PFAS
From hero to zero

NVVA Symposium

9 april 2025

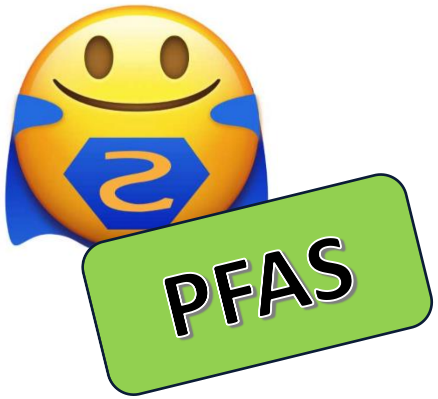
Erik Kateman

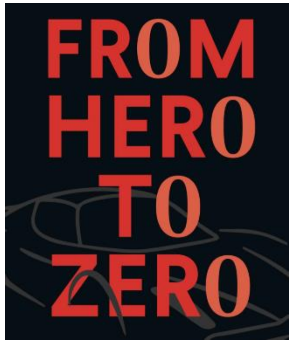
Arbeidshygiënist

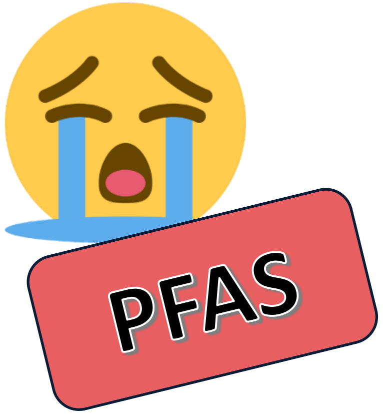
aspen OSS B.V.

Agenda

- Inleiding
- Eigenschappen
- Toepassingen
- Restrictie voorstel
- Stand van zaken
- Discussie







Conflict of interest

Werkzaam in bedrijf dat farmaceutische grondstoffen produceert & arbeidshygiënist

API productie = **bouwen van biologisch actieve moleculen**

- Complexe chemische reacties
- Reactieve chemicaliën
- Onzuiverheden voorkomen
- Veel regelgeving (Arbowet, medicijnen, Seveso)

- Keuze chemicaliën op basis efficiency, kwaliteit & opbrengst API
- Keuze materialen voor proces installaties op basis van duurzaamheid en veilige producties

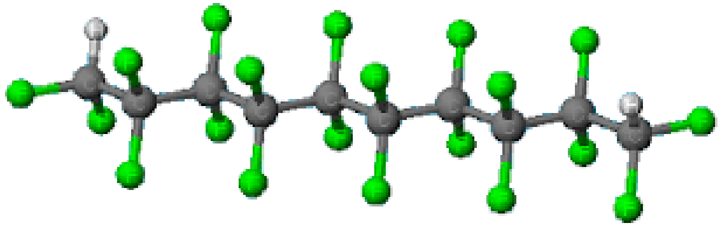
aspen OSS B.V.

Even voorstellen - PFAS

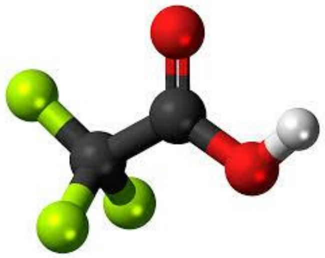
PFAS = Per- and polyfluoroalkyl substances

Definitie vanuit EU perspectief (Restrictievoorstel):
Any substance that contains at least one fully fluorinated methyl (CF_3-) or methylene (-CF_2-) carbon atom (without any H/Cl/Br/I attached tot it).

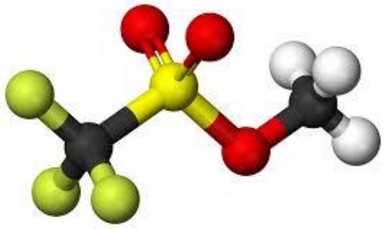
Schatting : 10.000 stoffen



Teflon, $-(CF_2CF_2)-$



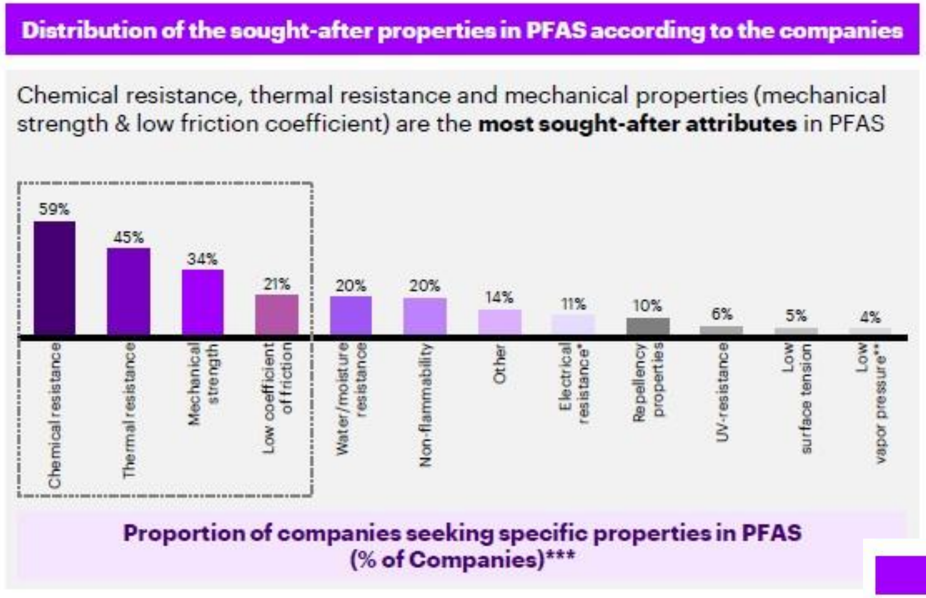
Trifluoroacetic Acid



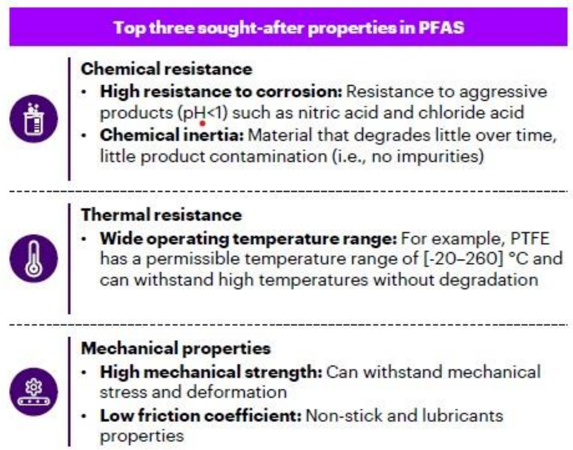
TMS Triflate

Eigenschappen

- Fluoropolymers – zoals PFTE
  - Hoge chemische bestendigheid
  - Hoge temperatuur bestendigheid
  - Mechanisch sterk
  - Lage frictie
  - Inert



Bron: Accenture/CEFIC The Use of PFAS in Chemical Plant Equipement



- Proces chemicaliën
  - Voldoen aan criteria voor efficiënte and effectieve chemische reactie
  - TFA in Peptide synthese
  - Hoge zuurgraad, makkelijke eliminatie, hoge oplosbaarheid in water/organische oplosmiddelen

Toepassingen – procesinstallaties productie API

- Fluoropolymers
  - O-ringen/pakkingen
  - Coating van leidingen & slangen/pijpen
  - Kleppen

Charging isolator

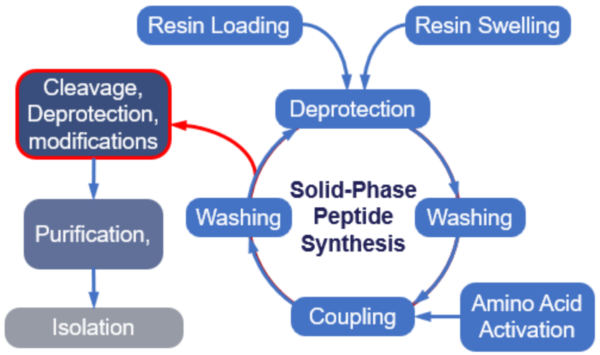
Glas gecoate reactor

Bron: ISPE/EFPIA Use of Fluoropolymers and Fluoro-Elastomers in Medicinal Products Manufacturing Facilities

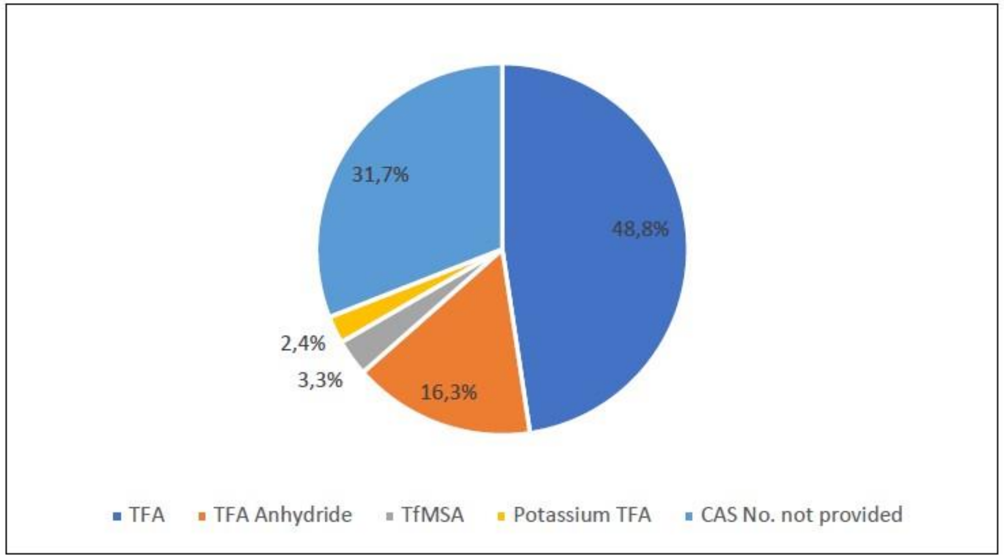
aspen OSS B.V.

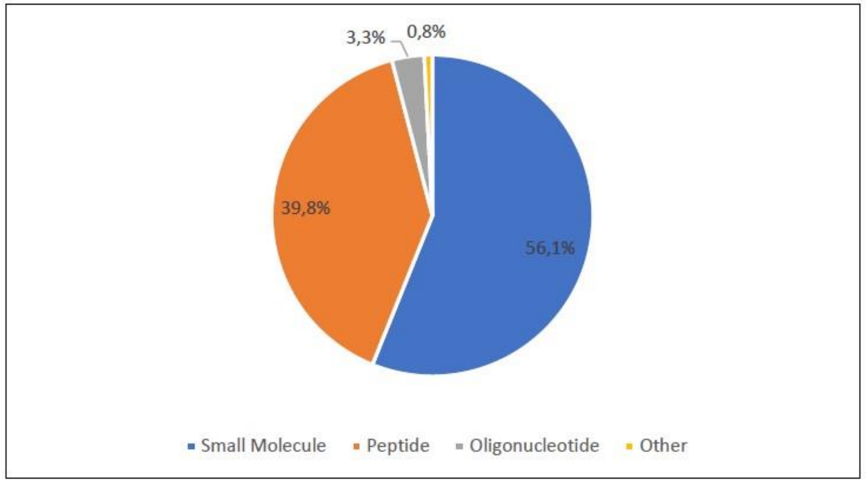
Toepassingen – synthese API

- Chemicaliën
  - Trifluoroacetic Acid (TFA)
  - Trifluoromethanesulfonic acid,
  - Trimethylsilyl trifluoromethanesulfonate
  - Trifluoroacetic Acid Anhydride
  - Potassium TFA



TFA used in acidolytic deprotection step. All commonly used to protect groups in peptide synthesis are designed for deprotecting with TFA. This concept is in use since early '60s





Bron: AESGP/EFCG/EFPIA/Medicines for Europe/VE
Human Health Medicinal Products Sector Survey – Impact of proposed PFAS Restriction

Toepassingen – laboratorium apparatuur

51191306	PTFE dosing tube Ø 3.2 mm
Material	PTFE
Size	Ø 3.2 mm, length 2.5 m
Quantity	1

	PTFE cover plate, 6 ports 1 x ST10, 2 x ST14, 2 x 1/2" NPT, center 3/8" NPT
Material	PTFE
Size	Inner Ø 52 mm
Quantity	1

Catalogus Synthesis Workstations bevat 369 onderdelen and accessoires gemaakt van PTFE

51162682	Half-moon stirrer blade One-piece reactor, 1000 mL
Material	PTFE
Size	19 mm x 71 mm
Quantity	1

Needed items: 51162681 Glass stirrer shaft
30138110 Stirrer shaft, magnetic drive

Toepassingen – arbeidshygiënische metingen

PTFE Filtermedia

Aerosol monitor

UHPLC/Mass Spectrometer

Toepassingen – arbeidshygiënische metingen

Aerosol monitor

PTFE Filtermedia

UHPLC/Mass Spectrometer

Informatie verzamelen is lastig.
“Wij houden ons aan de wet”
Maar uitspraken doen over wetgeving in wording: blijkt moeizaam.
PTFE (Teflon) een PFAS: veel onbekendheid

PFAS Restrictievoorstel – ingediend

ECHA
EUROPEAN CHEMICALS AGENCY

ANNEX XV RESTRICTION REPORT

PROPOSAL FOR A RESTRICTION

SUBSTANCE NAME(S): Per- and polyfluoroalkyl substances (PFASs)

IUPAC NAME(S): n.a.

EC NUMBER(S): n.a.

CAS NUMBER(S): n.a.

CONTACT DETAILS OF THE DOSSIER SUBMITTERS:

Ingediend op
13 januari 2023 door:

Nederland
Duitsland
Zweden
Noorwegen
Denemarken

Voorpublicatie door
ECHA op 7 Februari 2023

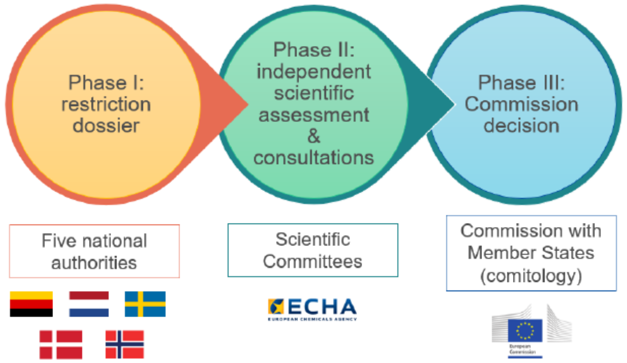
REACH Restrictie – Artikel 67

- Een Risk Management Optie binnen REACH om het gebruik van schadelijke chemicaliën te verminderen
- Tot op dit moment zijn er 74 restricties opgenomen in Annex XVII van REACH

- Vaak gaat het om een beperking van een specifieke stof voor een specifiek gebruik
  - Methanol mag niet gebruikt mag worden in ruitensproeivloeistof voor consumenten
  - Dichloormetaan mag niet gebruikt mag worden in verfstripper voor consumenten en professionals

- Maar ook bredere restricties van gebruik in consumentenproducten komen voor:
  - CMR stoffen in kleding
  - CMR, sensiterende, corrosieve stoffen in tattoo vloeistoffen

- Het wetgevende proces bestaat uit:
  - Publicatie restrictievoorstel
  - Publieke consultaties & beoordeling
  - Eindbeslissing over wetgeving door Europese Commissie



aspen OSS B.V.

PFAS Restrictievoorstel – hoofdlijn & derogatie “active substances”

Proposed restriction - Annex XVII entry PFASs (Restriction Option 2)

Column 1 Designation of the substance, of the group of substances or of the mixture	**Column 2** Conditions of restriction
Per- and polyfluoroalkyl substances (PFASs) defined as: Any substance that contains at least one fully fluorinated methyl (CF_3-) or methylene (-CF_2-) carbon atom (without any H/Cl/Br/I attached to it). A substance that only contains the following structural elements is excluded from the scope of the restriction: CF_3-X or X-CF_2-X′, where X = -OR or -NRR′ and X′ = methyl (-CH_3), methylene (-CH_2-), an aromatic group, a carbonyl group (-C(O)-), -OR″, -SR″ or –NR″R‴; and where R/R′/R″/R‴ is a hydrogen (-H), methyl (-CH_3), methylene (-CH_2-), an aromatic group or a carbonyl group (-C(O)-).	1. Shall not be manufactured, used or placed on the market as substances on their own; 2. Shall not be placed on the market in: a. another substance, as a constituent; b. a mixture, c. an article in a concentration of or above: i. 25 ppb for any PFAS as measured with targeted PFAS analysis (polymeric PFASs excluded from quantification) ii. 250 ppb for the sum of PFASs measured as sum of targeted PFAS analysis, optionally with prior degradation of precursors (polymeric PFASs excluded from quantification) iii. 50 ppm for PFASs (polymeric PFASs included). If total fluorine exceeds 50 mg F/kg the manufacturer, importer or downstream user shall upon request provide to the enforcement authorities a proof for the fluorine measured as content of either PFASs or non-PFASs. 3. Paragraphs 1 and 2 shall apply 18 months from entry into force of the restriction. 4. By way of derogation, paragraphs 1 and 2 shall not apply to a. active substances in biocidal products within the scope of Regulation (EU) 528/2012 b. active substances in plant protection products within the scope of Regulation (EC) 1107/2009 c. active substances in human and veterinary medicinal products within the scope of Regulation (EC) No 726/2004, Regulation (EU) 2019/6 and Directive 2001/83/EC

The use of certain fluorinated fragments in PPP, BP and MP contributes to the release of PFASs to the environment. In the sense that persistent PFASs are formed as degradation products, the ambition should be a minimization. This could be achieved by including the active substances that fulfil the PFAS definition in the current restriction proposal. However, it is recognized that the use of these substances is specifically regulated in the EU with extensive evaluations and approval processes by designated bodies with specific expertise and experience. Hence, it is proposed to derogate the use of PFASs as active substances (but not the use of PFASs as co-formulants) in PPP, BP and MP in the restriction proposal for PFASs. At the same time, however, it is acknowledged that the predominant concern for the restriction, i.e. persistence, is not sufficiently taken into account during the current authorization processes following PPP, BP and MP regulations. Given the risks associated with

Zeer beperkte derogatie voor API:
enkel als ze ook een PFAS zijn

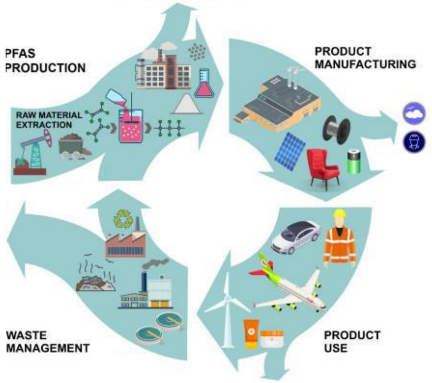
Geen derogatie voor gebruik van PFAS:
- tijdens de synthese van API
- in productie apparatuur chemische industrie
- in lab/analytische apparatuur

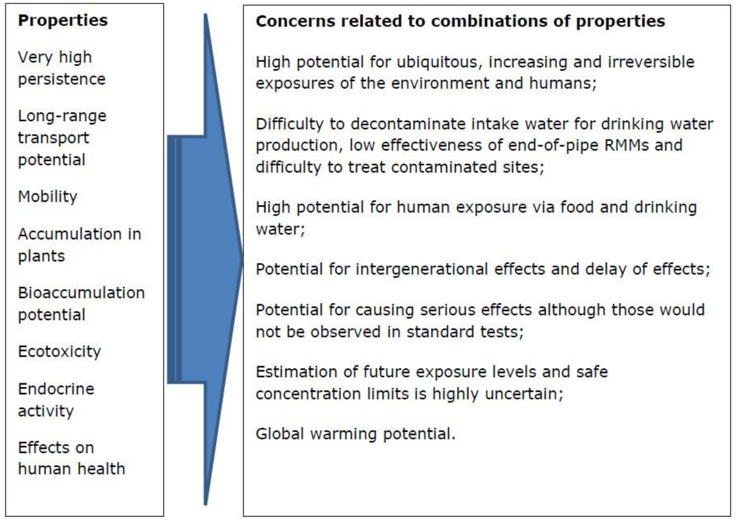
PFAS Restrictievoorstel – hoofdlijnen

- Scope is heel breed
  - Gaat over (bijna) alle stoffen met C-F bond (+-10.000 stuks)
  - Inclusief fluoropolymers and F-gassen
- Persistentie is maatgevend in termen van risico
  - Argumentatie wisselend voor verschillende PFAS-en
  - Geschatte emissie 4.4 miljoen ton over 30 jaar als er geen maatregelen genomen worden
- Derogaties zijn toegestaan op basis van beschikbare alternatieven
  - Voor zover bekend bij opstellers voorstel
- Derogaties zijn gebruik specifiek en meestal in tijdsduur beperkt

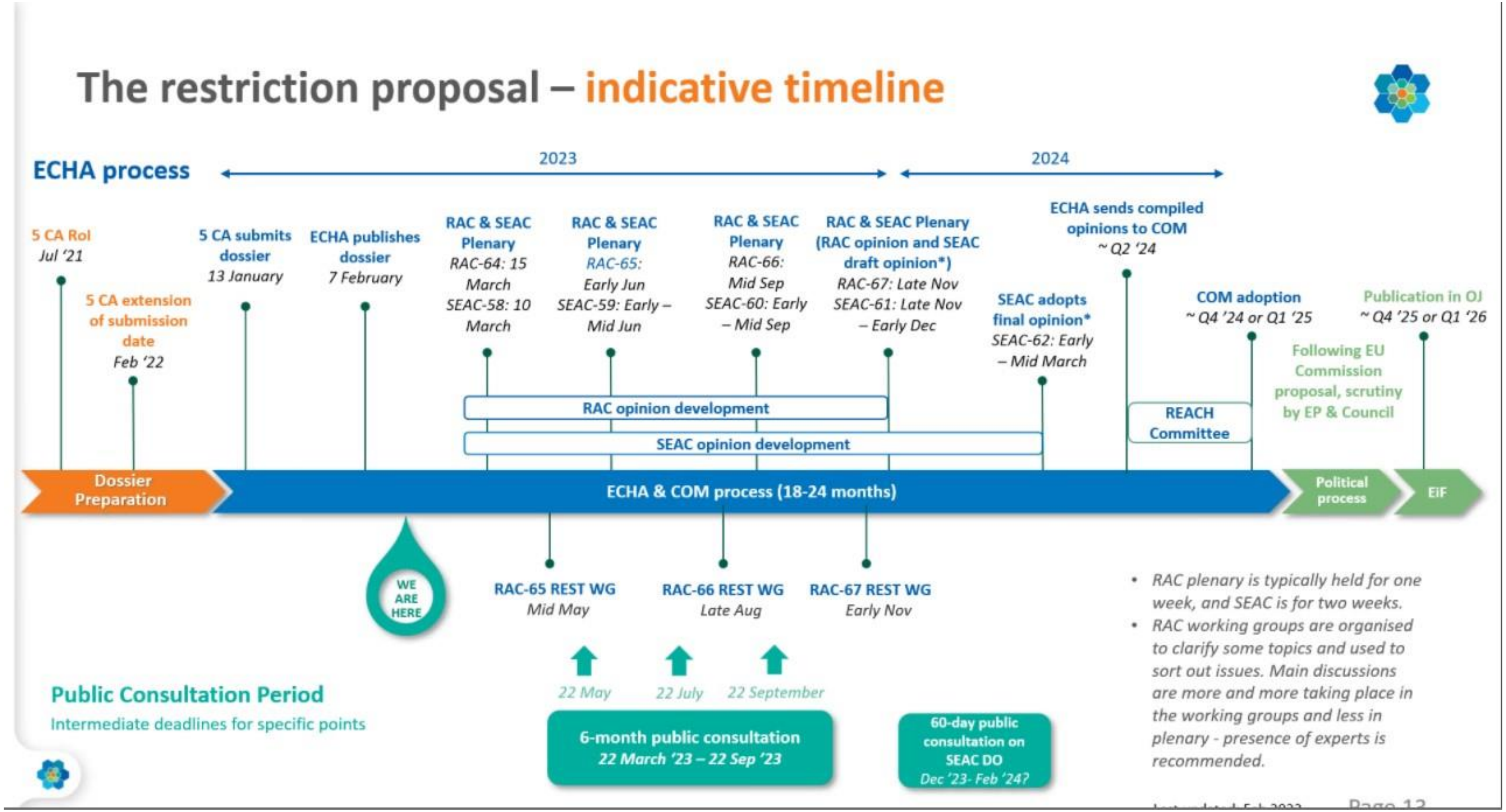
RO1: Volledig verbod

RO2: Verbod met derogaties





PFAS Restrictievoorstel – tijdslijnen (als verwacht in februari 2023)



Publieke consultatie – chemische en farmaceutische industrie

Chemische industry – focus op fluoropolymers

Human Health medical products sector – focus op fluoropolymers en process chemicaliën

AESGP efcg efpia medicines for europe

Human Health Medicinal Products Sector Survey - Impact of Proposed PFAS Restriction on Patient Access to Medicines & EU Strategic Autonomy

Public Consultation PFAS Restriction proposal
Missing uses: PFAS in synthesis of active pharmaceutic ingedients

PFAS in chemical synthesis of Active Pharmaceutic Ingredients
From the user perspective of Aspen Oss

September 22th, 2023

CONFIDENTIAL

ISPE efpia

Use of Fluoropolymers and Fluoro-Elastomers in Medicinal Product Manufacturing Facilities

Public Consultation PFAS Restriction proposal
Missing uses: fluoropolymers in manufacturing Active Pharmaceutic Ingredients

Fluoropolymers in the manufacturing of Active Pharmaceutical Ingredients
From the user perspective of Aspen Oss

September 22th, 2023

CONFIDENTIAL

Ook arbeidshygiëne !!!!

aspen OSS B.V.

Publieke consultatie – alle inzendingen (5642)

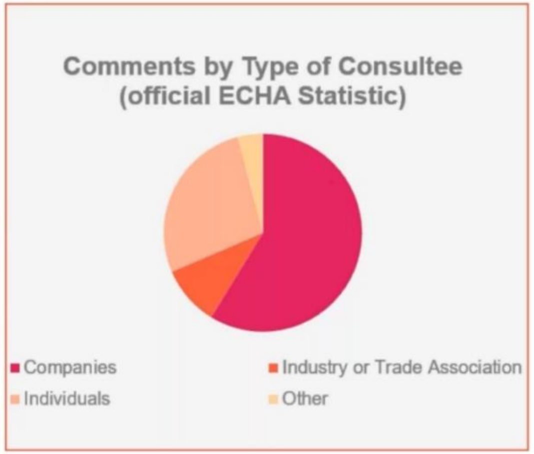
Consultation Insights – Analyzing the Data

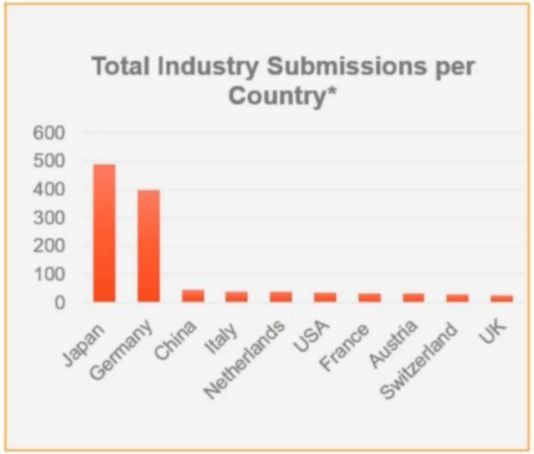
>5,600
total submissions

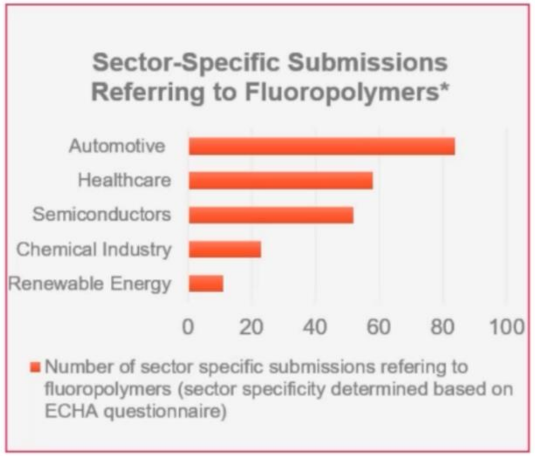
>4,400
individual organizations, companies and individuals

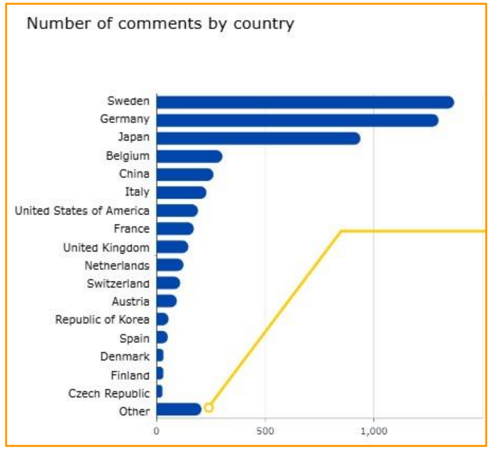
Numerous industry submissions
defending the critical uses of fluoropolymers

Alle bijdragen aan de consulatie moeten bekeken worden!

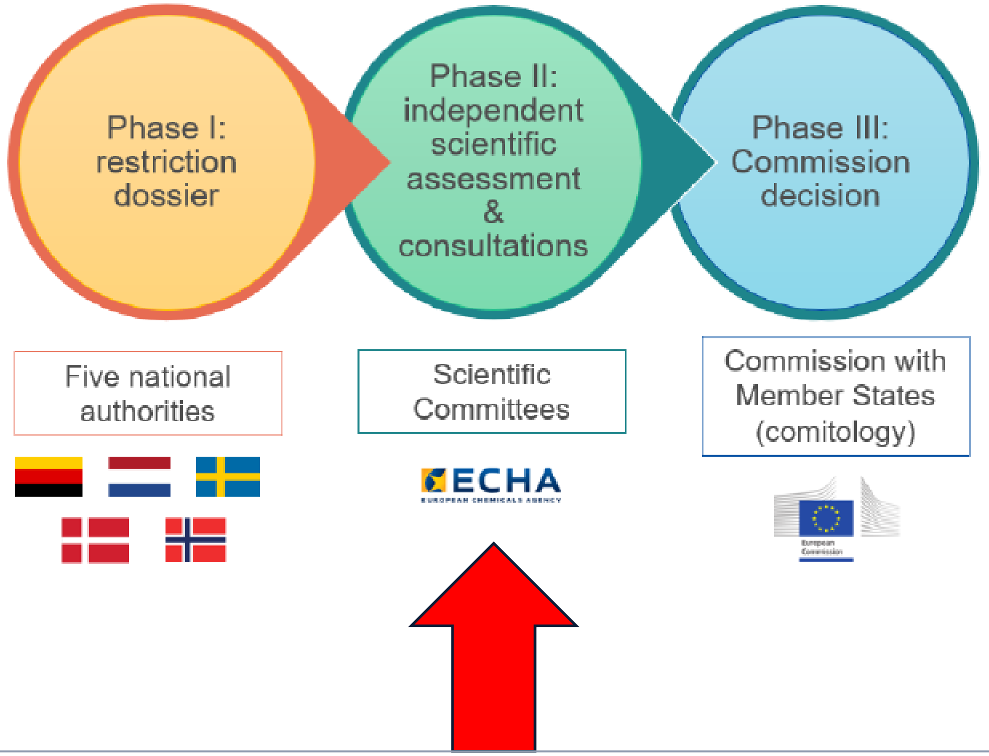








PFAS Restrictievoorstel – Stand van zaken



Risk Assessment Committee (RAC)
Socio-economic Analysis Committee (SEAC)

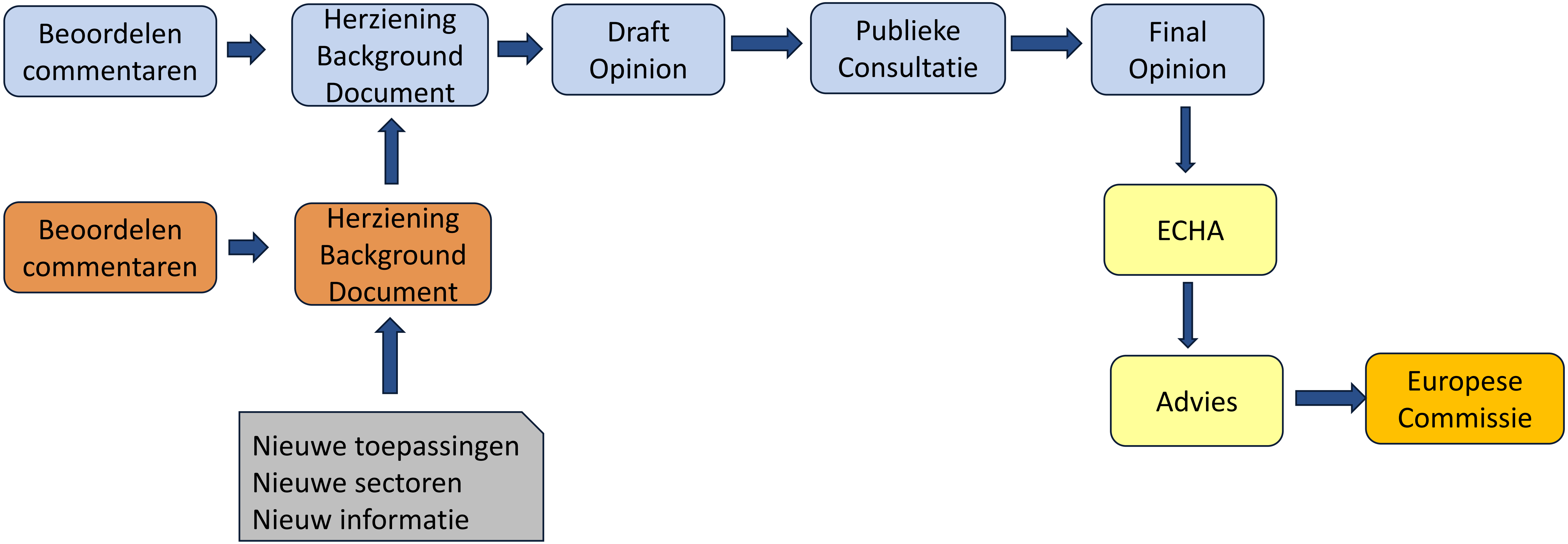
Dit zijn onafhankelijke wetenschappelijke commissies

Fase II - Beoordelen 5642 commentaren

Dossier indieners

RAC/SEAC

ECHA



Fase II – Behandeling commentaren in RAC/SEAC

- **Sectorgewijze bespreking & beoordeling door RAC/SEAC**
  - Juni 2024: consumentenproducten, cosmetica, skiwas, metaalbehandeling
  - September 2024: textiel, bekleding, leer, tapijten, kleding, voedselverpakkingen, olie- en mijnbouw
  - November 2024: bouwmaterialen, textiel, bekleding, leer, tapijten, kleding, voedselverpakkingen,
  - Maart 2025: fluorhoudende gassen, transport & energie
  - Juni 2025: medische hulpmiddelen, smeermiddelen, transport & energie, elektronica & semiconductors
  - Na Juni 2025: elektronica & semiconductors, **resterende toepassingen**

- Draft opinion RAC/SEAC ????
- Final opinion RAC/SEAC ????
- Advies ECHA aan EC ????

Nieuw:
- RO3: andere restrictie opties (strict conditions)
- Nieuw sectoren & toepassingen worden toegevoegd

Tijdslijnen onbekend

!!!!

Fase II – laatste ontwikkelingen

ECHA/Dossier indieners

- Geen wijzigingen in prioritering op basis van economisch belang verschillende sectoren
- Geen splitsing in voorstel voor wat betreft consumenten en industrieel gebruik
- RO 3: nieuwe restrictieoptie; derogatie voor gebruik met "strict conditions"

French lawmakers vote to ban 'forever chemicals' except in cooking utensils
(Cosmetics, clothing ski-wax)

ECHA
EUROPEAN CHEMICALS AGENCY

Forum for Exchange of Information on Enforcement

Advice on enforceability of the Annex XV restriction proposal regarding:

"Per-and polyfluoroalkyl substances (PFAS)"

Lidstaten EU

- Frankrijk heeft wetgeving geïmplementeerd met verbod PFAS in consumenten producten (ski wax, textiel)
- Denemarken (= indiener!) heeft verbod PFAS in consumenten producten in voorbereiding

Germany's Scholz calls for pragmatic approach to 'forever chemicals'

Politici

- Robert Habeck: wetgeving zou ontheffingen voor "key technologies" mogelijk moeten maken
- Macron & Scholz: chemicaliën wetgeving beter risk-based dan het toepassen van breed verbod groepen stoffen (May 29th 2024)
- Scholz: Pragmatische benadering van forever chemicals (August 28th 2024)

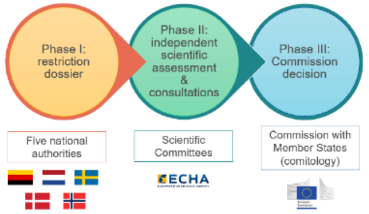
European Commissie

- Mission letters nieuwe Europese Commissarissen : Chemicals Industry Package – snel duidelijkheid verschaffen over PFAS

aspen
OSS B.V.

Fase III – Besluit Europese Commissie

REACH Committee → European Commission Adoption → European Parliament Scrutiny → Entry into force



Tijdslijnen onduidelijk.
Sommige suggereren Draft opinion eind 2025, Final opinion eind 2026, In werking 2028

Jessika Roswall
Commissioner
Environment, Water Resilience and a Competitive Circular Economy

BAN THE USE OF PFAS IN CONSUMER PRODUCTS IS IMPORTANT TO PROVIDE CLARITY ON PFAS AS SOON AS POSSIBLE, NOTABLY ON THE USE OF PFAS IN CONSUMER AND INDUSTRIAL APPLICATIONS IS A PRIORITY. I WOULD SEEK TO BAN PFAS IN CONSUMER PRODUCTS.

Stéphane Séjourné
Executive Vice-President
Prosperity and Industrial Strategy

I WILL TRY TO SPEED UP THE DEADLINES FOR PFAS. A REPORT ON PFAS IS EXPECTED IN MID-2026 BUT THIS IS TOO LATE. CONSUMER USES WILL BE BANNED BUT BEFORE TAKING A DECISION ON OTHER USES, SCIENTIFIC AND FACTUAL INFORMATION WILL BE CONSIDERED.

En in de tussentijd ……

- Onduidelijkheid over publicatie draft opinion SEAC
- Onduidelijkheid over tijdslijnen over besluitvorming Europese Commissie
- Onduidelijkheid over besluit Europese Commissie

- Wetenschappelijke & feitelijke bijdragen aan publieke consultatie helpen
- Deel praktijkvoorbeelden met wetgevers & politiek
- Besteed aandacht aan de belangrijkste drijfveer – vrijkomen van PFAS in het milieu

Neem contact op met:

Leveranciers meetapparatuur
Fabrikanten meetapparatuur
Laboratoria AH metingen
……..

Vergeet niet deel te nemen aan de volgende publieke consultatie!

Lidstaten EU besluiten!


FPP4EU

ABOUT US · ABOUT PFAS · BENEFITS & APPLICATIONS · NEWS AND EVENTS · LIBRARY · CONTACT US

Case studies

PFAS enabling the synthesis of therapeutic peptides

Therapeutic peptides are a promising and novel approach to treat many diseases including cancer, cardiovascular and autoimmune diseases. Some of them, such as Oxytocin and Leuprolide and are also included in the World Health Organization's (WHO) Essential Medicines List.

Trifluoroacetic Acid (TFA), a derivative of PFAS, is required as part of the production process. Peptides are built through a process called peptide synthesis, which involves the stepwise addition of amino acids to form a peptide chain. To make sure no unwanted chemical reactions occur, so called "chemical locks" are created, which need to be removed at the end of the process. In nearly all peptide synthesis the substance used for removing these "chemical locks" is TFA.

The use of TFA in peptide synthesis is a well established and effective method, due to its strong acidity, volatility and compatibility with most organic solvents. Some efforts have been made in order to find viable alternatives, but up to date there are no other solutions offering the same set of properties required in the process.

Under the Pharmaceutical Strategy for Europe, strategic autonomy is described as essential to enhance security of supply and address shortages in the pharmaceuticals manufacturing value chain. It is thus vital to ensure that the production of these medicines can be continued within the European Union, in order to ensure both domestic needs and exports to other parts of the world.

aspen OSS B.V.

Maar wel actief blijven !

Table 10. Current health impacts in the general population due to exposure to the most analysed PFASs (see Annex B.5.3.).

Health impact category	Type of health effects
Immune outcomes	Reduced vaccine responses in children
	Increased propensity of lower respiratory tract infections
	Increased risk of atopic dermatitis
	Asthma- and allergy-related outcomes (hypersensitivity)
Liver toxicity and metabolic disruption	Increased serum alanine transferase (ALT) which is a marker of liver toxicity and fatty liver diseases
	Increased total and LDL-cholesterol
	Increased risk of cardiovascular diseases
Reproduction and development	Reduced birth weight
	Effects on male and female fertility
	Effects on sex hormones and related outcomes
	Preterm delivery
	Miscarriage and preeclampsia
Carcinogenicity	Increased risk of renal cell carcinoma and kidney cancer
Thyroid functioning	Thyroid disease or changes in thyroid hormones

Table legend

- Evidence of an association between exposure and health effect, strengthened by new studies.
- Limited evidence of an association between exposure and health effect, supported by new studies.
- Suggestive evidence of an association between exposure and health effect, inconclusive new studies.

PFAS Restriction Proposal – Back-up slides

PFAS	RPF	Opmerking	Bron
TFA	0,002		2
PFBA	0,05		1
PFPeA	0,05	bovengrens; range 0,01 ≤ RPF ≤ 0,05	1
PFHxA	0,01		1
PFHpA	1	bovengrens; range 0,01 ≤ RPF ≤ 1	1
PFOA	1	**INDEX**	1
PFNA	10		1
PFDA	10	bovengrens; range 4 ≤ RPF ≤ 10	1
PFUnDA	4		1
PFDoDA	3		1
PFTrDA	3	bovengrens; range 0,3 ≤ RPF ≤ 3	1
PFTeDA	0,3		1
PFHxDA	0,02		1
PFODA	0,02		1
PFBS	0,001		1
PFPeS	0,6		1
PFHxS	0,6		1
PFHpS	2	bovengrens; range 0,6 ≤ RPF ≤ 2	1
PFOS	2		1
PFDS	2		1
HFPO-DA	0,06		1
DONA	0,03		1
6:2 FTOH	0,02		1
8:2 FTOH	0,04		1

Table 1. PFAS RPFs for assessment of direct oral intake exposure (matrices); https://www.rivm.nl/pfas/rpf

Tim Nonner (Unverified)

Example: assessment of drinking water

PFAS	Fictive concentration [ng/L]	RPF	PEQ [ng/L]
PFBS	5	0.001	0.005
PFHxS	1	0.6	0.6
PFHpS	1	2	2
PFOS	3	2	6
PFBA	5	0.05	0.25
PFPeA	5	0.05	0.25
PFHxA	6	0.01	0.06
PFHpA	3	1	3
PFOA	4	1	4
HFPO-DA	6	0.06	0.36
ΣPEQ			**16.5**

Sum of the equivalents can be further assessed as PFOA

[1] Bil et al., EC&T 40(3) 2021.
[2] Affourtit et al. 2023, RIVM-VSP Advies 14434A02.

PEQ calculation tool: https://www.rivm.nl/documenten/rivm-peq-tool-v2-16-mei-2024

aspen OSS B.V.