-sulfonamide	PFOSA	Oui
14	6:2 Fluorotélomère alcool	6:2-FTOH	Oui
15	8:2 Fluorotélomère alcool	8:2-FTOH	Oui

Si possible:			
16	Perfuorobutane sulfonate	PFBS	Oui
17	Perfuoropentane sulfonate	PFPeS	Oui
18	Perfuorohexane sulfonate	PFHxS	Oui
19	Perfuoroheptane sulfonate	PFHpS	Oui
20	Perfuorodecane sulfonate	PFDS	Oui
21	Acide perfluoro-undecanoïque	PFUnDA	Oui
22	Acide perfluoro-dodecanoïque	PFDoDA	Oui
23	Acide perfluoro-tridecanoïque	PFTrDA	Oui
24	Acide perfluoro-tetradecanoïque	PFTeDA	Oui
25	Acide perfluoro-hexadecanoïque	PFHxDA	Oui
26	Acide perfluoro-octadecanoïque	PFODA	Oui
27	Acide Hexafluoro-propylèneoxydimer	HFPO-DA	Oui
28	Acide 3H-perfluoro-3-[(3-methoxy-propoxy) propanoïc	ADONA	Oui

Fig. 12: Minimum recommended PFAS analysis parameters

As it stands today, the analysis of the 20 individual PFAS of European Directive 2020/2184 can be carried out but also extended to 40 individual PFAS. : According to European Directive 2020/2184, which concerns the quality of water for human consumption, the following 20 PFAS are targeted:

Somme des 20 PFAS de la Directive européenne Eau potable 2020 :
- Acide perfluoroctanoïque (PFOA) [5347]
- Acide perfluoroheptanoïque (PFHpA) [5977]
- Acide perfluorohexanoïque (PFHxA) [5978]
- Acide perfluoropentanoïque (PFPeA)[5979]
- Acide perfluorobutanoïque (PFBA) [5980]
- Acide perfluorobutane sulfonique (PFBS) [6025]
- Acide perfluorododécanoïque (PFDoDA) [6507]
- Acide perfluorononanoique (PFNA) [6508]
- Acide perfluorodécanoïque (PFDA) [6509]
- Acide perfluoroundécanoïque (PFUnDA) [6510]
- Acide perfluoroheptane sulfonique (PFHpS) [6542]
- Acide perfluorotridecanoïque (PFTrDA) [6549]
- Acide perfluorodécane sulfonique (PFDS) [6550]
- Acide perfluorooctane sulfonique (PFOS) [6561]
- Acide perfluorohexane sulfonique (PFHxS) [6830]
- Acide perfluoropentane sulfonique (PFPeS) [8738]
- Acide perfluorononane sulfonique (PFNS) [8739]
- Acide perfluoroundécane sulfonique [8740]
- Acide perfluorododécane sulfonique [8741]
- Acide perfluorotridécane sulfonique [8742]

4. Health Risk Assessments (TERQ : Toxicological Exposure Risk Quantification)

For the assessment of health risks, toxicological data (TRV: Toxicological Reference Values) must be sought and updated at international level almost on a weekly basis. The most recent TRVs are available mainly in the USA (EPA, etc.), ATSDR and EFSA. ANSES also published PFAS TRVs in 2017, but given the forced advancement of toxicological studies, these TRVs are for the most part already outdated.

In the case of FTOHs present in soils, groundwater and soil gases, it will also be imperative to carry out FTOH investigations in the ambient air of buildings with sensitive uses (ERP: Schools, Nurseries, etc.) or residential, on the basis of quantification thresholds (or at least for the detection thresholds), of the order of 4 – 8 ng/m3, in order to have a good exploitable basis for the EQRS: Quantitative Assessment of Health Risks.

A first simplified risk assessment approach is possible via existing limit values, e.g. in Germany, or published by the European Community. In Germany there are limit values for drinking water, soil and groundwater.

The US-EPA considers that the majority of exposure today comes from drinking water, outside of polluted sites, due to the lack of monitoring and treatment of PFAS. According to Directive (EU) 2013/39/EU "Water Framework" (WFD), concerning PFOS & derivatives (and other priority substances) an Environmental Quality Standard (EQS-MA) of 0.65 ng/l for surface waters and 0.13 ng/l for waters from the marine environment (and EQS-MAC: Maximum Allowable Concentrations) has been set.

It is important to note that a simple application of the Limit Values, generic and individual within the framework of a simplified risk assessment does not take into account specific exposure scenarios and exposures to mixtures ("Cocktails") pollutants with, at a minimum, taking into account the additivity of the risks of pollutants having the same targets and toxicological effects. Consequently, it is preferable to carry out EQRS (or ARR, HRA, TERQ), which corresponds well to the French Methodology for the Management of Polluted Sites, according to the note from the Ministry in charge of the Environment, of 04/19/ 2017.

Another important aspect is that only an EQRS (or ARR, TERQ, HRA) will make it possible to define Health Compliance Control Values, in the form of MAC (Maximum Admissible Concentration) for maximally acceptable Excess Individual Risks (of cancer): ERI < 10E-5 or a Systemic Risk Index of IR < 1 (= DJE / DJT: Daily Exposure Dose over the Tolerable Daily Intake). Regarding the EQRS: Quantitative Assessment of Health Risks, the basis is either the measurement of concentrations in the exposure media, or the modeling of the transfer of pollutants from one compartment to another (e.g. pollutants in groundwater or from the ground to the gases of the ground and the ambient air. An important step in the EQRS is the choice of TRVs (Toxicological Reference Values), because their evolution is rapid.

For example, the 2017 ANSES PFAS guide includes certain TRVs for PFAS, but given the many TRV publications to date, these values are partially outdated, and in particular much more restrictive to date. A Tolerable Weekly Intake (DHT) of 4.4 ng/kg/Week (or the Tolerable Daily Intake (TDI) of 0.63 ng/kg/d for PFAS: PFOA, PFOS, PFNA & PFHxS) has been published by EFSA, 09/17/2020. In 2020, toxicity equivalence factors with respect to PFOA were also published by W. Bil et al. in the form of RPF: Relative Potency Factors.

In order to ensure the correct choice of TRVs for PFAS, it is recommended to apply scientific selection criteria and not national criteria. Fig. The following shows criteria for choosing the applicable TRVs, in order to take into account the best toxicological knowledge concerning the dose-effect relationships of PFAS.

No	TRD: Toxicological Reference Dose Choice Criteria	Appreciation			
		Favorable	Correct	Not favorable	Exclusion
1	Variability of indicated TRD	(+/- 0 %)	≤ (+/- 30 %)	> (+/- 30 %)	
2	Class (potential) Carcinogenic: EC: Class 3/ US-EPA: Class B2, C / IARC: Group 1	3 Organisms : CE, US-EPA, IARC, etc.	2 Organisms	1 Organisms	
3	Several Organisms shows similar TRD (+/- 50 %)	➢ 3 Organisms	2 Organisms	1 Organism	
4	Age of base Study	≤ 15 a	15 – 25 a	< 25 a	
5	Mechanistic toxicological basement Study (for ex. Genotoxicity):	Epidemiology	Mamifer	In-Vitro / In-silico	
6	Basement Study : Klimisch Quality Criteria	Class 1	Class 2	Class 3	Class 3
7	Verified Purity of Compound	Yes	< 95 %	No	
8	Excipient potentially toxic	Non		Yes	
9	Presence of population without exposure (test witness)	Yes		No	
10	General Quality Criteria (Klimisch) of toxicological effect studies	Standardized Study (OCDE, UE, US EPA, FDA, etc.)	Standardized Study without Details, but correctly documented	Document insufficient for evaluation, systematic deficiencies	
11	POD : Point of Departure	Quantified Epidemiological Data, BMLD, etc. (PBPK)	NOAEL sensitive NOAEL	LOAEL sensitive, LOAEL, Other	
12	Uncertainty (or Assessment) Factors	1 – 100	> 100 – 1000	> 1 000 – 10 000	> 10 000
13a	Transpositions: Between Exposure Pathways	Non		Yes	
13b	Transposition: Animal to Human	Non	Yes		
13c	Transpositions : From in-Vitro	Non		Yes	
13d	Transpositions : From in-Silico	Non		Yes	
14	Study time-representatively	≥ chronic (> 180 d)	sub-chronic (90 d) to chronic (180 d)	< sub-chronic (< 90 d)	
15	Integration of bio-disponibility / Bio-resorption capacity (ex.: DIN 19 738)	Yes	Not known (100 %)	Known, but not considered	

Fig. 12: TRV selection criteria (F. KARG 2022)

Based on these selection criteria, it is possible to define e.g. the TRVs indicated in FIG. following (dating from the beginning of the year 2023). It is important to take into account that the Administrations of certain US States are very advanced in toxicological research and the publication of TRVs concerning PFAS, due to their strong presence in the chemical and oil industries (with heavy uses history of AFFF) or the strong presence of large industrial landfills (and the associated environmental pollution). These include the states of Texas, Michigan and New Jersey. These TRVs are often the basis for federal US-EPA PFAS TRV publications.

Substance	Cancerogen / not cancerogen	Chronic toxicological value			Species	Sigle	Security Factor	Organization
		Exposure path	Target organ	Value				
PFBA	NC	oral	Hepatic	2,9 µg/kg/d	Rate	RfD	NOAEL / 2400	TCEQ 2016
		inhalation	Hepatic	10 µg/m³	Rate	RfC	from oral value	TCEQ 2016
PFPeA	NC	oral	Hepatic	3,8 µg/kg/d	Rate	RfD	same than PFHxS LOAEL/(263*300)	TCEQ 2016
PFHxA	NC	oral	Hepatic	3,8 µg/kg/d	Rate	RfD	same than PFHxS LOAEL/(263*300)	TCEQ 2016
PFHpA	NC	oral	Hepatic	25 ng/kg/d	Rate	DJT	Extrapolation of DJT of Health Canada	ANSES 2017
PFOA	NC	oral	Hematologic	0,86 ng/kg/d	Rate	TDI	BMDL5	UBA 2020 BfR & EFSA 2018
			Hepatic, Mammar, Hematologic	12 ng/kg/d	Mice	RfD	LOAEL (81*100)	TECQ 2016
		inhalation	Hepatic	4,1 ng/m³	Rate	RfC	NOAEL / (81*3000)	TCEQ 2016
	C	oral	Testicular tumors	2,52 (mg/kg/d)⁻¹	Epidemio	SF	-	New Jersey 2017
PFNA	NC	oral	Hematologic	2,5 ng/kg/d	Mouse	RfD	NOAEL / 300	EPA IRIS 2019 New Hampsire DES 2019
		inhalation	Lung, respiratory system	28 ng/m³	Rate	RfC	NOAEL / (81*30 000)	EPA IRIS 2019 TCEQ 2018
PFDA	NC	oral	Hepatic	15 ng/kg/d	Rate	RfD	NOAEL / (81*1000)	TCEQ 2016
		inhalation		53 ng/m³	Rate	RfC	from oral value	TCEQ 2016
PFBS	NC	oral	Hematologic and renal	1,4 µg/kg/d	Rate	RfD	NOAEL / (142*300)	TCEQ 2016
		inhalation		4,9 µg/m³	Rate	RfC	from oral value	TCEQ 2016
PFHxS	NC	oral	Hematologic and thyroïdal	3,8 µg/kg/d	Rate	RfD	LOAEL / (263*300)	TCEQ 2016
		inhalation		13 ng/m³	Rate	RfC	from oral value	TCEQ 2016
PFHpS	NC	oral	Hepatic	0,43 ng/kg/d	Rate	TDI	Potency Factor : 0,6-2	UBA 2020, EFSA 2018, BfR 2018
PFOS	NC	oral	Hepatic	1,86 ng/kg/d	Monkey	TDI	NOAEL	UBA 2020 BfR & EFSA 2018
		inhalation	Thyroidal, neurological and foetal development	81 ng/m³	Rate	RfC	from oral value (23 ng/kg/j)	TCEQ 2016
PFOSA	NC	oral	Mammary glands	12 ng/kg/d	Mice	RfD	Same than PFOA NOAEL/(81*300)	TCEQ 2016
		inhalation		4,1 ng/m³	Rate	RfC	same than PFOA NOAEL/(81*3000)	TCEQ 2016

Fig. 13: Choice of certain TRVs according to the criteria in FIG. 7 (F. KARG 2022):

ANSES: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (2017)
ATSDR: Agency for Toxic Substances and Disease Registry
EFSA: European Food and Safety Authority
IRIS : Integrated Risk Information of Substances (U.S. - EPA)
UBA : Umweltbundesamt (Germany)
BfR: Bundesinstitut für Risikobewertung (Germany)
OEHHA : Office of Environmental Health Hazard Assessment
WHO: World Health Organization
RIVM : Netherlands Environmental & Health Institute
MDHHS: Michigan Department of Health and Human Services, Division of Environmental Health
TCEQ: Texas Commission on Environmental Quality
NJ-DWQIHES: New Jersey Drinking Water Quality Institute Health Effects Subcommittee
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A complementary step to the EQRS (or ARR, TERQ, HRA) is the definition of health compliance control values, in the form of MACs (Maximum Admissible Concentrations) by integrating an additivity of the risks of pollutants concerning the same targets and toxicological effects, for maximally acceptable Excess Individual Risks (of cancer): ERI < 10E-5 or a Systemic Risk Index of IR < 1 (= DJE / DJT: Daily Exposure Dose over Tolerable Daily Dose). MACs are commonly used in the form of Sanitary Control Values, in order to verify or co-develop corrective action objectives, or even depollution objectives. Management measures, e.g. depollution are based in France on a Management Plan, a definition of the Source Zones of concentrated pollution and then a Cost-Benefit Balance Sheet of the different management and treatment methods and technologies.

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