Christopher Correnti

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evaluations (with the exception of those eight new sectors[21] not evaluated in detail by RAC). As an overarching principle, RAC generally considers a full ban (RO1) to be more effective in limiting emission and uncontrolled risks than a ban with derogations (RO2 and RO3) that would result in continued emissions. An exception is the targeted derogation proposed by SEAC under "TULAC" for certain types of PPE to avoid possible serious risks to workers.

RAC acknowledges that the decision maker may decide to implement sector-/use specific derogations as proposed by the Dossier Submitter and/or SEAC. In such cases, RAC recommends adopting additional risk management measures to ensure associated emissions are minimised as described in section 3.4.2.1.3 of the RAC Opinion. This includes:

- The implementation of site-specific PFAS management plans to minimise PFAS emissions at industrial sites where PFAS and/or PFAS containing mixtures or articles above the concentration limits defined in section 3.4.3.1.3 are in use.
- The supply of information of the content of PFAS and instructions for safe use and disposal to downstream users (industrial and professional) and consumers of PFAS and/or PFAS containing mixtures or articles above the concentration limits defined in section 3.4.2.1.3.

RAC recognises that continued use of PFAS in (time-limited and unlimited) derogated uses as well as in spare parts would result in a need for continued manufacturing of PFAS. In such a case, RAC recognises that a derogation for PFAS manufacturing would be needed (see RAC sector-specific evaluation of PFAS manufacturing).

In this regard, the Dossier Submitter proposes a time unlimited derogation under 4m for the manufacturing of PFAS coupled with emission control measures reaching a specific minimum effectiveness (in the form of emission factors). RAC could not provide any view on the technical feasibility of the emission factors because this needs to be assessed specifically for each individual site. In addition, RAC has identified several challenges related to practicality of the calculation of the emission factors. RAC notes that in the case of a time-unlimited derogation, the emissions will continue beyond the assessment period.

Should the decision-maker consider a derogation for PFAS manufacturing is appropriate, RAC acknowledges that the establishment of emission limits (emission permits and environmental management system established by the Industrial Emissions Directive) is the most adequate measure to reduce the risk. This, if fully applied by local authorities and if supported by up-to-date BAT conclusions for PFAS manufacturing could offer a significant emission reduction potential; an effective enforcement would also be instrumental to achieve emission minimisation. However, at present and with the information available, RAC is not able to identify such emission limits.

RAC emphasises the importance of minimising emissions from PFAS manufacturing in case a derogation under 4 m is supported by the decision-maker. In view of the unfeasibility for RAC to define emission limits with the information available and the possible long time needed to develop BAT conclusions for PFAS manufacturing, RAC suggests to introduce requirements to implement site-specific PFAS management plans, including monitoring of emissions to the environment, for each PFAS manufacturing site. This is in line with the requirements proposed for other industrial sites, should their use of PFAS be allowed to continue. In addition, PFAS manufacturers should provide instructions for safe use and disposal to their downstream users

[21] The eight new sectors not evaluated by RAC are Printing applications, Sealing applications, Machinery applications, Other medical applications, Military applications, Explosives, Technical textiles and Broader industrial uses. See Annex I for a short description.

to ensure PFAS emissions are controlled along the whole life cycle.

3.4.3.1.6. Conditions for continued use

3.4.3.1.6.1. Reporting requirements (paragraphs 4 and 7)

The Dossier Submitter proposes that manufacturers, importers of PFAS or PFAS-containing articles as well as downstream users formulating PFAS-containing mixtures making use of any of the 13.5-year or longer derogations and for derogations relating to applications of fluorinated gases report annually to the Agency on the derogation that the intended use belongs to and the identity and quantity of the substances placed on the market in the previous year. Similar reporting requirements are proposed also for active substances derogated under paragraph 4 of the restriction proposal.

RAC considers these reporting requirements practical and enforceable. Although they may not have any direct impact on risk reduction, they would provide EU-level data on the use of PFAS in these derogated uses; RAC considers this information very relevant e.g. for the future review of the restriction and its effectiveness. RAC notes that the reporting obligations apply only to manufacturers, importers of articles and formulators, but not to downstream users of PFAS-containing articles and mixtures. RAC agrees with the Dossier Submitter that inclusion of down-stream users (except for industrial formulators) would have been impractical. RAC also recommends that reporting should apply to importers of PFAS-containing mixtures.

It is recognised that manufacturers, importers and formulators may have limited information on all the uses. However, RAC notices that importers of PFAS-containing mixtures are not specifically mentioned in paragraph 7 and should also be included. RAC notes Forum's proposal to automatize reporting as much as possible to allow automated data analysis as well as to provide enforcement with online tools to facilitate their work. RAC supports this proposal.

3.4.3.1.6.2. Site-specific PFAS management plans (paragraph 8)

RAC has reviewed the Dossier Submitter proposal on site-specific PFAS management plans. RAC concludes that they are not sufficient to achieve a significant risk reduction. Therefore, RAC has outlined its own proposal to improve PFAS site-specific management plans, which are considered more effective in minimising the emissions and subsequent risk. They shall be made available to competent authorities on demand. The site-specific PFAS management plans should describe measures taken and planned to minimise the emissions to the environment (Section 3.4.2.1.3 provides additional details on RAC recommendations for PFAS site specific management plan). RAC proposes that monitoring data on emissions collected by industrial users as part of the PFAS management plan should be reported to the Agency. For those actors with reporting obligations on PFAS as discussed in section 3.4.3.1.6.1. above, this reporting could be done simultaneously.

Furthermore, RAC considers that:

- this requirement should apply to industrial uses of PFAS with high emission potential and in particular to the industrial use of PFAS and PFAS-containing mixtures (e.g. formulation of mixtures, production of articles, etc.) that will be allowed to continue (e.g. derogated) once the 18-month transition period comes to an end as well as to PFAS manufacturing.

- PFAS management plans should cover all type of PFAS and should not be restricted to

fluoropolymers and PFPE, as proposed by the Dossier Submitter.

3.4.3.1.6.3. Additional conditions considered by RAC

RAC considers supply-chain communication on presence of PFAS essential to ensure minimisation of emissions in all relevant stages of life cycle. Therefore, conditions for manufacturers and importers of PFAS-containing materials/products for derogated uses should include also requirements ensuring effective supply-chain communication. This may occur via safety datasheets/technical datasheets or e.g. product passports. RAC notes that some sectors where RO3s have been developed by the Dossier Submitter, already contain a mention of such communication requirements.

RAC considers that a similar requirement ensuring effective supply-chain communication should be introduced for manufacturers and importers of PFAS-containing materials/products for all derogated industrial uses.

RAC recognises that for professional and consumer uses the above measures (site-specific management plans or supply-chain communication) would not be effective in reducing associated emissions. RAC notes the requirements in the restriction of synthetic polymer microparticles [microplastics] (Entry 78 of Annex XVII) which require products to be labelled with a statement: "This product contains microplastics." following information e.g. on safe use and disposal.

Similarly, RAC considers that for professional and consumer uses of articles and mixtures containing PFAS, labelling requirements should be introduced; those labelling requirements should inform on the presence of PFAS and recommend disposal practices to minimise emissions during such uses.

3.4.3.1.7. Interaction with other relevant legislation (paragraph 9)

According to RAC's understanding, the Dossier Submitter's intention is to avoid overlap with any existing substance- or use-specific PFAS restrictions and instead aim to ensure that the strictest EU regulation applies. For instance, is noted that entries 28-30 of Annex XVII of REACH (covering restrictions of use of substances classified as carcinogenic, mutagenic or reproductive toxic) could partially overlap with the proposed restriction on PFAS

RAC notes that Forum commented on the wording of the first sentence in paragraph 9, which was considered ambiguous. Also, RAC has doubts whether the current text proposed by the Dossier submitter under paragraph 9 of the restriction proposal is clear enough to ensure that in cases of existing specific restrictions, the most stringent condition always applies and considers that this may need further clarification by the decision maker (e.g. guidance might be helpful in clarifying interactions across different restrictions).

3.4.3.2. SEAC conclusion(s)

See SEAC opinion.

3.5. SUMMARY OF UNCERTAINTIES

3.5.1. Uncertainties evaluated by RAC

RAC conclusion(s):

- Related to the hazard assessment, there are uncertainties related to the high number of PFAS falling under the scope of the restriction. Although persistence can be considered as a shared property of PFAS, other hazardous properties may vary qualitatively or quantitatively. This have not been considered in the assessment, but all PFAAs and PFAA precursors (including side-chain fluorinated polymers, PFPEs and fluorinated gases) have been considered as equal. RAC, however, has distinguished between PFAAs/PFAA precursors and fluoropolymer particles.
- RAC highlights several uncertainties related to the RAC assessment of emissions: the main uncertainties are related to the limited information on use volumes, unclear description of uses and to the fact that due to lack of detailed information, emission estimates are generally based on the use of default emission factors
- In addition, for many sectors, there is limited or lack of data on imports. In addition, RAC wants to emphasise the issue of cross-border pollution which have not been considered. For example, in the case of fluorinated gases, majority of manufacturing (and related emissions) occur outside EU and have not been covered in the assessment.
- RAC also points out that RAC emission estimates focus on PFAA/PFAA precursors and do not account for fluoropolymer particle emissions.
- However, although RAC recognises several uncertainties related to the assessment of emissions, RAC is rather confident on the order of magnitude of estimated emissions.
- The main uncertainties related to the assessment of the risks of alternatives are related to the fact that conclusions are based on hazard data only, which in some cases may have been limited.
- There are some uncertainties concerning the sensitivity and harmonisation/standardization of the analytical monitoring methods and related to the practical enforcement and monitoring of requirements related to the site-specific management plans and labelling/supply-chain communication.
- Regardless of these uncertainties, RAC is however confident that its overall conclusions are robust.

Key elements underpinning the RAC conclusion(s):

An overview of the main uncertainties identified are given below.

Table 9: Overview of uncertainties identified by RAC

Topic	Uncertainty	Impact (minor/moderate/ major)
Sector specific evaluations: Scope	Different terminology – of uses in the Background Documents and unclarities in the boundaries across categories and sub-uses	Minor
	For some sectors (e.g. "Medical Devices", "Construction Products") the linkages to other sectors may result in overlaps and double counting. On the other hand, some uses and niche applications may not have been fully covered under a certain sector.	Minor/Moderate

Topic	Uncertainty	Impact (minor/moderate/ major)
Scope and Hazards	The Dossier Submitter has excluded some PFAS groups from the scope as non-persistent. RAC was not able to ascertain non-persistence of these compound groups although RAC recognised that some compounds within those groups may be non-persistent. Exclusion of chemicals from the scope due to their non-persistence requires case-by-case evaluation.	Moderate
Scope and Hazards	The restriction includes an extensive number of compounds, whose hazardous properties may vary qualitatively and/or quantitatively. The impact assessment makes no distinction between PFCAs/PFSAs, side-chain fluorinated polymers, PFPEs and various groups of fluorinated gases, despite the fact that they differ in potency, ability to form persistent arrowhead compounds and type of adverse effects. The only difference taken into account in the RAC evaluation is the difference between the toxicity of PFAAs/PFAA precursors and fluoropolymer particles.	Moderate
Scope / Volumes / Emissions	For some sectors, the Dossier Submitter was not able to allocate quantities to each use/sub-use. It is therefore unclear to what extent volume data covers the sub-uses defined in the scope of the assessment. This will also impact the emissions' estimation.	Minor/Moderate
Volumes	For some sectors, there is lack of correspondence between the applications described in the scope (Annex A) and the uses for which volume data is provided (Annex A). It is not clear to what extent volume data provided represents the defined scope.	Minor/Moderate
	For some sectors, there is no specific data for several uses and the volume data is based on general statistics. In other cases, the volume is based on single company data, raising concerns about the representativeness of the figure across the entire sub-use.	Minor/Moderate
	For some (sub-)uses, in some sectors, there is incomplete information on the PFAS total tonnage, the tonnage per use and the PFAS type used. Moreover, some uses might have not been captured by the respective sectors. In such cases, RAC concludes that volumes are underestimated.	Moderate/Major

Topic	Uncertainty	Impact (minor/moderate/ major)
	For some sectors, the data received from stakeholders was for the products on the market (i.e. use stage). The volumes for the "production" stage were based on "reverse calculation".	Minor
	For some sectors, there is limited or lack of data on imports.	Moderate
Volumes / Emissions / Effectiveness	Assumptions on the growth rate. RAC acknowledges that the growth rate is difficult to predict, given the various influences and challenges to take those into account (e.g. impact of legislative measures, technological developments).	Moderate
Emissions: release factors for waste	The available data on PFAS mineralisation during incineration are still limited and do not even allow to conclude about the order of the magnitude of the release factor. It is assumed that the RFs for incineration used in the RAC assessment probably represent the upper range of the true RF (and therefore do not underestimate emissions) but even this is uncertain given the scarcity of data on municipal waste incinerators.	Moderate/Major
Emissions	RAC has focused in its fluoropolymer emissions assessment on the emissions of monomeric leachables (PFAAs/PFAA precursors). There are uncertainties related to the RAC assumptions on the levels of leachable fractions in fluoropolymers. In addition, in the assessment of emissions from the use of fluoropolymers for the manufacturing of articles, RAC could not fully account for the emissions from hot processes.	Moderate
Emissions	The life-cycle stages considered by the Dossier Submitter partially differ from those established in ECHA Guidance R.12, R.16 and R.18 and the processes involved in each life stage are not described in detail. The difference in terminology of life cycle stages and the lack of detail descriptions of the processes associated to each life stage makes it challenging for RAC to determine whether all relevant stages have been thoroughly evaluated.	Moderate
	Use of default release factors, due to lack of monitoring data. The use of default release factors represents a worst-case approach that may lead to an overestimation of emissions.	Minor/Moderate

Topic	Uncertainty	Impact (minor/moderate/ major)
	However, in the absence of more specific data, default release factors are considered adequate.	
	The Dossier Submitter modified some release factors of standard ERCs, based on assumptions, which are difficult to verify. RAC understands modifications were made based on expert judgment and generally agrees with them.	Minor
	For some sectors, there are uncertainties related to volume and scope. In combination with the lack of a detailed description of the processes covered during the life-cycle stages and the potential omission of emissions from certain life-cycle stages (e.g., article manufacturing), there is uncertainty in the emission estimates.	Moderate
	For some sectors, the Dossier Submitter was not able to apply release factors to individual uses/sub-uses and merged them into broader categories. This approach reduces the granularity of the analysis and limits the accuracy that a use-specific application of release factors would provide.	Minor/Moderate
	Emissions from PFAS manufacturing were not considered in individual sectors. Emissions from manufacturing of PFAS used in the PFAS sector have not been quantified (are assessed horizontally under 'PFAS manufacturing' sector).	Moderate
Risk of alternatives	Limited information on identity, chemical composition and hazard of some alternatives. No assessment is possible in such cases.	Moderate
	For a substantial number of alternatives, the Dossier Submitter did not perform a hazard assessment. The relevance of these alternatives (included in Annex E but not in Appendix E2) is unknown to RAC.	Minor/Moderate
	Conclusions are mainly based on hazard data and CLP classification which was often based on notified classifications which is considered uncertain. No risk assessment was performed	Moderate
Effectiveness	For some sectors, the Dossier Submitter was not able to evaluate the impact on the effectiveness of the restriction of new legislation or recent regulatory measures (e.g. F-Gases Regulation, Batteries Regulation, ELV Regulation, WEE Directive, recently adopted PFHxA restriction).	Minor/Moderate

Topic	Uncertainty	Impact (minor/moderate/ major)
	The new legislation will impact the overall emissions estimate, which would probably be lower. The same applies with the new technological developments (e.g. rapid development of battery technologies). However, in many cases the overall conclusion is that emissions are underestimated due to data gaps in subuses/subsectors.	
Effectiveness and derogation analysis	RAC is not able to properly assess the possibility to implement the RO3 options presented by the Dossier Submitter for some sectors.	Moderate
Enforceability/ Monitorability	Proposed targeted concentration limits may not be currently achievable for certain PFAS with the available analytical methods.	Moderate
Enforceability/ Monitorability	There is lack of harmonisation/standardization of sampling, sample pre-treatment and analytical methods, which makes enforcement challenging.	Major
Enforceability/ Monitorability	There are uncertainties related to the practical enforcement and monitoring of site-specific management plans and proposed labelling/communication requirements.	Moderate

3.5.2. Uncertainties evaluated by SEAC

See SEAC Opinion

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Other references are included in the Background Document.

ANNEX I

Descriptions for the sectors containing uses of PFAS as identified in the Background Document

Note that RAC did not carry out detailed sector-specific evaluations for sectors 16 to 23, which are shown with their sector names in *italics*.

Sector	Description
01. PFAS manufacturing	The assessment of the PFAS manufacturing sector covers all process steps in the manufacture of PFAS compounds at the manufacture site, including the processing of PFAS at the manufacturing site. This category also covers the use of PFAS as polymerisation aids in the manufacture of fluoropolymers. Note that processing PFAS into articles or mixtures offsite (e.g., foam moulding or fluoropolymer extrusion) is excluded and considered as part of other relevant sectors (e.g., Transport or Food contact materials and packaging).
02. Textiles, upholstery, leather, apparel and carpets (TULAC)	The assessment of the TULAC sector covers the uses of PFAS in home textiles, consumer apparel, professional apparel and personal protective equipment (PPE), leather and home fabric treatment sprays. PFAS uses related to TULAC but NOT considered as part of this sector: • Packaging (considered as part of the Food contact materials and packaging sector) • Optical fibre weaving (considered as part of the Electronics and semiconductors sector) • Latex printing inks, including inks for printing on textile (considered as part of the Printing applications sector) • Components related to textile industry e.g., conveyor belts (considered as part of the Machinery applications sector) • Outdoor technical textiles, architectural membranes, other tensile fabrics and other construction applications, filtration and separation media, removable covers for industrial process equipment, medical applications, technical textiles in transport vehicles (considered as part of the Technical textiles sector) • Textiles in engine bays (considered as part of the Technical textiles sector)
03. Food contact materials (FCM) and packaging	The assessment of the Food contact materials and packaging sector covers the uses of PFAS in food and non-food packaging applications, non-stick coatings in consumer cookware and domestic appliances, and non-stick coatings in industrial bakeware. PFAS uses related to Food contact materials and packaging but NOT considered as part of this sector: • Packaging of medical devices (considered as part of the Medical devices sector) • Immediate/primary packaging of medicinal and pharmaceutical products for human and veterinary uses (considered as part of the Other medical applications sector) • Inks, lacquers and waxes used in non-FCM applications (considered as part of the Printing applications sector) • Non-intentionally added substances in (recycled) packaging materials (considered and discussed in the Impacts on Recycling and Circular Economy section, please see e.g. section E.3.4. of Annex E) • Advanced semiconductor packaging (considered as part of the Electronics and semiconductors sector) • Sealings, gaskets, piping and linings used in food and feed production (considered as part of the Sealing applications sector)

	• Conveyor belts, production/assembly line equipment, bearings and rollers used in food and feed production (considered as part of the Machinery applications sector) • Lubricants in industrial settings (considered as part of the Lubricants sector) • Membranes and filtration materials used in drinking water treatment (considered as part of the Technical textiles sector)
04. Metal plating and manufacture of metal products	The assessment of the Metal plating and manufacture of metal products sector covers the uses of PFAS in metal plating processes as well as in the manufacture of other metal products. Examples include wetting agents, mist/fume suppressing agents and processing aids in metal plating baths, coating of metal products and solvents in metal manufacturing. PFAS uses related to the manufacture of metal products but NOT considered as part of this sector: • Production of parts for engines and other applications in technical components (considered as part of the Transport sector) • Production of parts in machinery, as well as other industrial applications, such as sealings (considered as part of the Sealing applications or Machinery applications sectors) • Production of parts for military equipment (considered as part of the Military Applications sector) • Coatings and paints for metal components specifically used in construction and machinery (considered as part of the Construction Products and Machinery applications sectors) • Cover gases for use in magnesium casting (considered as part of the Applications of fluorinated gases sector) • Precision cleaning fluids (considered as part of the Broader industrial uses sector)
05. Consumer mixtures and miscellaneous consumer articles	The assessment of the Consumer mixtures and miscellaneous consumer articles sector covers the uses of PFAS in various mixtures and articles intended specifically for consumer use. Examples include cleaners and cleaning products, waxes and polishes, automotive windscreen care products, anti-fogging agents for eyewear, fishing lines, synthetic turf as well as lubricants and string materials used in musical instruments. PFAS uses related to Consumer mixtures and miscellaneous consumer articles but NOT considered as part of this sector: • Cosmetics (considered as part of the Cosmetics sector) • Ski waxes (considered as part of the Ski wax sector) • Home fabric treatments e.g. sprays used for stain repellence purposes (considered as part of the Textiles, upholstery, leather, apparel and carpets (TULAC) sector) • Consumer uses of lubricants, except for piano keys and strings of musical instruments (considered as part of the Lubricants sector) • Razor blade coatings (considered as part of the Metal plating and manufacture of metal products sector) • Electrical components for musical instruments (considered as part of the Electronics and semiconductors sector) • Spare parts are assessed as an overarching issue (please see Annex E, Section 3.3, of the Background Document)
06. Cosmetics	The assessment of the Cosmetics sector covers the uses of PFAS in cosmetic products and the use of trifluoroacetic acid (TFA) in the synthesis of peptides as cosmetic ingredients. PFAS uses related to Cosmetics but NOT considered as part of this sector: • Applications in manufacturing equipment used for the manufacture of cosmetics (depending on the application, these may be considered as

	part of e.g., the Sealing applications or Machinery applications sectors) • Packaging of cosmetics products (considered as part of the Food Contact Materials and Packaging sector) • Analytical instruments and equipment parts used in the cosmetics sector e.g., valves, tubing and connectors (considered as part of the Sealing applications sector. Analytical equipment in general is assessed as an overarching issue, please see the explanatory notes of the main report of the Background Document and in particular the sub-heading '*Scientific research and development*'). • Uses of PFAS in excipients, immediate packaging and drug delivery devices (considered as part of Other Medical Applications) • Active substances in human and veterinary medicinal products are exempted from the restriction proposal (please see in particular Section 2.2.3 of the Background Document main report)
07. Ski wax	The assessment of the Ski wax sector covers the uses of PFAS in ski wax that can be applied to traditional skis, snowboards and skin skis across different kinds of snow sports. Examples include blocks of wax, liquid wax, paste wax, powder wax, spray wax or mixtures for cleaning and impregnation. PFAS uses related to Ski wax but NOT considered as part of this sector: • Shoes and textiles for skiing (considered as part of the Textiles, upholstery, leather, apparel and carpets (TULAC) sector)
08. Applications of fluorinated gases	The assessment of the Applications of fluorinated gases sector covers uses of PFAS gases in various applications and uses. Examples include refrigeration, air conditioning and heat pumps, foam blowing agents, propellants, cover gases, clean fire suppressants, preservation of cultural paper-based materials and insulating gases. PFAS uses related to Applications of fluorinated gases but NOT considered as part of this sector: • Mobile air conditioning (MAC) (considered as part of the Transport sector) • Transport refrigeration (considered as part of the Transport sector) • Heat transfer fluids (i.e. fluids that guide heat/cold away from an application but do not actively cool the application) for immersion cooling and indirect cooling of electronics and semiconductors (considered as part of the Electronics and semiconductors sector) • Semiconductor manufacture (considered as part of the Electronics and semiconductors sector) • Solvents for cleaning (considered as part of the Broader industrial uses, Electronics and semiconductors, or Metal plating and manufacture of metal products sectors) • Carrier solvents for lubricants (considered as part of the Lubricants sector) • Metered dose inhalers (MDI) (considered as part of the Other medical applications sector) • Use of fluoropolymers in equipment e.g. O-rings, gaskets, or similar components (considered as part of the Sealing applications and Machinery applications sectors) • Use of fluorinated gases in various military both mobile and stationary applications (considered as part of the Military applications sector)
09. Medical devices	The assessment of the Medical devices sector covers uses of PFAS in various instruments, appliances and other articles intended for medical purposes in humans. Examples include implantable medical devices, invasive medical devices, non-implantable/non-invasive medical devices and packaging of medical devices. PFAS uses related to Medical devices but NOT considered as part of this sector:

	• Electronic equipment for medical imaging, MRI, X-ray, etc. (considered as part of the Electronic and semiconductors sector) • Medical electronics (considered as part of the Electronic and semiconductors sector), except electronics in implantable and invasive medical devices (considered as part of the Medical devices sector) • Diagnostic laboratory testing (considered as an overarching issue, please see the explanatory notes of the Main report of the Background Document and in particular the sub-heading '*Scientific research and development*') • Excipients in pharmaceutical products (considered as part of the Other medical applications sector) • Drug delivery devices where the device is part of a drug-device combination product, e.g. pressurized metered-dose inhalers (pMDIs), pre-filled syringes, pre-filled injection pens, autoinjectors and pre-filled on-body delivery system, transdermal patches (considered as part of the Other medical applications sector) • Immediate packaging for medicines (considered as part of the Other medical applications sector) • Engineered fluids for diagnostic laboratory (considered as an overarching issue, please see the explanatory notes of the Main report of the Background Document and in particular the sub-heading '*Scientific research and development*') • Fluorinated gases used in industrial processes related to medical applications e.g. medical lasers (considered as part of the Broader industrial uses sector) • Medical textiles, including blood filtration filters, transducer membranes, membranes for venting, and virus and contaminant filters and membranes from water, air and other media (considered as part of the Technical textiles sector) • Personal protective equipment (PPE) e.g., clothing and drapes (considered as part of the TULAC sector) • Construction applications in hospitals (considered as part of the Construction products sector) • Parts of analytical and medical equipment e.g. valves, tubing, connectors (considered as part of the Sealing applications sector) • Packaging other than for medical devices and medicines (considered as part of the Food contact materials and packaging sector)
10. Transport	The assessment of the Transport sector covers the uses of PFAS in transport vehicles, mobile machinery, and associated infrastructure. Examples are automotive vehicles, aerospace vehicles, watercraft vehicles, rail vehicles, agricultural and forestry vehicles, construction and industrial vehicles, and transport-related infrastructure. PFAS uses related to Transport but NOT considered as part of this sector: • Sealing applications e.g., gaskets, O-rings, pipe/tank linings (considered as part of the Sealing applications sector, except for hoses in combustion engines and hose linings in aerospace applications which are considered part of the Transport sector) • Machinery and equipment e.g., robotic arms, presses (considered as part of the Machinery applications sector) • Lubricants e.g., lubricants in engines and self-lubricating parts (considered as part of the Lubricants and Machinery applications sectors) • Metal plating e.g., mist suppressants (considered as part of the Metal plating and manufacture of metal products sector) • Electronical and electronic equipment in transport vehicles, excluding cable linings and coatings in transport vehicles (considered as part of the Electronics and semiconductors sector) • Batteries and fuel cells (considered as part of the Energy sector) • Immersion cooling (considered as part of the Electronics and semiconductors sector)

	• Optical fibres (considered as part of the Electronics and semiconductors sector) • Membrane textiles for mould-injection (considered as part of the Technical textiles sector) • Textiles in engine bays (considered as part of the Technical textiles sector) • Textile cover sheets e.g., convertible tops, vehicle protection covers (considered as part of the Technical textiles sector) • Filters e.g., for air conditioning systems (considered as part of the Technical textiles sector) • Interior textile treatments e.g., seats, carpets, roof linings (considered as part of the TULAC sector) • Anti-drip additives/flame-retardant additives in plastics (considered as part of the Electronics and semiconductors sector) • Acrylic foam tape (considered as part of the Sealing applications sector) • Fire extinguishers for aircraft e.g., 2-BTP (considered as part of the Applications of fluorinated gases sector) • Propellants for spray biocides in aircraft (considered as part of the Applications of fluorinated gases sector)
11. Electronics and semiconductors (Electronics)	The assessment of electronics covers the uses of PFAS uses in electronic components and assemblies including wires and cables, circuit boards, connectors, sensors, insulation of electrical components, coatings of electrical components, photonics, etc. Plastic additives (e.g., flame retardancy and anti-drip performance), heat transfer fluids for immersion cooling, cold plate cooling and vapor phase soldering in relation to electronics are also in scope. PFAS uses related to electronics but NOT considered as part of this sector: • Sealing applications e.g., gaskets, O-rings, pipe lining (considered as part of the Sealing applications sector) • Machinery applications e.g., conveyor systems, robotic arms (considered as part of the Machinery applications sector) • Technical textiles e.g., membranes, vents and filters (considered as part of the Technical textiles sector) • Lubricants e.g., for use in magnetic recording media (considered as part of the Lubricants sector) • Non-electronic industrial automation monitoring and control (IAMC) parts (considered as part of the Sealing applications or Machinery applications sectors) • All electrical parts (including wires) which are part of an implantable or invasive medical device (considered as part of the Medical devices sector) • Refrigerants (chillers) for cooling in electronics and semiconductor sector (considered as part of the Applications for fluorinated gases sector) • Electrical insulation gases (considered as part of the Applications for fluorinated gases sector) • Industrial precision cleaning other than specific uses related to chemical vapor deposition and etch cleaning in electronics and semiconductors (considered as part of the Broader industrial uses sector) • Non-electronic parts of sensors e.g. liners, filters, membranes and gaskets (considered as part of the Sealing applications, Machinery applications and Technical textiles sectors)
11. Electronics and semiconductors (Semiconductors)	The assessment of semiconductors covers the uses of PFAS in semiconductor manufacturing processes, including etching, chamber cleaning, wafer processing, photolithography and micro-electromechanical systems (MEMS). PFAS in semiconductor inspection equipment and semiconductor packaging are also in scope.

	PFAS uses related to semiconductors but NOT considered as part of this sector: • Sealing applications e.g., gaskets, O-rings, pipe linings (considered as part of the Sealing applications sector) • Machinery applications e.g., conveyor systems, robotic arms (considered as part of the Machinery applications sector) • Technical textiles e.g., membranes, vents and filters (considered as part of the Technical textiles sector) • Lubricants e.g., for use in magnetic recording media (considered as part of the Lubricants sector) • Non-electronic industrial automation monitoring and control (IAMC) parts (considered as part of the Sealing applications or Machinery applications sectors) • All electrical parts (including wires) which are part of an implantable or invasive medical device (considered as part of the Medical devices sector) • Refrigerants (chillers) for cooling in electronics and semiconductor sector (considered as part of the Applications for fluorinated gases sector) • Electrical insulation gases (considered as part of the Applications for fluorinated gases sector) • Industrial precision cleaning other than specific uses related to chemical vapor deposition and etch cleaning in electronics and semiconductors (considered as part of the Broader industrial uses sector) • Non-electronic parts of sensors e.g. liners, filters, membranes and gaskets (considered as part of the Sealing applications, Machinery applications and Technical textiles sectors)
12. Energy	The assessment of the Energy sector covers the uses of PFAS in renewable energy generation, hydrogen technology, manufacturing of chemicals via electrolysis, batteries and electrical grids. PFAS uses related to Energy but NOT considered as part of this sector: • Sealing applications e.g., pipe linings, tubing, tanks, O-rings, gaskets etc. (considered as part of the Sealing applications sector. Note that, in relation to sealing applications, PFAS used in the 'core' of membrane electrode assemblies (MEA) in fuel cells and electrolysers in energy applications are assessed in the Energy sector as part of hydrogen technology and manufacture of chemicals via electrolysis) • Machinery applications and equipment e.g., robotic arms, production and assembly line equipment (considered as part of the Machinery applications sector) • Lubricants in relation to energy applications (considered as part of the Lubricants sector) • Hydropower applications (considered as part of the Sealing applications and Machinery applications sectors) • Anti-drip additives in polymers (considered as part of the Electronics and semiconductors sector) • Power plants, including fossil fuel power plants, nuclear power plants, waste-to-energy plants and engine power plants (considered cross-sectorally as part of sectors such as Sealing applications, Machinery applications, and Electronics and semiconductors) • Oil and gas applications (considered cross-sectorally as part of sectors such as the Sealing applications, Machinery applications, Electronics and semiconductors, and Lubricants sectors) • Membranes e.g., HEPA-filter, H2 and zinc-air battery membranes, excluding membranes for fuel cells and electrolysers (considered as part of the Technical textiles sector)

	• Solid oxide electrolyser cell (SOEC) and Solid oxide fuel cell (SOFC) (considered as part of the Sealing applications sector) • Storage, refuelling and transport of hydrogen (considered as part of the Sealing applications and Machinery applications sectors) • Solvents for cleaning (considered as part of the Electronics and semiconductors, Broader industrial uses, or Metal plating and manufacture of metal products sectors) • Electrical grids, excluding PFAS uses in switchgear and circuit breakers, such as PTFE nozzles for arc quenching (considered as part of the Sealing applications, Machinery applications, Electronics and semiconductors, and Applications of fluorinated gases sectors) • Electronics e.g., wires and cables (considered as part of the Electronics and semiconductors sector) • Industrial automation monitoring and control (IAMC) (considered as part of the Sealing applications, Machinery applications and Electronics and semiconductors sectors) • Spare parts are assessed as an overarching issue (please see Annex E, Section 3.3)
13. Construction products	The assessment of the Construction products sector covers the uses of PFAS in building materials and construction products. Examples include roofing materials, paints and coatings, polymer additives for fire-safety purposes, impregnations, sealants, and adhesives. PFAS uses related to Construction products but NOT considered as part of the Construction products sector: • Architectural membranes and weatherproofing membranes, including vapour barriers, coated fabric and fiberglass coating (considered as part of the Technical textiles sector) • Sealings, PTFE thread sealing tape, valves and pipes (considered as part of the Sealing applications sector) • Flexible solar panels, renewable energy systems and film/coating of wind turbines/solar panels (considered as part of the Energy sector) • Foam blowing agents in roofing and fluorinated gases in foam insulation (considered as part of the Applications of fluorinated gases) • Wires and cables (incl. insulation) and electrochromic functionalities in e.g. glazing (considered as part of the Electronics and semiconductors sector) • Coil coating of metal products (considered as part of the Metal plating and manufacture of metal products sector) • Lubricants in manufacturing PEX-pipes and compression sleeves for underfloor heating (considered as part of the Lubricants sector) • Plain bearings for non-building applications (e.g. energy systems, cranes, lifts or elevators) in machinery/equipment, pumps, valves, gas installations and coil coating in manufacturing process (considered as part of the Machinery applications sector) • Anti-drip agents and flame retardants for electronics (considered as part of the Electronics and Semiconductors sector) • Explosives used in the construction applications (considered as part of the Explosives sector)
14. Lubricants	The assessment of the Lubricants sector covers the uses of PFAS in liquid or semi-fluid lubricant mixtures designed to remain viscous throughout their lifecycle, as well as PFAS additives in coatings that provide low-friction properties once cured or solidified. Examples include low-viscosity lubricants (base oils, mineral or synthetic, sometimes with additives), greases (base oil combined with a thickening agent and additives), solid/dry films (lubricant mixed with alcohol, water, or other volatile solvents), release agents (such as dry films used in manufacturing thermoplastics and elastomers) and carrier solvents for lubricants. PFAS uses related to Lubricants but NOT considered as part of this sector: • Lubricants for piano keys or the strings of musical instruments e.g., guitars, harps, ukuleles, violins, violas, lutes, and other old stringed

	instruments (considered as part of the Consumer mixtures and miscellaneous consumer articles sector) • Articles and complex objects e.g., bearings, bearing liners, pumps (considered as part of the Machinery applications sector) • Low friction sealings (considered as part of the Sealing applications sector) • Solvents e.g., for cleaning and dissolving purposes (considered as part of the Electronics and semiconductors and Metal plating and manufacture of metal products sectors) • General industrial precision cleaning fluids (considered as part of the Broader Industrial Uses sector) • EEE (electrical and electronic equipment) specialist equipment (considered as part of the Electronics and semiconductors sector) • Hydraulic oils (considered as part of the Transport or Broader industrial uses sectors)
15. Petroleum and mining	The assessment of the Petroleum and mining sector covers the uses of PFAS in petroleum extraction, mining operations, and downstream industries such as refineries, petrochemical plants, carbon capture and storage, and geothermal applications. Note that only non-polymeric PFAS are in the scope of this sector, while polymeric PFAS used in these industries are addressed cross-sectorial. PFAS uses related to Petroleum and mining, but NOT considered as part of this sector: • Piping, tubing, tanks etc. used in the production and transportation of oil and gas (considered as part of the Sealing applications sector) • Sealing devices in petroleum and mining applications e.g., sealants in O-rings, V-rings, gaskets, fittings, and seals (considered as part of the Sealing applications sector) • Anti-corrosive coatings of equipment and infrastructure (considered as part of the Construction products sector and the Machinery applications sector) • Cables, specialised uses in petroleum and mining (considered as part of the Electronics and semiconductors sector) • Membranes, diaphragms, filters etc. in petroleum and mining applications (considered as part of the Technical textiles sector) • Machinery, valves, pumps etc. in petroleum and mining applications (considered as part of the Sealing applications and Machinery applications sectors) • Bearings, skidways etc. in petroleum and mining applications (considered as part of the Machinery applications sector) • Lubrication of equipment (considered as part of the Lubricants sector) • Personal protective equipment (PPE) (considered as part of the TULAC sector) • Explosives in mining (considered as part of the Explosives sector)
16. Printing applications	The assessment of the Printing applications sector covers the uses of PFAS in various specific applications within printing, which are further organised in two use categories: consumables (e.g. toners, latex printing inks, PTFE wax, pigments and colourants, PTFE powders, photosensitive materials, surfactants used in printing equipment) and permanent parts (e.g. electrophotographic press units, kinetic printing components, printing plates (offset and letterpress printing), rollers). It should be noted that 'permanent parts' refer to components that are not consumed during use. However, while they are not used at the rate of consumables, they may still require replacement multiple times throughout the printer's lifespan - in some cases several times per year. PFAS uses related to Printing applications but NOT considered as part of this sector: • PFAS in printing inks, lacquers and coatings that are used for food contact materials (considered as part of the Food contact materials and

	packaging sector) • Solvents for 3D-printing (considered as part of the Broader industrial uses sector) • Lubricants (considered as part of the Lubricants sector) • Printed circuit boards and sensors (considered as part of the Electronics and semiconductors sector) • Components that are used in printing machinery, but are not directly associated with the actual printing process (considered as part of other sectors, e.g. sealing applications are considered in the Sealing applications sector)
17. Sealing applications	The assessment of the Sealing applications sector covers the uses of fluoropolymers (FPs) and perfluoropolyethers (PFPEs) in applications designed to (i) prevent unintended substance migration, (ii) contain pressure, and (iii) avoid contamination. Sealing applications are used across multiple sectors and may entail the use of FPs and PFPEs as substances/mixtures, in the manufacturing of FP/PFPE-containing sealing articles and during their service life as components in complex objects. Examples of sealing applications include seals, gaskets, piping, linings, valve parts, and packing. PFAS uses related to Sealing applications but NOT considered as part of this sector: • Hoses in combustion engines and hose linings in aerospace applications (considered as part of the Transport sector) • Cable linings (considered as part of the Electronics and semiconductors sector) • Vents for electronic components (considered as part of the Technical textiles sector) • PFAS used in the 'core' of fuel cells and electrolysers i.e., membrane electrode assemblies (MEA) or similar assemblies (considered as part of the Energy sector) • Sealants and adhesive products for specific construction purposes (considered as part of the Construction Products sector) • Lubrication of dynamic seals related to use cases where PFAS-based lubricants are applied, not the seals themselves (considered as part of the Lubricants sector) • Spare Parts (considered as an overarching issue in Annex E.3.3.)
18. Machinery applications	The assessment of the Machinery applications sector covers uses of fluoropolymers (FPs) and perfluoropolyethers (PFPEs) in industrial process equipment across various sectors, as well as in machinery applied for both professional and consumer uses, when such uses are not covered elsewhere in the Background Document. It includes the use of FPs and PFPEs as substances/mixtures, in the manufacture of FP/PFPE-containing machinery parts, and during their service life as components in complex objects. Examples include self-lubricating/low-friction elements, structural parts, machinery components and parts (e.g. bearings, belts, rollers, etc.) and protective/durable coatings in stationary and portable machinery not covered in the Transport sector. PFAS uses related to Machinery applications but NOT considered as part of this sector: • FP/PFPE coatings e.g., on needles, surgical equipment, tubes (such as implantable probes and stents), endoscopes and medical devices (considered as part of the Medical devices sector) • Wind turbine-blade protection coatings and PTFE nozzles for the quenching of electrical arcs in switchgear (considered as part of the Energy sector) • FP/PFPE used in bridge and building bearings, coatings for metal components, skidways for specific construction purposes (considered as part of the Construction products sector) • PFAS-based lubricant mixtures used for specialised 'external' coatings of the contact surfaces of articles where the primary function is to provide low-friction (considered as part of the Lubricants sector)

	• FP/PFPE used in diaphragms and membranes (considered as part of the Technical textiles sector) • Spare Parts (considered as an overarching issue in Annex E.3.3.)
19. Other medical applications	The assessment of the Other medical applications sector covers the uses of PFAS in excipients, immediate packaging and drug delivery devices. Examples include propellants in pressurized metered dose inhalers (pMDIs), excipients in medicinal products for ophthalmic and dermatological therapies, coatings in release liners and backing films for transdermal patches, PFOB as a processing aid in the manufacture of porous particles (excipients in pMDIs), blisters for solid oral dose formulations, coated rubber stoppers for vials/flasks for injectable medicinal products, coated packaging for transdermal patches, fluorinated HDPE packaging (FHDPE) used for some veterinary medicinal products, coated canisters in pMDIs, coated plungers in prefilled syringes, and pre-filled injection pens, and autoinjectors. PFAS uses related to Other medical applications but NOT considered as part of this sector: • Fluoropolymer-coated electronics in pre-filled on-body delivery systems (considered as part of the Electronic and semiconductors sector) • Lubricants in drug delivery devices (considered as part of the Lubricants sector) • Process chemicals (considered as part of the Broader industrial uses sector)
20. Military applications	The assessment of the Military applications sector covers the uses of PFAS (including fluoropolymers and fluorinated gases) in articles intended for military personnel. Examples include fluorinated gases used as refrigerants in military applications, fluorinated gases used in fire extinguishing systems for military vessels, vehicles, and aircraft, as well as other military uses. PFAS uses related to Military applications but NOT considered as part of this sector: • Military electrical systems e.g. coatings and cabling of electronics (considered as part of the Electronic and semiconductors sector) • Military applications of sealing materials (considered as part of the Sealing applications sector) • Military explosives e.g. munitions, flares and explosive charges (considered as part of the Explosives sector) • Military textiles e.g. tents, parachutes, filtration and separation media, medical textiles and textiles used in military vehicles (considered as part of the Technical textiles sector) • Military protective garments, uniforms and personal protective equipment (PPE) (considered as part of the TULAC sector)
21. Explosives	The assessment of the Explosives sector covers the uses of PFAS in products or compositions designed to provide a useful liberation of energy, typically causing a release of heat, light, gas/smoke or a combination of the above. Civil products with uses of explosives include professional/consumer uses (e.g. ammunition for hunting and sport shooting, fireworks, flares) and transport (e.g. safety pyro mechanisms). Additionally, explosives can be used independently in industrial processes such as mining and blasting or in military applications (e.g. large calibre ammunition). PFAS uses related to Explosives but NOT considered as part of this sector: • Related uses of PFAS in petroleum and mining applications (considered as part of the Petroleum and mining sector) • Related uses of PFAS in military applications (considered as part of the Military applications sector) • Related uses of PFAS in transport applications (considered as part of the Transport sector)
22. Technical textiles	The assessment of the Technical textiles sector covers the uses of PFAS in textile materials (such as woven fabrics, knitted fabrics, non-wovens and felts) and textile manufactured products that are used primarily for their technical and functional properties and not for their aesthetic and decorative character. The assessment covers the uses of PFAS in outdoor technical textiles, architectural membranes, other tensile fabrics and other construction applications, filtration and separation media (e.g. virus and contaminant removal membranes and filters in water treatment and water,

	gas/air and other media filtration applications, purification applications), removable covers for industrial process equipment, technical textiles in medical applications (e.g., blood filtration textiles, transducer membranes, sterile ventilation membranes in medical devices, sound-permeable vent filters), and technical textiles for transport vehicles. PFAS uses related to Technical textiles but NOT considered as part of this sector: • Home textiles, including comparable uses in vehicles (such as carpets and seat covers) and public settings, e.g. hospital settings and public transport (considered as part of the TULAC sector) • Consumer apparel (considered as part of the TULAC sector) • Professional apparel and personal protective equipment (PPE) (considered as part of the TULAC sector) • Leather (considered as part of the TULAC sector) • Home fabric treatments (considered as part of the TULAC sector) • Packaging (considered as part of the Food contact materials and packaging sector) • Optical fibre weaving solutions for lighting applications in health, costumes, automotive, safety, environment, communication, architecture and industrial applications (considered as part of the Electronics and semiconductors sector) • Latex printing inks, including applications for printing on textiles (considered as part of the Printing applications sector) • Solvents for dry-cleaning of textiles (considered as part of the Applications of fluorinated gases sector) • Uses of PFAS in electrical components, sealing applications or machinery applications related to the manufacture of textiles or textile products (considered as part of the Electronics and semiconductors, Sealing applications and Machinery applications sectors respectively) • Conveyor belts (considered as part of the Machinery applications sector) • PTFE fibres/yarns used for the manufacture of braided packings for sealing applications (considered as part of the Sealing applications sector) • Use of PTFE in chemically inert fabrics used by the chemical and petrochemical industry for flange protection (considered as part of the Sealing applications sector) • Coating of fabric expansion joints (considered as part of the Sealing applications sector) • Uses of PFAS in relation to textiles used for self-lubricating /low-friction purposes (considered as part of the Machinery applications sector) • Uses of PFAS for textiles used for anti-adhesive/release purposes (considered as part of the Machinery applications sector) • Fuel-cell membranes and ion-exchange membranes for the manufacture of chemicals via electrolysis (considered as part of the Energy sector)
23. Broader industrial uses	The assessment of the Broader industrial uses sector covers the uses of PFAS in hydraulic fluids (if not covered under the Transport sector), solvents (solvents and reaction media for precision cleaning, extraction solvents and 3D printing), and catalysts and processing aids (catalytic reaction media and processing aids, including ionic liquids). These uses apply across different use sectors involving different actors (producers and users) along the supply/value chain. PFAS uses related to Broader industrial uses but NOT considered as part of this sector: • Precision cleaning in electronics and semiconductor manufacturing (considered as part of the Electronics and semiconductors sector)

	• Hydraulic fluids in transport (considered as part of the Transport sector, mainly for aviation) • Analytical and laboratory applications (considered as an overarching issue, please see the explanatory notes of the main report of the Background Document and in particular the sub-heading '*Scientific research and development*') • Engineered fluids: Fluids used for lubrication (considered as part of the Lubricants sector), cooling applications (considered as part of the Electronics and semiconductors sector), or precision cleaning agents (partly considered as part of the Broader industrial uses sector, partly considered as part of the Electronics and semiconductors sector) • Heat transfer fluids for immersion cooling and cold plate cooling (considered as part of the Electronics and semiconductors sector) • Engineered fluids for diagnostic laboratory applications (considered as an overarching issue, please see the explanatory notes of the main report of the Background Document and in particular the sub-heading '*Scientific research and development*') • Coatings for metals (considered as part of several different sectors, e.g. anti-acid coatings for metals are considered as part of the Metal plating and manufacture of metal products sector) • Solvents e.g., for cleaning and dissolving purposes (considered as part of the Electronics and semiconductors and Metal plating and manufacture of metal products sectors) • Solvents for dry-cleaning of textiles (considered as part of the Applications of fluorinated gases sector) • Carrier solvents for lubricants (considered as part of the Lubricants sector)

ANNEX II

Detailed analysis of degradability of PFAS proposed to be excluded from the scope

The Dossier Submitter indicates that specific PFAS types (i.e. trifluoromethanol, trifluoromethylamine and difluoromethanediol) are inherently unstable and therefore more complex molecules containing these moieties will also degrade. It supports this initial claim with various publications (e.g.: (Christe et al., 2007; Redwood and Willis, 1965; Seppelt, 1977; Taniguchi et al., 2003, Klöter and Seppelt, 1979, Francisco, 1993) on the fate of CF_3OH, CF_3NH_2 and $CF_3(OH)_2$. Later the Dossier Submitter provides experimental data with more complex substances containing these moieties to prove their hypothesis.

It is to be noted that the Dossier Submitters have not concluded that all substances in these PFAS subgroups are non-persistent, as they might contain non-perfluorinated moieties which could show some persistence themselves, but the persistence in such cases would not follow from the PFAS-fragments and the PFAS chemistry. This is explained to be different from the PFAS subgroups included in scope, that are either highly persistent themselves, or contain PFAS elements that warrant persistent arrowhead substances to be formed.

RAC has evaluated the information provided to justify the exclusion of certain PFAS subgroups looking at both to the degradation potential of trifluoromethanol, trifluoromethylamine and difluoromethanediol and of more complex molecules containing these moieties. RAC evaluations are based on Annex XIII REACH criteria for Persistency Assessment and ECHA Guideline R11.

For the case of trifluoromethanol, RAC notes that different publications have examined via modelling the fate of this substance in the atmosphere (e.g.: Buszek and Francisco 2009, Parandaman et al 2018, Long et al 2010, Nguyen et al 2008). Scientific data shows that trifluoromethanol rapidly transforms into carbonyl difluoride and HF. For instance, Nguyen et al 2008 derived rate constants (k) for different decomposition pathways of CF3OH. For the most likely decomposition pathway a first order k constant of 10^{-2} s^{-1} was determined with a calculated half-life of less than one minute in the gas phase, whereas for another likely decomposition pathway a much smaller first order k constant of merely 10^{-9} s^{-1} was derived. Other authors provide much slower decomposition kinetics (see Parandaman et al 2018 who reports first order k values of 10^{-8} seconds or lower). RAC notes that the different degradation rates found in literature points to the fact that CF_3OH likely disappears fast in the atmosphere, although the rate of degradation can be slow depending on the presence of catalysts. It remains therefore uncertain how fast CF_3OH would degrade under different environmental conditions, at low substance concentrations and without the presence of catalysts, also considering that the photolytic lifetime of trifluoromethanol below 40 km in the atmosphere is on the million-year scale and therefore photolysis of CF_30H is insignificant (Buszek and Francisco 2009).

Further, although RAC recognizes that carbonyl fluoride [C(O)F2], a degradation product of trifluoromethanol, is not a PFAS compound, this substance is toxic and its half-life in the environment is not clear. Whereas Uchimaru et al. (2004) reports a hydrolysis first order reaction coefficient of 3.3 s-1, in Figure B.41. of the report, the Dossier Submitter indicates that the residence time of carbonyl fluoride can be five years. Further, Wallington et al 1994 indicates that the potential lifetime of this substance in the ocean could be up to two years.

For the other two molecules, trifluoromethylamine and difluoromethanediol, RAC notes they are likely unstable, although the information provided by the Dossier Submitter to justify this is limited. Assuming that CF_3OH, CF_3NH_2 and $CF_3(OH)_2$ degrade fast in the atmosphere, this only represents a degradation process which cannot be used on its own for persistence

assessment, but may be used as part of a Weight-of-Evidence approach. However, the Dossier Submitter did not provide any evidence on whether these substances could partition to other compartments: water, sediment or soil.

The Dossier Submitter also provides data on degradability of Trifluoromethanol derivatives. The hypothesis is that a larger molecule containing a trifluoromethoxy-group attached to a degradable moiety (CF3-X, where X = -OR and where R = methyl (-CH3), methylene (-CH2-), an aromatic group or a carbonyl group (-C(O)-)) is expected to degrade with formation of trifluoromethanol.

The studies presented with trifluoromethanol derivatives show that the substances tested defluorinate and degrade under the test conditions (see Peschka et al 2008, Fromel and Knepper 2015 or (soil degradation study)). However, except for the test performed according to Guideline OECD 307, the inherent test performed by Peschka et al 2008 and hydrolysis data provided by Schiesser et al 2020, experiments provided are of limited relevance for Persistence Assessment according to REACH. They could be used as part of a weight of evidence approach

In **Peschka et al 2008**, 10-(trifluoromethoxy)decane-1-sulfonate was inherent biodegradable in a Zahn-Wellens test with a degradation > 75% in less than 28 days. As the degradation was not ≤20% the results do not suggest that degradation in the environment would be slow (ECHA guidance R.11). Unfortunately, based on the information provided in the Peschka paper, it is not possible to conclusively determine whether the criteria outlined for not fulfilling the persistence (P/vP) criteria for an inherent test are met. Essential details such as the percentage of mineralization within 7 days, the length of the log phase, and the percentage removal before degradation starts are not specified in the paper (see ECHA Guideline R-11). General study details were also limited to allow comparison of test conditions and results against guideline requirements. Therefore, RAC considers that it is not possible to make definite conclusions on persistence based on this study.

In the fixed-bed bioreactor tests (FBBR) performed also from Peschka et al 2008, results showed that the substance defluorinated more than 60% by day 70 (less than 60% by day 28). Two degradation pathways were proposed, one of them (minor degradation pathway accounting for ca. 10% of the total amount) lead to the formation of oxo-10-(trifluoromethoxy)decane-1-sulfonate) whose degradation was quite slow. This stands in coherence with the slow release of fluoride at the end of the experiment, i.e. between days 43 and 87.

RAC notes that in terms of standardised test conditions recognised in REACH for persistence determination, it is not possible to benchmark the results of the FBBR studies. It is also relevant to consider that FBBRs favour biodegradation and are an efficient method (hosting a high density of microbes in a small area) for treating waters with medium to high BOD. Yet, under these favorable conditions for degradation the substance degraded into a PFAS metabolite which could be potentially vP due to the C-F bond. Based on the above and given the uncertainties described for the inherent test it is not possible to reach definite conclusions on the non persistence (P/vP) of the proposed substance.

In **Fromel and Knepper 201**5, two substances (6-(trifluoromethoxy)-hexan-1-ol (TFMHxOH) and 3-(trifluoromethoxy)-propan-1-ol (TFMPrOH)) were tested under test conditions that RAC cannot unequivocally relate to any of the guidelines used to evaluate the persistence of chemicals according to Annex XIII of REACH since the level of reporting is not detailed enough. In addition, considering that the experiments were carried out under aerobic conditions with effluent water from a municipal wastewater treatment plant it is not possible to obtain half-lives for directly comparing to Annex XIII criteria from this study.

Results show that 6-(trifluoromethoxy) hexan-1-ol (TFMHxOH) was almost completely mineralized after 37 days as judged from the fluoride release. Two acidic transformation products were detected for TFMHxOH, 6-(trifluoromethoxy)hexanoic acid (TFMHxA) and trifluoromethyl carbonate (TFMC). Both compounds were generated rapidly with TFMC showing a maximum after only four days and no signal after 11 days. TFMHxA showed its maximum concentration after five days and was completely degraded (mineralised) afterwards showing complete degradation also after 11 days.

On the contrary, 3-(Trifluoromethoxy)-1-propanol (TFMPrOH) only mineralised to the extent of 15% and transformed into a metabolite (3-trifluoromethoxy-propanoic acid (TFMPrA)) which did not show any further degradation under these conditions within a 47 days period. This metabolite is a PFAS and could be very persistent in the environment. RAC notes that the study authors indicated that the reason for the dissimilar stability of TFMHxA and TFMPrA could not be entirely explained with the knowledge obtained. *"One possible reason could be a different accessibility of the methylene group in vicinity to the TFM group in the two compounds. In TFMPrA, the methylene group might be shielded by the polar carboxylic acid function, so that it cannot be hydroxylated enzymatically, which in turn could be possible in TFMHxA, where the carboxylic acid group is separated by more methylene groups. However, these suggestions remain speculative unless one or several transient transformation products are detected in other studies."*

The Dossier Submitter indicated that based on the chemical structure of TFMPrA, it should not be regarded as an arrowhead, but rather a relatively stable intermediate that is likely to mineralize under environmentally relevant conditions over time. To support this assertion in the Dossier Submitter utilized EAWAG-BBD pathway prediction. However, RAC's analysis of EAWAG-BBD for TFMPrA flagged a warning, stating, *"The rules used by the PPS do not accurately predict the unique characteristics of these materials. All per- and highly-fluorinated chemicals should not have their biodegradation predicted."* Similar findings were observed with CATALOGIC software, which deemed the substance beyond its applicability domain. Consequently, RAC concluded that these predictions lack reliability to supersede test results.

Overall, RAC notes that test conditions, duration and concentrations do not allow a comparison of this study with any of the accepted test methods used for persistence assessment in accordance with Annex XIII of REACH, making interpretation of the results difficult. Whereas 6-(trifluoromethoxy) hexan-1-ol (TFMHxOH) was almost completely mineralized after 37 days suggesting this substance could degrade in the environment, results show that TFMPrOH only mineralises to the extent of 15% and transforms into a metabolite (3-trifluoromethoxy-propanoic acid) which did not show any further degradation under these conditions within a 47 days period. Based on this, RAC considers this study contradicts the Dossier Submitter Hypothesis that *trifluoromethoxy-derivatives* can be labelled as "fully degradable" PFAS for which very persistence concerns do not exist. this trifluoromethoxy-derivative.

Another study provided by the Dossier Submitter evaluates the metabolism of OSI 390 **(Dihel et al 2009).** RAC notes that mammalian metabolism studies could be informative for environmental persistence evaluation of substances but not conclusive. In the present restriction proposal, the information refers to xenobiotic metabolism of mammals, and no justifications are presented that the same metabolism would occur e.g., by micro-organisms.

During the consultation to the Annex XV report a study according to OECD 307 with a trifluoromethoxy derivative radio-labeled directly at the CF3- group was provided (confidential comment).

Study findings:

The study revealed that the substance mineralised in the three soils tested by day 28. The mass balances were adequate during the 28 days. For the extended sampling lower mass balances were observed together with unusually high radioactivity values in the second NaOH trapping solutions. For each application group, the amount of CO2 at 56/57 DAT was lower than the one at 28 DAT. According to the authors, this indicates that the low mass balances at 56/57 DAT are caused by losses of CO2 due to the insufficient capacity of the NaOH trapping solutions to capture the still evolving $^{14}CO2$.

The non-extractable residues peak at 2-6 days and then decreased to some extent after 56/57 days. The study authors explain that this indicates that part of the parent test item was bound to the humic matrix in soil. However, the proceeding defluorination and mineralization (increasing CO2-levels) would show that this does not stop the further degradation of trifluoromethoxy-group but just slows it down to a certain extent.

In the original study, DegT50s were calculated using the parent concentration decline in the test system and considering NER as degraded parent substance using SFO as the best fitting model. This led to DegT50s < 6 at 12 degrees, well below the P criteria according to Annex XIII of REACH. The authors of the study propose as a degradation pathway the release of carbon dioxide and the formation of non-extractable residues which would further degrade to CO2.

In the evaluation of extractable residues, the authors of the study indicate that beside the parent compound, a few unknown metabolites were detected, but all below levels of 0.2% TAR. No further characterization of non-extractable residues was performed.

RAC has evaluated the study results following the advice provided in Guideline R.11: PBT/vPvB assessment (ECHA, 2023b). First, following comments provided by a RAC member, RAC has looked to whether the mineralisation half-life for the whole system is below the respective half-life value of P/vP criteria. In such a case, the substance would be considered not persistent in the tested environmental compartment, although an investigation of degradation pathways/transformation/degradation products would be needed since it cannot be excluded that a second transformation route forms a persistent transformation/degradation product in concentrations relevant for the P assessment. For this RAC has derived mineralisation half-life (based solely on CO2 evolution) for the whole system at days 0-28 and 0-56.

Second, RAC has calculated a DegT50s based on CO2 evolution. In addition, RAC calculated a DegT50 considering NERs as non-degraded parent substance since NERs were not characterised. This aligns with ECHA Guidance R.11 which indicates that "in the context of persistence assessment, the Total NER is considered as a non-degraded parent substance unless further characterisation of the Total NER is performed."

Recalculations were done following FOCUS Kinetic Guideline 2014 and the model CAKE:

<u>Recalculations based on CO2 evolution for 28 days</u>

- In soil 1, the FOMC, DFOP, and Hockey Stick (HS) models exhibited superior visual fits over the Single First Order (SFO) model, with HS displaying the most favourable fit. HS results in a lower chi-square value (4.5) compared to SFO (8.16), FOMC (5.79), and DFOP (5.72). Although DFOP's slow phase yielded a DegT50 of 78.1 days, potentially suggesting persistence, it failed the t-test. Conversely, HS's slow phase yielded a DegT50 of 21.9 days, deemed the most accurate estimation.
- In soil 2, the best visual fit is obtained with FOMC, DFOP and HS. None of the models predict a DT50 higher than the P/vP criteria.
- Similarly, in Soil 3, FOMC, DFOP, and HS models exhibited the best visual fits, with

DFOP and HS outperforming. Modelling results show a bi-phasic CO2 evolution for this soil. DFOP failed the t-test for k2. HS, however, passed the t-test, yielding a k1 DegT50 of 3.72 days, below the P criteria and k2 DegT50 of 87.6 days, which at 12 degrees is 166 days exceeding the P criteria at 12 degrees.

In soil 3, fitting biphasic models to cumulative $^{14}CO_2$ over 0–28 days results in a k1 DT50 below the P criterion and a slow-phase DegT50 (HS) corresponding to 166 days at 12 °C. The CO_2 time course shows that >50% mineralisation is reached early (by approximately day 7–10), followed by a plateau with only limited additional CO_2 formation. RAC notes, however, the slow-phase DegT50 derived from cumulative CO_2 needs to be interpreted with caution. As explained in OECD Guideline 309, *"when the 14C-labelled part of an organic substance is biodegraded, the major part of the 14C is converted to 14CO2, while another part is used for growth of biomass and/or synthesis of extra-cellular metabolites. Therefore, complete "ultimate" biodegradation of a substance does not result in a 100% conversion of its carbon into 14CO2. The 14C built into products formed by biosynthesis is subsequently released slowly as 14CO2 due to "secondary mineralisation". This complicates a kinetic interpretation of the data and for this purpose, only the initial part of the curve (after ended lag phase and before approx. 50% degradation is reached) should normally be used for the estimation of a degradation rate constant."*

Recalculations based on CO2 evolution for 56 days

- In soil 1 SFO resulted in a bad visual fit and a chi square of 15%. The model was discarded. DFOP and HS have the best visual fit and lower chi-square (6.05 and 6.99%) in comparison to FOMC (8.56). DegT50 of FOMC is 9.22. DegT50s for DFOP and HS are above 10000 but they fail the t-test reflecting that from day 28 to day 56 CO2 evolution does not increase but plateaus or even decreases.
- For soil 2 and 3 a similar situation to the one of soil 1 occurs.

RAC notes that the t-test likely fails in the above calculations because CO2 evolution did not increase from day 28 to day 56, and the model accurately represents this lack of variation.

Recalculations with Parent + Ners:

An acceptable single-first order fitting was not possible, the biphasic kinetic models (HS, DFOP) were the best-fit models, based on visual assessment, X^2 values and t-test values Recalculations lead to the following results:

- For soil 1 (Li10) recalculation results in a DegT50 = 74.2 days at 20 degrees = 140 days at 12 degrees, with HS as best model.
- For soil 2 (Lufa 2.2) DegT50 = 90.5 at 20 degrees = 171 days at 12 degrees, with DFOP as best model
- For soil 3, Lufa 2.4, DegT50 = 108 days at 20 degrees = 204 days at 12 degrees, with HS as best model.

RAC interpretation and conclusion

The study shows rapid and extensive mineralisation of the CF3-labelled moiety and the parent can be considered not P/vP in soil based on the mineralization half-lives calculated from 0-28 days (see above explanation on tailing effect). Also, DegT50 values calculated from the decline of parent substance concentration are below the Annex XIII P/vP thresholds.

Further evidence is that the significant mineralization coupled with the limited formation of metabolites suggests that the NERs may lack substantial quantities of the parent compound or transformation products featuring a -CF3 group. In addition, the extraction method used

was limited to solvent extraction and did not include exhaustive extraction methods like pressurized liquid extraction. This limitation could have led to an overestimation of NERs.

However, some uncertainties exist mainly due to the substantial NER fraction that was formed and the fact that NERs were not further characterised into Type I, II or III; therefore, it cannot be excluded that total NER fraction includes Type I NER which might include parent and/or transformation product with a -CF3 group. Further, when considering the total NERs as non-degradable parent substance the Parent+NER modelling gives a $DegT_{50}$ above the P trigger in one soil.

Therefore, while the parent shows rapid degradation and can be considered not P/vP in soil based on the mineralization half-lives calculated from 0-28 days, some uncertainty remains related to the nature and relevance of the NER fraction and the possibility that a second transformation route forms a (very) persistent transformation/degradation product in concentrations relevant for the P assessment.

For **trifluoromehylamino derivatives** the Dossier Submitter only presented an experiment **(Schiesser et al 2020)** were the hydrolytic stability of twelve trifluoromethylamino-derivatives and N-Trifluoromethyl azoles in aqueous media was investigated. RAC notes this study shows that N-trifluoromethyl amines are prone to hydrolysis, whereas N-trifluoromethyl azoles have excellent aqueous stability. Data also shows that several trifluormethyl amines transformed into carbamoyl fluoride which is no longer a PFAS. Others, however, such as N-trifluoromethyl piperazine transformed into secondary amine. The identity of the secondary amines formed are unknown to RAC, additionally it is unknown if they still contain a perfluorinated moiety and whether they decomposed fast.

RAC further notes that according to the PBT Guidance R11, concern for P/vP cannot be ruled out by significant and substantial loss of the parent substance by hydrolysis alone. Additional evidence is also needed to examine the persistence of the degradation products, whether the fate properties of the substance would cause attenuation of the hydrolysis rate in sediment or soil, or whether DOC would similarly affect the rate in aquatic media such as river or sea water. There are substances reaching rapid hydrolysis rates which are well known to be persistent or very persistent in soil and/or sediment, e.g. endosulfan and Octamethylcyclotetrasiloxane (D4) (ECHA, 2015). Therefore, rapid hydrolysis rates cannot alone lead to concluding that a substance is not persistent. RAC cannot therefore reach a firm conclusion on the basis of this study alone.

Finally, for confirmation of the degradation of **Difluoromethanediol** derivates, the DS presented a mechanistic study by **(Bygd et al., 2021)**, where the microbial degradation of model compound 2,2-difluoro-1,3-benzodioxole (DFBD) by *Pseudomonas* strains was investigated. In this study, wild-type cells of P. putida F1 were grown on toluene vapors to induce toluene dioxygenase and related enzymes. Bacteria expressing toluene dioxygenase, were able to degrade the substance and a rapid fluoride release was observed that declined within hours. RAC agrees with the authors of the paper that their study demonstrates degradation only under certain conditions and after having induced toluene dioxygenase. RAC further notes that the study does not allow for any comparison with standard degradation test considered for Persistence analysis and is not environmentally relevant and therefore not adequate to conclude that the substance is not very persistent.

The study by **Alexandrino et al. (2020)** reports the degradation of fludioxonil by enriched microbial consortia from estuarine sediment and agricultural soil. After an enrichment period of 6 months, four microbial consortia were able to completely remove and defluorinate the fungicide in co-metabolic conditions. RAC agrees with the authors of the paper and considers it relevant for bioremediation but not to evaluate persistence criteria following the

requirements of Annex XIII of REACH. RAC also notes that for the harmonised classification of Fludioxonil the substance was considered hydrolytically stable and not readily biodegradable (ECHA, 2017). Degradation half lives in sediment were considered to be 1326 and 855 days at 12 °C, and 502 days in soil. Further, according to EFSA Journal 2007, "Conclusion regarding the peer review of the pesticide risk assessment of the active substance fludioxonil" fludioxonil is high to very high persistent in soil (DT50 lab 20ºC = 119 – 599 days) (EFSA, 2007). A very limited amount of metabolites was formed. This would lead to the consideration of the substance as vP.

Data pertaining to **Flurprimidol (see EFSA 2011),** an additional pesticide not covered in the initial assessment performed by the Dossier Submitter but that would fall under the exemption, reveals the substance is stable to hydrolysis and is not ready biodegradable. The route of degradation of flurprimidol in soil was investigated at 20 degrees under dark aerobic conditions in two studies with a total of seven soils (pH 6.0 – 8.3; OC 0.9 – 41.9 %; clay 7 – 38.4 %) with flurprimidol ^{14}C labelled at the phenyl ring. In the first study, four metabolites were found. of the metabolites (M1 and M2)9 exceeded 5 % AR in two consecutive data points. These metabolites were not adequately characterized and a data gap was identified for an adequate route of degradation. The rate of degradation of the substance was calculated to range from 98 to 183 days under aerobic conditions at 20 degrees Celsius, or 185 to 347 days at the environmentally relevant temperature of 12 degrees Celsius. As for the case of fludioxonil, this result suggests that vP substances could be regrettably exempted. RAC notes however that in this case, study results did not allow to ascertain whether the associated persistence is related to parent, to a PFAS metabolite or to a non PFAS metabolite.

Overall, RAC acknowledges the weight of evidence presented by the Dossier Submitter, suggesting that some PFAS substances within the exemption group may not exhibit the very persistent properties typically associated with PFAS (at least in some environmental compartments e.g., soil, which is the primary concern for restriction. Moreover, the evidence suggests that there are PFAS substances that may not be persistent (e.g., soil). However, RAC disagrees with the Dossier Submitter that the available evidence leads to the conclusion that all PFAS from the subgroups described above are expected to fully mineralize in the environment and do not have any vP concern warranting a broad exemption.

RAC notes for excluding the P/vP concern and disregard the stability of the C-F bond, sufficient evidence, e.g. based on ready biodegradation data, inherent degradation data fulfilling certain conditions or data on degradation rates/half-lives should be available and representative for degradation in all environmental compartments (water, water-sediment and soil) for relevant conditions. Neither sole hydrolysis data nor fast degradation or instability in one compartment (atmosphere) or degradation under very specific conditions (see for instance Bygd et al 2021, Alexandrino et al 2020 or Peschka et al 2008) are sufficient to render a substance automatically as non-persistent according to REACH Regulation Annex XIII. In the absence of adequate data to exclude the P/vP concern a substance can be generally considered "potentially P/vP" whereas a definitive conclusion P or vP is possible only when there is sufficient data to indicate that Annex XIII criteria are fulfilled.

Further, RAC notes that degradation data of a particular substance within a subgroup does not necessarily justify extrapolation of non-persistence to other substances in the group. A case needs to be built to demonstrate how degradation data of a particular substance can be extrapolated to other group members, taking into account how different chemical structures (e.g.: branching and alkyl chain length) would affect degradation rates and pathways and the stability of the C-F bond. No conclusive evidence is provided in this sense. On the contrary, evidence shows that some of the claimed fully degradable PFAS such as Fludioxonil exhibit very persistent properties with half-lives in soil of almost two years and half-lives in water

sediment of 2.3 and 3.6 years. Additionally, some proposed PFAS degraded in the performed tests into PFAS metabolites (oxidized 10-(trifluoromethoxy)decane-1-sulfonate and 3-trifluoromethoxy-propanoic acid) that could be potentially persistent or very persistent themselves. Following the above, RAC does not support the group exemption proposed by the Dossier Submitter.

MEDICAL DEVICE MATERIAL PERFORMANCE STUDY

PTFE Safety Profile

Report Details

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Ed Margerrison, PhD

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Center for Devices and Radiological He
U.S. Food and Drug Administration

ECRI Corporate Governance

Michael Argentieri, MS
Vice President, Technology and Safety
Phone: (610) 316-2766
Email: margentieri@ECRI.org

Dheerendra Kommala, MD
Chief Medical Officer
Phone: (215) 341-5171
Email: dkommala@ECRI.org

Project Manager

Scott R. Lucas, PhD, PE
Principal & Director, Accident and Forensic Investigation
Phone: (804) 690-8542
Email: slucas@ECRI.org

If you have any questions or require additional information, please do not hesitate to call the Project Manager.

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Executive Summary

Key Points

1. Searches identified 1,782 citations; 52 articles were selected for inclusion.
2. The included studies most often found no difference in local responses, including patency, thrombosis, stenosis, or occlusion, when comparing a PTFE graft to a reference material or technique. The quality of evidence is low.
3. Studies indicate there is no difference in systemic responses, including mortality, myocardial infarction, and ischemia, when comparing a PTFE graft to other materials or techniques. The quality of evidence is low.
4. Studies of stent-grafts indicate PTFE stent-grafts yield better patency and stenosis results than percutaneous transluminal angioplasty (PTA). The quality of evidence is moderate, as this was reported in almost all human studies. Some studies found PTFE stent-grafts to have better patency than bare metal stents, but other studies found no difference.
5. The accident investigation and PRN data on PTFE devices was limited and generally involved a component braking or migrating resulting in a foreign body.
6. The PSO data included 4 reports of complication with associated harm scores indicating error, but no harm to the patient.
7. The healthcare technology alerts database returned the most relevant results (32 alerts). These consisted of IFU and labeling recalls, but also more serious hazards such as graft and stent component separation and graft tears.
8. Evidence gaps:
    a. Only 1 animal study met inclusion for PTFE as a material and reported inflammation, which could result in oxidative destruction of devices. Additional animal studies are indicated.
    b. The majority of studies included investigated the use of PTFE grafts, stents, and stent-grafts. There was relatively little on the use of PTFE for catheters, filters, and sutures.
    c. Multivariable controlled studies on grafts to confirm the trend of no differences between PTFE grafts and grafts made from other materials.
    d. RCTs on stents to confirm observed trend of low adverse events with PTFE stents relative to control groups.
    e. Research on outcomes other than occlusion and restenosis in PTFE stent-grafts compared to other materials.

Overview - Polytetrafluoroethylene (PTFE)

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Additionally, data derived from ECRI's Patient Safety Organization (PSO), accident investigations, Problem Reporting Network (PRN), and healthcare technology alerts were analyzed. This report focuses on answering 5 key questions provided by FDA and summarized below, regarding a host's local and systemic response to PTFE. If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

1. What is the typical/expected local host response to PTFE?

Patency, thrombosis, stenosis, and occlusion were the most investigated local responses among the studies included, which mostly addressed vessel repair or reconstruction. Pseudoaneurysm, re-exploration/reoperation, hematoma, and complication rate were also reported in several studies. The studies we reviewed most often found no difference in these responses when comparing a PTFE graft to a reference material or technique. Several studies report responses without a comparison to a reference material or technique. The available ECRI surveillance data were related, in part, to component separation or broken parts; however, it was unclear in the data whether this was related to material response due to insufficient biocompatibility or mechanical integrity and use of the device.

a. Can that response vary by location or the type of tissue the device is implanted in or near?

i. PTFE (Teflon) peripheral intravenous catheters (PICs) may have a higher rate of phlebitis than polyurethane PICs in adult patients. No inflammation or blockage was observed in a randomized control trial (RCT) of newborns.
ii. Evidence suggests PTFE stent grafts provide better patency rates than percutaneous transluminal angioplasty (3 RCTs).
iii. PTFE may provide better patency rates than a bare-metal stent. 1 RCT and 1 non-randomized controlled study (NRCS) found better, 1 RCT and 2 NRCSs found no difference.
iv. 1 systematic review (SR) and 1 RCT found PTFE to have worse patency rates than Dacron and bovine carotid artery graft, respectively.
v. Other studies reported PTFE to have similar or worse rates than polyurethane, autogenous grafts, and basilic vein transposition.

b. Over what time course does this local host response appear?

i. Signs of inflammation may appear within 24 to 48 hours.
ii. Other responses occurred within a few days to several years after implantation.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

Mortality, myocardial infarction, and ischemia are the most investigated systemic responses among the studies included. The studies indicate there is no difference in these responses when comparing a PTFE graft to other materials or techniques.

a. What evidence exists to suggest or support this?

i. Several studies reported no difference in mortality between PTFE and Dacron (1 SR), bare-metal stent (4 RCT, 3 NRCS), or autologous vein (2 NRCS).
ii. Studies reported no difference in major cardiac events between PTFE and bare-metal stent (2 RCT), or vein graft (3 NRCS).
iii. Studies investigated ischemia were mostly single-arm studies.

b. What are the likely systemic manifestations?

Studies indicate there is no difference in systemic responses, including mortality, myocardial infarction, and ischemia, when comparing a PTFE graft to other materials or techniques.

c. What is the observed timeline(s) for the systemic manifestations?

Systematic responses occurred within a few days to several years after implantation.

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

5 non-randomized studies investigated cytokines and white blood cell response, but did not specify a specific mechanism for manifestation of systemic response.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

Most studies did not report any patient-related factors regarding a systemic response. One study reported atrial fibrillation was a significant risk factor for patient mortality.[1] One study reported hepatic encephalopathy was influenced by albumin, and survival was influenced by total bilirubin, albumin, and model for end-stage liver disease score.

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

The included studies did not strongly indicate any associations between material-related factors and systemic responses.

5. **What critical information gaps exist and what research is needed to better understand this issue?**

   All gaps listed here could benefit from future research.

   a. Only 1 animal study met inclusion for PTFE as a material and reported inflammation, which could result in oxidative destruction of devices. Additional studies are indicated.
   b. The majority of studies included investigated the use of PTFE grafts, stents, and stent-grafts. There was relatively little on the use of PTFE for catheters, filters, and sutures.
   c. Multivariable controlled studies on grafts to confirm the trend of no differences between PTFE grafts and grafts made from other materials.
   d. RCTs on stents to confirm observed trend of low adverse events with PTFE stents relative to control groups.
   e. Research on outcomes other than occlusion and restenosis in PTFE stent-grafts compared to other materials.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials or topics were selected by FDA based on current priority. For the first quarter of 2021, the following six topics were chosen:

1. Magnesium (Mg)
2. Complications associated with Polypropylene Mesh in Pre-, Peri-, and Post-Menopausal Women
3. Polytetrafluoroethylene (PTFE)
4. Acrylics 1: PMMA,
5. Acrylics 2: pHEMA
6. Acrylics 3: Cyanoacrylates

The systematic review was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions

1. What is the typical/expected local host response to PTFE?

   a. *Can that response vary by location or type of tissue the device is implanted in or near?*
   b. *Over what time course does this local host response appear?*

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

   a. *What evidence exists to suggest or support this?*
   b. *What are the likely systemic manifestations?*
   c. *What is the observed timeline(s) for the systemic manifestations?*
   d. *Have particular cellular/molecular mechanisms been identified for such manifestations?*

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

5. What critical information gaps exist and what research is needed to better understand this issue?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the six materials listed above to include the summary of key findings from the systematic review and surveillance search and are included in this report.

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and in peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search nonclinical literature; however, it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication dates between 2010 and 2020 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
  - Strength
  - Embrittlement
  - Degradation
  - Migration
  - Delamination
  - Leaching

- **Host Response**
  - Local
    - Inflammation
    - Sensitization
    - Irritation
    - Scarring/fibrosis
      - *Keloid formation*
      - *Contracture*
    - Ingrowth
    - Erosion
  - Systemic
    - Cancer
      - Lymphoma
    - Inflammation
    - Immune Response
    - Fatigue
    - Memory Loss
    - Rash
    - Joint Pain
    - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and

contextual information are presented in Appendix B. Text mining, logistic regression, and a search for "random" and "systematic" in titles and abstracts were used to prioritize only the top 35%-40% of the identified literature. This subset was screened against the inclusion criteria, first by title/abstract review, and then by full article review. An evidence prioritization scheme was used to ensure the inclusion of approximately 50 studies. Data were extracted from the resulting articles.

ECRI Surveillance Search Strategy

There are four key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

ECRI surveillance data comprise ECRI Patient Safety Organization (PSO) event reports, accident investigations, problem reporting network (PRN) reports, and alerts. The PSO, investigations, and PRN reports included in this report include mostly acute patient events. We rarely find chronic conditions or patient follow-up reports, which are more prevalent in the clinical literature. Complications are reported directly by clinical staff, thus reports vary greatly in the level of detail provided.

ECRI Patient Safety Organization (PSO)

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through January 2021, unless otherwise noted.

Category A (No Error)

Circumstances or events that have the capacity to cause error.

Category B (Error, no harm)

An error occurred, but the error did not reach the patient (an "error of omission" does reach the patient).

Category C (Error, no harm)

An error occurred that reached the patient but did not cause patient harm.

Category D (Error, no harm)
An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E (Error, harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

Category F (Error, harm)

An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G (Error, harm)

An error occurred that may have contributed to or resulted in permanent patient harm.

Category H (Error, harm)

An error occurred that required intervention necessary to sustain life.

Category I (Error, death)
An error occurred that may have contributed to or resulted in patient's death.

Definitions

Harm: Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.
Monitoring: To observe or record relevant physiological or psychological signs.
Intervention: may include change in therapy or active medical/ surgical treatment.
Intervention Necessary to Sustain Life: includes cardiovascular and respiratory support (e.g., CPR, defibrillation, intubation)

Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile - Polytetrafluoroethylene (PTFE)

Full Name: Polytetrafluoroethylene
CAS Registry Number: 9002-84-0

Safety Brief - Systematic Review Results

The systematic review included clinical and engineering literature on biocompatibility (i.e., host response and material response) of polytetrafluoroethylene (PTFE) used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of PTFE. The devices in **Error! Reference source not found.** were identified in the ECRI literature search and acknowledged by FDA to be within scope. These guided ECRI in review of this literature and ECRI's surveillance data. In the latter, only those devices listed in **Error! Reference source not found.** were included.

Table 1: Medical Devices Containing PTFE provided by FDA to Guide ECRI Searches

Regulatory Description	Product Code	Class
Diagnostic Intravascular Catheter	DQO	2
Percutaneous Catheter	DQY	2
Catheter, Intravascular Occluding, Temporary	MJN	2
Prosthesis, Vascular Graft, Of 6mm And Greater Diameter	DSY	2
Prosthesis, Vascular Graft, of less than 6mm Diameter	DYF	2
System, Endovascular Graft, Aortic Aneurysm Treatment	MIH	3
System, Endovascular Graft, Arteriovenous (Av) Dialysis Access Circuit Stenosis Treatment	PFV	3
Iliac Covered Stent, Arterial	PRL	3
Suture, Surgical, Nonabsorbable, Expanded, Polytetraflouroethylene	NBY	2
Nonabsorbable Expanded Polytetrafluoroethylene Surgical Suture For Chordae Tendinae Repair Or Replacement	PAW	2
Stent, Carotid	NIM	3
Stent, Superficial Femoral Artery	NIP	3
Coronary Covered Stent	NIV	HDE/3
Cardiovascular intravascular filter	DTK	2
Shunt, Portosystemic, Endoprosthesis	MIR	3

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of PTFE. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices document. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies),

consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose response or response over time. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in **Error! Reference source not found.**. We then turn to a detailed discussion of research on PTFE as a material as well as research on the various device categories.

Table 2: Summary of Investigated Responses from the Systematic Review

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
PTFE as a material (1 animal study)	Foreign Body Response	Very low	No studies	Very low (no evidence)
Catheters (2 human studies)	Phlebitis	Low	No studies	Very low (no evidence)
Filters (2 human studies)	Thrombosis	Low	Death Myocardial infarction Pulmonary embolism Stroke	Low
Grafts (22 human studies)	Patency, Thrombosis, Occlusion, Hematoma, Overall complications, Pseudoaneurysm, Displacement, Re-exploration/Re-operation, Small-for size syndrome, Conduit events, Non-maturation, Early allograft dysfunction, Bile leak, Edema, Stenosis, Extrusion, Biliary stricture, Acute cellular rejection, Inflammation, Granuloma	Low	Death, Pneumonia, Renal failure/insufficiency, Congestive heart failure, Mycardial infarction, Hypertension, Arrythmia, Respiratory complications, Skin rash, Sepsis, Diarrhea, Delirium, Hypovolemic shock, Ileus, Inflammation	Low
Stents (9 human studies)	Restenosis, Patency, Shunt dysfunction, Hepatic encephalopathy, Variceal rebleeding, Hepatic function decline, Thrombosis,	Low	Mortality, major cardiac events, myocardial infarction, Hospitalization, Respiratory failure/embolism, Dialysis,	Low

Application	Local Host Responses/Device Events	Quality of Evidence (local responses)	Systemic Responses	Quality of Evidence (systemic responses)
	Pericardial effusion, Tissue ingrowth, Granulation tissue, Stent migration, Recoarctation, Pseudoaneurysm		Hypertension, Distal embolization	
Stent Grafts (15 human studies)	Primary patency, Restenosis, Occlusion, Thrombosis, Embolism, Hematoma, Stent fracture, Endoleak, Migration, Target vessel failure, Hemorrhage, Pseudoaneurysm,	Moderate for Occlusion and Restenosis Low for other local responses	Post-implantation syndrome, Inflammatory markers, Hepatic encephalopathy, Mortality	Low
Sutures (1 human study)	Granuloma, Preseptal cellulitis, Abscess	Low	No Studies	Very low (no evidence)

PTFE as a Material

1 animal comparative study.[2] For further information see Table 1 in Appendix D.

Local Host Responses (human studies):

We did not identify any human studies reporting local host responses.

Local Responses (animal studies)

1 animal study (15 rats) reported whether there were local host reactions related to PTFE (Ovcharenko et al.).[2] At 2 weeks, a loose, 69 µm thick, collagen-based fibrous capsule was observed around the sample, indicating the end of the inflammatory process. Implantation sites demonstrated no foreign-body giant cells (FBGCs) or lymph nodes at two weeks. At 2 months, dense connective tissues 78 µm thick with evident collagen fibers were observed. FBGCs were present in the fibrous capsule. Such FBGCs can potentially contribute to oxidative damage and destruction of implanted devices. There were visible calcific deposits at the tissue/implant interaction.

Systemic Responses (human studies)

We did not identify any studies reporting systemic responses.

Overall Quality of Evidence

This summary was based on 1, small animal study, so the quality of evidence was very low.

Catheters

2 human studies (1 systematic review[3] and 1 randomized controlled trial[RCT][4]). For further information see Table 2 in Appendix D.

Local Responses/Device Events (human studies)

A systematic review of 35 studies concluded PTFE (Teflon) peripheral intravenous catheters (PICs) had a higher phlebitis incidence rate (33%, 95% CI: 25%, 41%) vs polyurethane Vialon (27%, 95% CI 21–32%).[3] Three of the studies included in

the review identified PTFE (Teflon) catheter use as a risk factor for the development of phlebitis. The mean patient age in this systematic review was 57 yrs.

An RCT of PIC use in newborns found no venous inflammation or blockage using either PTFE or PUR PICs.[4] Rates of catheter removal due to extravasation were similar between PTFE and PUR PIC's.

Local Responses/Device Events (animal studies)

We did not identify any animal studies reporting local host responses.

Systemic Responses

We did not identify any studies reporting systemic responses.

Overall Quality of Evidence

The occurrence of phlebitis/inflammation during the use of PTFE PICs was inconsistent, although that inconsistency may be related to the difference in age of the patients considered in each study. Overall, given the small amount of evidence, the quality of evidence supporting phlebitis/inflammation is low. Since systemic responses were not investigated in any study, the quality of evidence for systemic responses is very low.

Filters

Two human single-arm studies.[5,6] For further information see Table 3 in Appendix D.

Local Host Responses (human studies)

A single-arm study of embolic filters with a PTFE mesh observed thrombus in or near the filter in 9 out of 125 cases. No signs of filter migration or fracture were observed.[6]

Local Host Responses (animal studies)

We did not identify any animal studies reporting local host responses.

Systemic Responses

A single-arm study of an embolic filter with PTFE mesh found a major adverse event rate of 4%, including 2 deaths, 7 strokes, and 1 myocardial infarction out of 250 patients.[5] Another study reported 13 cases of lower-limb deep vein thrombosis and 5 cases of definitive or suspected pulmonary embolism in 125 patients who received an inferior vena cava filter.[6]

Overall Quality of Evidence

The evidence for thrombus is based on a single, moderately-sized, single-arm study. Therefore, the quality of evidence for thrombus is low. Similarly, each of the system responses is based on a single, moderately-sized, single-arm study. Therefore, the quality of evidence for systemic responses is also low.

Grafts

Twenty-one studies (22 human studies and 0 animal studies)

The human studies included 4 SRs,[7-10] 2 RCTs,[11,12] 14 non-randomized comparative studies,[1,13-25] and 2 single-arm studies.[26,27] For further information, see **Error! Reference source not found.**in Appendix D.

Local Host Responses (human studies)

The five most commonly investigated local responses were patency, thrombosis, occlusion, hematoma, and overall complication rate. The studies we reviewed most often found no difference in these responses or that the rate of these responses was less favorable using a PTFE graft compared to another graft material or technique. Several studies reported responses without a comparison to a reference material.

Below we detail some of the important findings from the SRs, RCTs, and prospective comparative studies. For all study results, see **Error! Reference source not found.**in Appendix D.

Medialization laryngoplasty: One SR (9 studies) from 2019 examined medialization laryngoplasty using **GORE-TEX** with or without arytenoid adduction.[8] Three studies reported no complications associated with Gor-Tex. Among the other 6 studies, there were 11 complications including 6 cases of extrusion into the lumen, 3 cases of persistent inflammation with granulation formation requiring removal of the **GORE-TEX** implant, and 2 cases of displacement. This review included studies with more than 10 cases of medialization laryngoplasty using GT, which contained information regarding complications and all reported series and case reports of patients with extrusion complications.[8]

Based on an in-depth review of 12 extrusions, voice function after removal of GT implant was reported in 7 cases. The consequences of these 7 removals were no substantive deterioration (1), speech/voice remained altered (1), injection of autologous fat was required to remedy glottal insufficiency (1), all symptoms resolved (1), voice not changed significantly (1), voice recovered (1), and MPT and perceptual vocal evaluation revealed slight deterioration (1). Details about the other 5 removals were not reported. The reports of extrusion included a follow-up period ranging from 1 month to 10 years.[8]

As for factors predicting response, the authors report "Use of excessively large implants in women and occurrence of postoperative hematoma followed by infection are factors that may cause complications. "There was no significant difference in the incidence of GT extrusion between patients with a preserved perichondrium (2 in 286) and those without a preserved perichondrium (4 in 269)."[8]

Hemodialysis: One 2019 SR examined Flixene and Acuseal early cannulation grafts and reported mean time to first cannulation was 2 to 21 days for Flixene and 1.3 to 15 days for Acuseal. Primary patency rates (43.3% and 43.6%) and secondary patency rates (73.4% and 70.5%) at 12 months were similar for Flixene and Acuseal, respectively. The rate of steal syndrome (0 to 8% and 0 to 11%) was also similar for Flixene and Acuseal, respectively. The percent of patients with access thrombosis was lower in those treated with Flixene (11 to 29%) compared with Acuseal (17 to 41%). Pseudoaneurysm was also slightly lower in the Flixene group (0 to 6% vs. 0 to 15%). Although this SR attempted to include RCTs and observational studies, mainly small retrospective cohorts were included. Follow-up was 9 to 36 months.[7]

This SR reported the same data for polycarbonate urethane for Avflo and polyurethane Vectra grafts. Time to first cannulation was for Avflo was 7 days; all patients cannulated within 48 hours. For Vectra, the range was 1 to 19 days. Primary and secondary patency rates at 12 months were 58.2% and 79.2%, respectively, for the Avflo graft. For Vectra the corresponding rates were 63.7% and 85.8%. Avflo had no cases of pseudoaneurysm and access thrombosis ranged from 16% to 42%. Steal syndrome was not reported. Vectra had a rate of 0 to 3.5% for steal syndrome, 23 to 37% access thrombosis, and 0 to 17% pseudoaneurysm.[7]

A second SR from 2015, reviewed the evidence for the Hemodialysis Reliable Outflow (HeRO) graft in complex hemodialysis patients. This review included both RCTs and nonrandomized studies. Follow-up ranged from 7 to 18.5 months. Primary and secondary pooled patency rates were 21.9% (9.6 to 37.2%) and 59.4% (39.4 to 78%), respectively. The authors reported that the rate of interventions required to maintain HeRO patency ranged from 1.5 to 3 procedures per year and the rate of dialysis access associated steal syndrome was 6.3% (range 1 to 14.7%).[9]

A 2015 single-arm study also examined PTFE for hemodialysis. The authors evaluated standard ePTFE graft or a heparin-bonded ePTFE graft for hemodialysis access.[27] They reported primary patency was 35% and 14% for heparin-bonded grafts and 29% and 12% for standard ePTFE grafts at 6 and 12 months, respectively. Assisted primary patency was 54%, 41%, and 27% for heparin-bonded grafts and 41%, 30%, and 23% for standard grafts at 12, 24, and 36 months, respectively. Secondary patency was 83%, 83%, and 81% for heparin-bonded grafts and 81%, 73%, and 68% for standard grafts at 12, 24, and 36 months, respectively. All the grafts were ready for cannulation between 2 and 4 weeks postoperatively with no difference between the groups.[27]

There were significantly fewer thromboses at 1 month in the heparin-bonded group compared with standard grafts. Six heparin-bonded grafts (8%) occluded in the first month compared with 16 standard grafts (20%). An anatomic cause for occlusion in the first month could be found in 5 (83%) of the 6 heparin-bonded grafts compared with only 8 (50%) of the 16 standard grafts (p=0.18). There were also significantly fewer thromboses in heparin-bonded grafts during the first 5 months. Fifty out of 80 heparin-bonded grafts thrombosed during the follow-up period and required 119 thrombolytic treatments (range 0-8) compared with 57/80 standard grafts, which required 145 thrombolytic treatments (range 0-8). Mean time to first thrombosis was 9.7±10 months in the heparin-bonded group and 7.8±10.6 months in the standard group.[27]

Bleeding complications, graft abandonment and intervention rates were similar in both groups. There were no differences between upper and lower arm accesses and between the two graft types in the upper arm and the two graft types in the lower arm. No patients developed heparin-induced thrombocytopenia. Steal syndrome occurred in 1 patient in each group.[27]

A 2011 RCT, mean follow-up 33 months, compared standard cuffed ePTFE graft (Venaflo) to the bovine carotid artery (BCA) graft (Artegraft) for permanent hemodialysis access. Although there was no significant difference in secondary patency rates, primary and assisted primary patency rates were significantly higher in BCA than in the ePTFE grafts (60.5% vs. 10.1% and 60.5% vs. 20.8% at 1 year, respectively). Total number of interventions per patient year needed to prolong patency was 1.45±0.19 in the BCA group and 1.99±0.25 in the ePTFE group. The most common intervention used to achieve this secondary patency was percutaneous angioplasty. There were 1.19±0.18 angioplasties per patient year compared to 1.86±0.24 in the BCA and ePTFE groups, respectively.[11]

The most common complication was graft thrombosis which occurred 0.77±0.16 times per patient year in the ePTFE group compared to 0.34± 0.09 times per patient year in the BCA group. In the BCA group, 4 patients underwent 7 interventions before the first episode of thrombosis, which was not significantly different from the ePTFE group (5 patients underwent 6 interventions). There was no significant difference found for pseudoaneurysm and steal syndrome between groups.[11]

The BCA graft survival advantage was most profound in the upper arm grafts with significantly higher primary and assisted patency rates. There was no statistically significant difference in the rate of thrombosis, pseudoaneurysm formation, or arterial steal syndrome between the BCA and ePTFE groups within either graft location subset.[11]

Another 2011 RCT compared frozen saphenous vein with synthetic **GORE-TEX** vascular graft for treating arteriovenous fistulas. At the end of the 12 month follow-up period, 70.50% of the saphenous vein group and 72% of the **GORE-TEX** group were still being dialyzed from their shunts. Flowmetry showed that at the end of the year, 41.66% of the **GORE-TEX** group had good flow, 41.66% had moderate flow, and 16.66% had poor flow. In the saphenous vein group, 40% had good flow, 50% had moderate flow, and 10% had poor flow, which did not show significant differences. One patient died from complications of renal insufficiency. Auscultatable murmur rates were similar with 75% in the saphenous vein group and 76.66% of the **GORE-TEX** group. There was no significant difference in thrill sensation between the two groups in any of the follow-up visits, and 71.42% of the saphenous vein group and 73.33% of the **GORE-TEX** group had sensible thrill on their fistulas at the end of the year. The overall thrombosis rates of the fistulas were also similar at the end of the follow-up period, with 25% in the saphenous vein group and 20% in the **GORE-TEX** group.[12]

One of the nonrandomized comparative studies, published in 2015, assessed AVG made of PTFE GORE-TEX vs. tunneled cuffed catheters (TCCs)for hemodialysis through 24 months follow-up. The rate of loss of vascular access was 54.8% with PTFE graft and 44.6% with TCC during a 1-year follow-up. At the 24-month follow-up, loss of the vascular access was observed in 71% in the PTFE graft group and in 58.9% in the TCC group. Median survival of PTFE grafts at 24 months was 8.7 ± 3.4 months, whereas TCC survival was 14.1 ± 3.1 months.[1]

Vascular access thrombosis caused vascular access loss in 64.5% of patients with a PTFE graft and in 7.1% of patients with TCC, a significant finding. The mean time interval between vascular access placement and the onset of these major complications was 7.5 ± 7.9 months in the PTFE group and 13.0 ± 14.9 months in the TCC group (p=ns). The time between vascular access placement and the diagnosis of thrombosis was 7.1 ± 8.1 months in the PTFE group and after 1.8 ± 1.2 months in the TCC group. The overall infectious and thrombotic complications of vascular access during the follow-up (any complication) were more frequent in the PTFE graft group compared with the TCC group: 41.9% vs 12.5%.[1]

One out of 31 patients with PTFE graft (3.2%) and 20/56 of TCC patients (35.7%) died during the 12-month follow-up (p=0.001). In adjusted Cox regression analyses at 12 months, the TCC group patients had a 10.2 times higher likelihood of death than the PTFE group. At 24 months, the same observations were confirmed: 5/31 (16.1%) patients in the PTFE group had died versus 28/56 (50%) patients in the TCC group. In the PTFE group, 3 patients died from cardiovascular diseases and 2 from sepsis. In the TCC group, 8 patients died from cardiovascular diseases, 7 from sepsis, 4 from cachexia, 3 from gastrointestinal disease, 2 from malignant neoplasm, and in 4 cases, the cause of death was not known. The Cox regression analysis revealed that TCC patients had a 3.2 times higher risk of death than the patients with PTFE graft.[1]

Multivariate analysis adjusted for age, gender, type of vascular access, number of previously created arterial venous fistulae, diabetes, atrial fibrillation, and cigarette smoking found diabetes and all thrombotic and infectious complications of vascular access to be significant independent predictors of access survival. After 12 months, nondiabetic patients experienced a vascular access survival 2.2 times higher than diabetic patients. Vascular access survived in 62.1% of nondiabetic patients, whereas it survived in 44.4% of diabetic patients during a 12-month follow-up. Moreover, patients experiencing any infectious or thrombotic complications had a 2.7 times higher risk of vascular access failure than those not experiencing complications. At the 24-month follow-up, only diabetes maintained its role as a risk factor for vascular access survival. Patients without

diabetes had a 1.9 times higher probability of vascular access survival than that of diabetic patients independently of the type of vascular access. Vascular access survival was 27.8% in diabetic patients and 43.1% in nondiabetic patients.[1]

Abdominal aortic aneurysm: One non-randomized comparative study compared the Anaconda, Zenith Excluder and Endurant grafts for the treatment of abdominal aortic aneurysm in a 2013 publication. Follow-up was through day 30. The authors found that mean blood loss during surgery did not differ among the 4 groups. Endografts were successfully implanted in all patients. There were no open conversions, no deaths, and no major perioperative complications. There was no postoperative increase in troponin levels. Minor complications included local hematomas in femoral incisions in 3 patients (1 each in Anaconda, Zenith and Excluder), who were treated conservatively.[24]

Mural thrombus classification in this study was as follows: 0%, 9 cases (10%); 0% to 25%, 31 cases (36%); 25% to 50%, 9 cases (10%); >50%, 38 cases (44%). No statistically significant association was recorded among classification of mural thrombus and different types of endografts. At 1-month follow-up, endoleaks were recorded in 17.9% of Anaconda patients, 11.5% of Zenith patients, 13.0% of Excluder patients, and in 10% of Endurant-treated patients. No statistically significant differences were found for endoleak, operative time, and contrast volume administered intraoperatively among the graft groups.[24]

The Anaconda group showed the highest mean value of IL-10 at 24 hours and differed significantly from the Excluder and Endurant groups. The Zenith group also showed higher mean values than the Excluder group. Comparisons among the groups of endograft types at 48 hours showed that mean values in patients treated with Anaconda endografts were higher compared with Endurant and Excluder endografts, whereas mean values in patients treated with Zenith endografts were significantly higher compared with Endurant and Excluder endografts.[24]

Patients treated with Anaconda endografts also showed the highest IL-6 mean values at 24 hours postoperatively. Comparisons at 48 hours showed significant differences for Anaconda vs. Excluder, Anaconda vs. Endurant, Zenith vs. Excluder, and Zenith vs. Endurant. With regard to IL-8, although patients treated with Anaconda endografts showed the highest mean values at 24 hours and 48 hours postoperatively, no statistical differences were observed among the patients treated with different types of endografts. Patients in the Excluder group showed statistically lower mean values at 24 hours and 48 hours postoperatively.[24]

Higher mean values of white blood cells were recorded after 24 hours in patients treated with the Anaconda endograft compared with the Excluder and Zenith endografts and the Endurant endograft compared with the Excluder and Zenith endografts. After 48 hours, statistically significant differences were observed among Anaconda and every other graft group as well as for the Endurant vs. Excluder and Zenith vs. Excluder groups. No statistically significant differences were observed among the different endograft types concerning platelet values at 24 hours and 48 hours postoperatively. No statistically significant correlation was found between the categories of the amount of clot in the abdominal aortic aneurysm (AAA) before repair and any marker of postimplantation syndrome. The group of patients had no clinical adverse events related to postimplantation inflammatory syndrome.[24]

No differences in the mortality and morbidity rates were observed among the 4 groups.[24]

Femoropopliteal artery bypass: One SR, conducted in 2014, compared Dacron to PTFE grafts for above-knee femoropopliteal artery bypass. The maximum study follow-up was 10 years. Data from 6 RCTs found that primary and secondary patency rates at 12 months were not significantly different for the 2 materials. However, at 24-, 36-, and 60-months primary patency rates were significantly better with Dacron compared with PTFE grafts (relative risk [RR] 0.79; p=0.003; RR 0.80; p=0.03; RR 0.85; p=0.02). Higher secondary patency rates were also found for Dacron at 24 months (RR, 0.75; p=0.02) and 60 months (RR 0.76-0.77; p=0.03-0.27). Although primary patency was similar between grafts (28% vs. 28%; p=0.12), secondary patencies were better with Dacron at 10 years (49% vs. 35%; p=0.01). There was no difference in amputation, overall morbidity, or mortality rates between the 2 surgical graft populations.[10]

One non-randomized comparative study, published in 2014, compared PTFE to saphenous vein graft for femoropopliteal bypass surgery for lower limb ischemia at 12 months mean follow-up. PTFE had a lower graft patency rate than saphenous vein grafts but the difference did not reach statistical significance.[22]

Local Host Responses (animal studies)

We did not identify any animal studies reporting local host responses.

Systemic Responses

Mortality and ischemia were the most investigated systemic responses among the studies included. Pneumonia, limb salvage, renal insufficiency, and cardiac events were also investigated in several studies. The studies we reviewed most often found no statistically significant difference in these responses when comparing the use of a PTFE graft to another graft material or technique, but a lack of statistical significance does not imply that the risks are similar. Several studies report responses without a comparison to a reference material.

Femorofemoral crossover: One 2018 retrospective comparative study found no statistically significant difference in the frequency of skin rashes at the 30-day follow-up visits for PTFE (4.5%) and femoral veins (3.3%) (autologous and cryopreserved).[15]

Hemodialysis: One prospective comparative study, published in 2015, on chronic hemodialysis patients reported mortality rates at up to 24 months follow-up. One out of 31 patients with PTFE graft (3.2%) and 20/56 of TCC patients (35.7%) died during the 12-month follow-up (p=0.001). In adjusted Cox regression analyses at 12 months, the TCC group patients had a 10.2 times higher likelihood of death than the PTFE group. At 24 months, the same observations were confirmed: 5/31 (16.1%) patients in the PTFE group had died vs. 28/56 (50%) patients in the TCC group. In the PTFE group, 3 patients died from cardiovascular diseases and 2 from sepsis. In the TCC group, 8 patients died from cardiovascular diseases, 7 from sepsis, 4 from cachexia, 3 from gastrointestinal disease, 2 from malignant neoplasm, and in 4 cases, the cause of death was not known. The Cox regression analysis revealed that TCC patients had a 3.2 times higher risk of death than the patients with PTFE graft.[1]

Peripheral arterial disease: One retrospective comparative study, published in 2014, reported systemic effects of precuffed ePTFE grafts compared with autologous saphenous vein (ASV) grafts used in patients with peripheral arterial disease through 5 years of follow-up. The following systemic responses were noted by study authors for PTFE vs. ASV: myocardial infarction 4 (2%) vs. 8 (3%); cord compression 6 (4%) vs. 5 (2%); arrhythmia 2 (1%) vs. 4 (1%); hypovolemic shock 0 vs. 1 (0%); pneumonia 5 (3%) vs. 4 (1%); respiratory insufficiency 5 (3%) vs. 2 (1%); cerebrovascular accident 1 (1%) vs. 2 (1%); neurologic 2 (1%) vs. 3 (1%); acute renal failure 2 (1%) vs. 5 (2%); diarrhea 3 (2%) vs. 2 (1%); ileus 0 vs. 1 (0%); and Delirium 5 (3%) vs. 4 (1%). None of these differences were statistically significant.[23]

Abdominal aortic aneurysm: One 2013 non-randomized prospective comparative study on treating AAA observed that fever was more intense in the group of patients receiving the Anaconda stent graft, mainly 24 hours postoperatively. The authors note that the maximum values of body temperature were positively correlated with the postoperative values of white blood cells (WBCs), IL-6, and IL-10, indicating a systemic inflammatory response. They recorded a more intense inflammatory response after Anaconda stent graft implantation compared with the other 3 endografts studied. Serum levels of IL-6 and IL-10 were significantly higher 24 hours and 48 hours postoperatively compared with preoperative levels in all groups. Patients in the Excluder group showed the smallest increase in levels of serum IL-6 and IL-10 at 24 hours and 48 hours postoperatively. Mean difference in cytokine levels after aneurysm exclusion was greater for Anaconda vs. Excluder compared with group Anaconda vs. Zenith.[24]

Anterior sector reconstruction: Finally, a 2018 retrospective comparative trial comparing nonringed ePTFE grafts to venous extension grafts for anterior segment reconstruction was unable to find a statistically significant difference in rates of sepsis between the two groups.[16]

Overall Quality of Evidence

The evidence base was large. While the bulk of the studies had control groups, the same intervention and comparator combination rarely occurred in more than one study. Therefore, the quality of evidence for local and systemic responses is low.

Stents

Nine human studies. (1 systematic review,[28] 3 RCTs,[29-31] and 5 non-randomized controlled studies[32-36]). For further information see Table 5 in Appendix D.

Local Host Responses (human studies)

The studies evaluated local responses of use of PTFE-covered stents for coronary procedures in 4 studies,[28,30,35,37] liver procedures in 3 studies,[29,32,36] and urethral procedures in 1 study.[34]

Coronary procedures: One systematic review[28] examined PTFE-covered stents and bare-metal stents for patients with focal infrarenal aortic occlusive disease, aortoiliac complex occlusive disease, or iliac artery occlusive disease in 49 studies, including RCTs and cohort studies/case series. Few included studies directly compared the 2 types of stents. The range of 1-year primary and secondary patency rates was similar in studies of covered stents and of bare stents. For recurrent stenosis and complications, the ranges of rates extended to greater frequencies in the studies of bare stents than in those of covered stents. One RCT[30] compared PTFE-covered stents and bare stents for patients with coarctation of aorta. Neither recoarctation nor pseudoaneurysm were significantly different between groups. There were no occurrences of obstruction, dissection, or post-coarctation of aorta syndrome in either group. One non-randomized controlled study[37] compared PTFE-covered stents and polyurethane-covered stents for patients with coronary artery perforation. Pericardial effusion was higher in the PTFE group (72% vs. 41%), but stent thrombosis and restenosis were not significantly different between the groups. One non-randomized controlled study[35] compared PTFE-covered stents with bare stents for patients with iliac artery occlusions. Overall primary patency was not statistically significant between the groups. Patency for Trans-Atlantic Intersociety Consensus (TASC) II D classified lesions significantly worse for the bare stent group (54% vs. 89%). No significant differences were found for TASC B and C classifications.

Liver procedures: One RCT[29] compared PTFE-covered stents with bare stents in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedures. The risk of shunt dysfunction was significantly reduced in the covered stent group compared to the bare stent group (HR 0.60),. Early complications of the procedure (including death, thrombosis, and fever up to the first month of follow-up) and the risk of hepatic encephalopathy were not significantly different between the groups. One non-randomized comparative study[36] compared PTFE-covered stents with bare stents in patients undergoing TIPS. The occurrence of shunt dysfunction and reinterventions for stenosis were lower in patients with covered stents than in those with bare stents (22% vs 57% and 19% vs 33%, respectively),. Hepatic function deterioration was similar in both groups. One non-randomized comparative study[32] compared PTFE-covered stents with endoscopic therapy plus non-selective beta-blocker drugs in patients with liver cirrhosis and endoscopically confirmed gastroesophageal variceal bleeding. Variceal rebleeding occurred significantly less frequently for the PTFE-stent group (7.8% vs. 39.2%), but hepatic encephalopathy and overall adverse events were not significantly different between groups.

Urethral: One non-randomized controlled study[34] compared PTFE-covered external stents, PTFE-covered internal stents, and polyurethane-covered stents in patients with recurrent benign urethral strictures. Overall complications were significantly higher for external PTFE stents than the other 2 groups. Tissue ingrowth or membrane separation and stent migration were significantly higher for the internal PTFE stent group than the others. Patency was improved for external PTFE stents compared to internal PTFE stents (but not polyurethane stents) for up to 6 months after the procedure, but there were no significant differences in maintained patency beyond 6 months and up to 18 years. Granulation tissue formation was not significantly different between any of the groups.

Systemic Responses (human studies)

The studies evaluated systemic responses of use of PTFE-covered stents for coronary procedures in 5 studies[28,30,31,35,37] and liver procedures in 3 studies.[29,32,36]

Coronary procedures: One systematic review[28] examined PTFE-covered stents and bare-metal stents for patients with focal infrarenal aortic occlusive disease, aortoiliac complex occlusive disease, or iliac artery occlusive disease in 49 studies, including RCTs and cohort studies/case series. Few included studies directly compared the two types of stents. The range of distal embolism rates extended to greater frequencies in the studies of bare stents than in those of covered stents. One RCT[30] compared PTFE-covered stents and bare stents for patients with coarctation of aorta. There were no significant differences between groups in terms of mortality, duration of hospitalization, or number of normotensive patients. One RCT[31] compared Symbiot-covered stents, bare stents plus FilterWire, and bare-metal stents alone in patients with degenerative saphenous vein graft lesions. There were no significant differences between the groups for 6-month mortality, 6-month myocardial infarction (MI), or long-term MI. One non-randomized controlled study[37] compared PTFE-covered stents and polyurethane-covered stents for patients with coronary artery perforation. All-cause mortality, major adverse cardiovascular events, cardiac death, and MI were all not significantly different between the groups. One non-randomized controlled study[35] compared PTFE-covered stents with bare stents for patients with iliac artery occlusions. There were no significant differences between the groups in terms of overall complications, major cardiac events, respiratory failure, dialysis, and mortality.

Liver procedures: One RCT[29] compared PTFE-covered stents with bare stents in patients undergoing TIPS. There were fewer hospitalizations and number of hospital days in the covered group than in the bare group. Mortality was not significantly different between the groups. One non-randomized controlled study[36] compared PTFE-covered stents with bare stents in

patients undergoing TIPS. Median survival time was not significantly different between the groups. One non-randomized controlled study[32] compared PTFE-covered stents with endoscopic therapy plus non-selective beta-blocker drugs in patients with liver cirrhosis and endoscopically confirmed gastroesophageal variceal bleeding. Survival and overall adverse events were not significantly different between the groups.

Overall Quality of Evidence

The evidence base was moderately sized. Current evidence consistently suggests that occurrence of adverse events is lower or not significantly worse with PTFE stents than in control groups, suggesting that PTFE stents cause no unique harms (neither local toxicity, nor device events, nor systemic responses). The majority of the evidence comes from study designs with greater limitations. The single identified systematic review primarily included studies without control groups. Among the non-randomized comparative studies identified, most did not identify or control for potential confounding variables. Therefore, the quality of the evidence that PTFE in stents causes no harm is low.

Stent Grafts

Fifteen human studies (2 SRs,[38,39] 6 RCTs,[40-45] and 7 non-randomized comparative studies[46-52]). For further information, see Table 6 in Appendix D.

Local host responses (human studies):

Primary patency. Two SRs reviewed Viabahn and Hemobahn stent-grafts, one for the treatment of long de novo lesions of the superficial femoral artery and one for the treatment of popliteal aneurysms, and reported that the primary patency rate at 1 year varied between 44% and 86%.[38,39] Four RCTs compared the primary patency of PTFE stent-grafts (Flair, Fluency Plus, Viabahn with Proptan surface) to percutaneous transluminal angioplasty (PTA) for the treatment of in-stent restenosis in the superficial femoral artery or failing hemodialysis access.[40,42,44,45] All studies reported primary patency was significantly higher for the stent-graft groups at 12 (ranging 47.6 to 74.8%) and 24 months (ranging 26.9 to 58.4%).[40,42,44,45] One controlled cohort study found that for patients with portal hypertension undergoing the TIPS procedure, the Josent PTFE-covered stent-graft showed significantly better primary patency after 14 days (100%), 6 months (95%), and 2 years (82.9%) compared to the bare metal stent.[46]

However, an RCT and a controlled cohort study comparing the PTFE-covered stent-grafts to a bare metal stent found that primary patency rates did not significantly differ between the stent-graft groups and the bare metal stent groups at 3 and 4 years.[43,49] Patency rates diminish most rapidly in the first year after device implantation.[43]

Two studies reported that stent-graft failure was primarily due to occlusion and stenosis.[39,46] Portal venous thrombosis was identified also as a major risk factor for technical failure.[46] One controlled cohort study found that renal dysfunction was significantly associated with renal stent occlusion or stenosis.[49] One SR found significantly better patency with devices with a diameter of 6 mm or larger.[38] One RCT identified greater residual stenosis after initial PTA as a risk factor for loss of patency, and smaller diameter of the reference segment adjacent to the stenosis and the use of a deep vein as the outflow as predictors of primary patency, when treating failing dialysis vascular access due to restenosis.[45]

Restenosis. Two SRs,[38,39] 3 RCTs,[40-42] and one controlled cohort study[49] reported the occurrence of restenosis. In one SR reviewing Viabahn and Hemobahn stent-grafts for the treatment of long de novo lesions of the superficial femoral artery (SFA), in-stent restenosis occurred in only 5 cases out of 747 at 5 years, less than 1%.[38] Two RCTs reported the rate of restenosis was significantly lower for PTFE-covered stent-grafts (ranging 19.7 to 63.0%) compared to PTA (ranging 73.4 to 82.6%).[40,42] One study, in patients undergoing endovascular aneurysm repair (EVAR), found freedom from stenosis in renal artery stents was 92.9% at 1 year and 86.7% at 4 years for stent-grafts, significantly higher than bare-metal stents (84.5% and 58.9%, respectively).[49]

Occlusion. One SR,[39] 1 CC,[51] and 2 RCTs[41,42] reported the occurrence of occlusion. The SR reviewing Viabahn and Hemobahn stent-grafts reported occlusion leading to endograft failure in 19.8% of cases (n=42).[39] One RCT reported that the 12-month device-related/procedure-related AE rate was 2.3% for the Flair stent-graft, significantly lower than the rate for PTA (8.7%), and the most common adverse event was thrombotic occlusion (n=60).[42] Another RCT reported that target vessel occlusion for the Jostent stent-graft (14%) was comparable to bare metal stent at 5 years.[41] While another comparative cohort study,

comparing PTFE stent-graft to transcatheter embolization for the treatment of visceral artery aneurysm and pseudoaneurysm, reported occlusion as a complication in 2 out of 30 stent-grafts (6.7%) at 6 months.[51]

Thrombosis. One SR[38] and 3 RCTs[41,45,47] reported the occurrence of thrombosis. One RCT reported that stent thrombosis (10.9%) for the Jostent stent-graft was comparable to bare metal stent (5.6%) at 5 years.[41] In another RCT, new-onset thrombus occurred in 21% of Excluder ePTFE stent-grafts used in EVAR, compared to 14% in the bare metal stent group.[47] One RCT reported a single case of thrombosis (5%).[45] One SR noted that graft failure was related to acute thrombosis because of local disease progression, causing edge-stenosis and stent kinking.[38] One comparative cohort study postulated that the lack of pores in PTFE may prevent the formation of a thrombus and improve tissue repair by preventing platelets and inflammatory cells from crossing the graft.[52]

Embolism. One SR[38] and 1 RCT[42] reported a low occurrence of embolism. A SR reported a distal embolism rate of 3% among 747 patients across 14 studies.[38] One RCT reported a single case of embolism among 128 patients undergoing repair of hemodialysis access using the Flair stent-graft.[42]

Hematoma. One SR[39] and 1 RCT[42] reported a low occurrence of hematoma postimplantation. One SR reported 3 cases of access site hematoma requiring surgical revision in Viabahn and Hemobahn stent-grafts.[39] One RCT reported 5 cases hematoma after implant (4%).[42]

Stent fracture. One SR,[39] one RCT,[43] and 1 controlled cohort study[49] reported stent fractures. One SR reported 14 cases of endograft fracture (5.6%), which resulted in occlusion and type III and IV endoleaks.[39] The RCT found that stent fractures (2.6%) were significantly less common with the stent-graft, compared to bare metal stent (50%).[43] Similarly, 1 comparative cohort study reported stent fractures in 2 covered stents (1.2%), significantly fewer than in the bare metal stent group (n=8).[49] Another RCT reported no stent fractures observed in the 39 stent-grafts through 12 months.[44] PTFE-covered stent-grafts may be less prone to fracture due to greater flexibility provided by a strong fixation of the PTFE layers to the arteries.[49] Repetitive motility of the knee joint may predispose the endograft to kinking, fracture, and occlusion.[39]

Endoleak. One SR[39] and 1 controlled cohort study[52] reported endoleak as a postoperative complication. One SR reported 15 cases of endoleak (6%).[39] In 1 controlled cohort study, postoperative endoleak occurred in 13 cases (35.1%) after EVAR with the Excluder ePTFE stent-graft, comparable to 11 endoleaks in the Zenith group (21.6%). A change in fibrinogen degradation product (FDP) of ≤3.1 µg/mL at day 7 was predictive of an endoleak.[52]

Migration. One SR reported that postoperative endograft migration occurred in 13 cases (5.2%).[39] One RCT stated that there were no instances of device migration or kinking among 128 patients receiving a PTFE stent-graft.[42]

TVF, TVR, TLV. One RCT reported the significantly higher incidence of target vessel failure (TVF) (68.3%), target vessel revascularization (TVR) (48.2%), and target lesion revascularization (TLR) (43.9%) after percutaneous coronary intervention (PCI) in the stent-graft group than in the bare metal stent group after 2 years and annually up to 5 years.[41] TVF and TVR occurred more frequently after 2 years.[41]

Hemorrhage. One RCT reported 10 cases of postoperative hemorrhage (7.8%) in the PTFE stent-graft group.[42] One controlled cohort study reported a single case of hemorrhage requiring stent-graft removal out of 30 patients (3.3%).

Pseudoaneurysm and vessel rupture. One RCT also reported 9 cases of pseudoaneurysm (7%) and 2 cases of vessel rupture (1.6%) among 128 patients in the stent-graft group.[42]

Systemic Responses (human studies):

PIS. Two comparative cohort studies reported the occurrence of postimplantation syndrome after EVAR, defined as the composite of a body temperature of >38°C coinciding with C-reactive protein (CRP) >10 mg/L. In 1 study, the incidence of postimplantation syndrome (PIS) was 17.9%, significantly lower than the polyester stent-graft group (56.1%).[48] In this study, PIS occurred almost exclusively in the first 2 days after ePTFE implantation, and the amount of graft material implanted and new-onset thrombus were not associated with PIS.[48] In the other study, PIS occurred in 46.6% of the ePTFE stent-graft group within 72 hours post-EVAR procedure, not significantly different than the chromium-cobalt endoskeleton group (33.29%).[47] In this study, the development of PIS was found in part to be due to new-onset mural thrombus releasing pro-inflammatory

cytokines.[47] Although postoperative hospital stay was longer for patients with PIS, adverse outcomes at 24 months did not differ between those with and without PIS.[47]

Inflammatory markers. Two comparative cohort studies reported an increase in inflammatory markers after stent-graft implantation.[50,52] In 1 study, pulse wave velocity (PWV), and serum levels of IL-8 and IL-10 significantly increased at 12 months from baseline in both groups.[50] However, the effect on PWV and interleukins were was significantly less pronounced for PTFE compared to polyester. Additionally, WBC, highly sensitive CRP (hsCRP), and OPG, and decreased significantly from baseline for the PTFE group. Mean blood pressure, osteoprotegerin (OPG), and AAA diameter were independently associated with PWV, a marker of arterial stiffness.[50] In another study, WBC and CRP increased on day 1 after EVAR, peaked at day 3, and returned to pre-treatment level by day 7 in both groups, but the magnitude of change was significantly less in the ePTFE group.[52]

Hepatic encephalopathy. In 1 comparative cohort study, the Viatorr stent-graft was compared to bare metal stent for patients with portal hypertension undergoing TIPS. Hepatic encephalopathy (HE) occurred in 19.3% of cases in the Viatorr group (n=16), and required at least 1 revision within the first year after implantation in 4.8% of cases (n=4).[46]

Death. One SR,[39] 4 RCTs,[40-43] and 2 comparative cohort studies[46,51] reported deaths. In 3 RCTs[40,42,43] and 1 of the controlled cohort studies,[51] death was determined to be unrelated to the device. In the other studies, it was not stated whether death was attributable to the device. One SR reported that 1 patient died within 30 days from acute endograft thrombosis leading to acute myocardial infarction (AMI).[39] An RCT reported that all-cause deaths (29.8%) and MI (26.2%) were comparable to bare metal stent at 5 years.[41] The controlled cohort study reported 8.4% of patients in the PTFE stent-graft group died during the first year, which was also comparable to the incidence of death in the bare metal stent group.[46]

Overall quality of evidence:

The evidence base was large and included randomized and non-randomized comparative studies with more than 50 patients. The quality of evidence for patency and restenosis in PTFE stent-grafts is moderate, as this was reported in almost all human studies. Other local responses/events were reported in fewer studies, so the quality of evidence is low. The quality of evidence for systemic responses was low, because these outcomes rarely occurred (affecting few patients in the studies that reported them) and it is often unclear whether the response was due to the material.

Sutures

One human systematic review.[53] For further information see Table 7 in Appendix D.

Local Host Responses (human studies)

One systematic review reported PTFE has a significantly lower overall incidence of complications (5%, 95% CI 0.6–13) compared to fascia lata (25%, CI 14%–39%). However, PTFE had a higher rate of infections (1.9%, CI 0.2–5.4 vs. 1%, CI 0.5–1.6).

Local Host Responses (animal studies)

We did not identify any animal studies reporting local host responses.

Systemic Responses

We did not identify any studies reporting systemic responses.

Overall Quality of Evidence

This summary was based on a systematic review of 53 studies of a single procedure type using 4 materials. The rate of complications was lower with PTFE sutures, suggesting that they cause no harm. A moderate to large sample size was included for each material, but the study excluded RCTs, so the quality of evidence supporting the statement that PTFE sutures do not cause harm is low.

ECRI Surveillance Data

ECRI surveillance database searches were guided by the terms listed in Appendix F. The accident investigation and PRN data on PTFE devices generally involved a component breaking or migrating, resulting in a foreign body. The PSO data included 4 reports of complication with associated harm scores indicating error, but no harm to the patient. The healthcare technology alerts database returned the most results (32 alerts). These consisted of IFU and labeling recalls, but also more serious hazards such as graft and stent component separation and graft tears.

Patient Safety Organization

Search Results:

ECRI PSO identified 39 reports that involved PTFE materials. These incidents occurred between May 2017 and November 2020. Four reports involved complications, of which 3 reported no harm to the patient and 1 did not report a harm score.

All individual PSO event reports are redacted and included in Appendix F.

Table 3: Complications in PTFE-related PSO Event Reports

Complication	Suture	Graft	Total
Retained foreign object	1		1
Device malfunction	1		1
Hematoma/Hemorrhage	1		1
Occlusion		1	1
Total	**3**	**1**	**4**

Table 4: Harm score associated with PTFE-related event reports.

Harm Scores (NCC-MERP)		Suture	Graft	Total
A	No Error			
B1	Error, No Harm			
B2				
C				
D		3		3
E	Error, Harm			
F				
G				

Harm Scores (NCC-MERP)		Suture	Graft	Total
H				
I	Error, Death			
NULL*			1	1
Total		**3**	**1**	**4**

**Harm score was not reported*

Accident Investigations

Investigation files from 2005-2020 were searched to recover cases pertaining to the PTFE device categories listed above.

Search Results: 21 investigations were recovered but only 2 were considered relevant due to the following:

- Involved a device believed to be made of PTFE
- Used for longer than a temporary basis

These are summarized in **Error! Reference source not found.**.

A redacted description of these investigations are included in Appendix F.

Table 5: Accident Investigations of Patient Incidents Involving PTFE-related Devices

Device Type	# Investigations	Reported Problem and Findings
Intra-aortic Balloon	1	Systemic thrombosis reported
Sling	1	Foreign material migrated to abdomen

ECRI Problem Reports

Search Results: The search returned 10 reports submitted by ECRI members.

Key Issues: The reports detail includes device- tips breaking off and lodging in organs. Some reports specified patient injury.

Safety Concerns: The reports specified device failures and broken off tips migrating and lodging in organs.

All problem reports are redacted and included in Appendix F

Table 6: ECRI Problem Report Summary

Device Type	# Problem Reports	Reported Problem (number problem reports)
System, Endovascular Graft, Arteriovenous (Av)	1	Device tip broke off and migrated to the lung

Device Type	# Problem Reports	Reported Problem (number problem reports)
Dialysis Access Circuit Stenosis Treatment (PFV)		
System, Endovascular Graft, Aortic Aneurysm Treatment (MIH)	1	Wire tip broke off and lodged in aortic bifurcation
Prosthesis, Vascular Graft, Of 6mm And Greater Diameter (DSY)	1	Wire pulled out of graft during implanting
Catheter, Intravascular Occluding, Temporary (MJN)	7	Pre-use test failures, one failure during use

Healthcare Technology Alerts

Search Results: The search returned 33 manufacturer or regulatory agency-issued alerts describing problems with labeling, IFU updates, no FDA clearance, suspended manufacturing, failure to meet specifications, inclusion of incorrect components, broken component, component detachment, graft tears, leakage, and deployment and withdrawal difficulty, summarized in **Error! Reference source not found.**.

Table 7: Summary of Regulatory and Manufacturer Alerts

Device Type	# Alerts	Reported Problem
DQY (Percutaneous Catheter)	2 Manufacturer-issued	• Mislabeling
DSY (Prosthesis, Vascular Graft, of 6mm and Greater)	8 Manufacturer-issued	• Suspended manufacturing • Packaging issue • Mislabeling • IFU update
DSY (Prosthesis, Vascular Graft, of 6mm and Greater); DYF (Prosthesis, Vascular Graft, of less than 6mm)	2 Manufacturer-issued	• Graft tears • Mislabeling
MIH (System, Endovascular Graft, Aortic Aneurysm Treatment)	1 FDA-issued 16 Manufacturer-issued	• Component separation • Continued surveillance required • Deployment and/or withdrawal complications • Mislabeling • Wrong silicone lubricant used • Out of spec part leads to tip detachment • Leakage • Broken components • Rapidly emptying fill polymer syringe • IFU update
PFV (System, Endovascular Graft, AV Dialysis Access Circuit Stenosis Treatment)	16 Manufacturer-issued	• Deployment and/or withdrawal complications
PNF (Aortic Stent)	1 Manufacturer-issued	• No FDA clearance
PRL (Iliac covered Stent, Arterial)	1 Manufacturer-issued	• IFU update
NIP (Stent, Superficial Femoral Artery)	1 Manufacturer-issued	• Component separation

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of PTFE. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. If the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

PTFE as a Material

Only 1 animal study was included that reported local response, and there were no studies on systemic responses for PTFE as a material. While the quality of evidence was very low, the single study did report inflammatory response and indicated potential for associated oxidative damage and destruction of implanted devices. This indicates an area of further research considering the complications noted in the surveillance data of components breaking and separating.

Catheters

A single systematic review on PTFE PICs reported a higher phlebitis incidence vs. polyurethane (PUR) PICs. One RCT of PIC use in newborns found no inflammation or blockage with PTFE or PUR PICs. Additional research is indicated in each patient population (adult and neonatal).

Filters

One study reported thrombus in or near a PTFE mesh filter. A second study reported major adverse events including 2 deaths, 7 strokes, and 1 MI out of 250 patients. There were no comparative studies in these reports. Controlled trials are indicated considering the severity of these outcomes.

Grafts

Included studies suggest no difference in local or system outcomes with PTFE grafts compared to another graft material or technique. While the bulk of the studies had control groups, the same intervention and comparator combination rarely occurred in more than 1 study. Additional controlled studies containing these variables together in the same study is indicated for confirmation of this trend.

Stents

Current evidence consistently suggests that occurrence of adverse events is lower or not significantly worse with PTFE stents than in control groups, however the quality of evidence is low. RCTs are indicated to confirm this observed trend.

Stent Grafts

There is moderate quality of evidence supporting lower or similar rate of occlusion and restenosis in PTFE stent-grafts compared to other materials. Additional research is indicated to confirm this observation with other local outcomes, which were not observed as frequently as occlusion and restenosis.

Sutures

Only one human systematic review was included that reported local responses, which reported lower overall complication rate, but a higher rate of infection. There were no systemic responses reported. Additional research is indicated for PTFE sutures to determine if its material properties affect infection rate.

Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

Inclusion Criteria

1. English language publication
2. Published between January 2010 and August 2020
3. Human studies
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of HA or priority devices that include this material

Exclusion Criteria

1. Foreign language publication
2. Published before January 2010
3. Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4. Off-topic study
5. On-topic study that does not address a key question
6. No device or material of interest
7. No relevant outcomes (adverse events or biocompatibility not reported)
8. Study is superseded by more recent or more comprehensive systematic review

Quality of Evidence Criteria

1. **Quality of comparison** – is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2. **Quantity of data** – number of systematic reviews and individual studies providing relevant data, as well as the proportion of included studies that reported a specific outcome.
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. Magnitude of effect – what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5. **Directness of evidence** – do human studies isolate the effect of the device (i.e., can the adverse effects be attributed to the device)?
6. Is there evidence of a **dose response or time response** (e.g., adverse effects increase with longer exposure time)?

Appendix B. Search Summary

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n=174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Literature Search for Polytetrafluoroethylene (PTFE)

Set Number	Concept	Search Statement
Material		
1.	**PTFE**	**'polytetrafluoroethylene'/exp OR polytetrafluoroethylen* OR polytetrafluorethylen* OR 'poly tetra fluoro ethylene*' OR 'poly tetra fluoroethylene*' OR 'polytetra fluoroethylene*' OR 'polytetrafluoro ethylene*' OR 'ptfe'/exp OR ptfe* OR epfte* OR 'e-ptfe*' OR cpfte* OR 'c-ptfe*' OR 'uptfe*' OR 'hd-ptfe*' OR 'hep-ptfe*'**
2.	PTFE Trade Names	'politef':ti,ab OR polytef:ti,ab OR teflon OR 'gore-tex*' OR goretex* OR 'gor-tex*' OR algoflo OR chemfluor OR dyneon OR fluon OR fluoroflex OR fluoroplast OR halon OR hostaflon OR novaflon OR polyfene OR softform OR tarflen OR tecnoflon OR technoflon OR tetron OR monotex OR cytoplast OR 'chord-x' OR sealptfe
3.	PTFE devices	'axs catalyst' OR 'scepter xc':ab OR 'scepter c' OR 'surefire spark' OR 'surefire precision' OR (('hero' OR 'haemodialysis reliable outflow' OR 'hemodialysis reliable outflow') NEXT/3 (graft* OR device)) OR 'fusion vascular graft' OR 'fusion bioline' OR (('spiral flow' OR 'spiral laminar flow' OR 'slf spiral') NEXT/3 (graft* OR prosthesis)) OR acuseal OR flixene OR exxcel* OR ((advanta OR venaflo OR carboflo OR distaflo OR impra OR dynaflo OR liefstream OR rebel) NEXT/4 (graft* OR stent*)) OR 'gore hybrid' OR propaten OR 'stretch vascular graft' OR 'ringed vascular graft' OR (gore*:ti,ab,kw,dn AND ('excluder*' OR tag OR 'carotid stent*' OR 'hybrid vascular graft*')) OR 'excluder'/dn OR 'aorfix*' OR 'ovation*' OR 'powerlink*' OR 'endograft power link'/dn OR covera OR 'fluency plus' OR 'cheatham platinum' OR 'cp stent*' OR 'afx'/dn OR 'viabahn*' OR 'via-bahn*' OR ('tigris' AND (gore* OR vascular OR stent*)) OR 'resolute microtrac' OR 'resolute integrity' OR graftmaster* OR jostent* OR 'advanta':dn OR 'afx'/dn OR 'aorfix'/dn

		OR 'cheatham platinum':dn OR 'cp stent*'/dn OR 'covered cp stent*':dn OR 'covered cheatham platinum stent*':dn OR 'excluder':dn OR 'fluency':dn OR 'fluency plus':dn OR 'gore excluder':dn OR 'gore tag'/dn OR 'graftmaster*':dn OR 'ovation':dn OR 'powerlink':dn OR 'propaten':dn OR 'tag'/dn OR 'acuseal':dn OR 'axs catalyst*':dn OR 'scepter xc':dn OR 'flixene':dn OR 'hero':dn OR 'jostent graftmaster':dn OR 'jostent selfx'/dn OR 'scepter c':dn OR 'sofia':dn OR 'sofia plus':dn OR 'viabahn*':dn
4.	Combine and Limit by language and publication date	(#1 OR #2 OR #3) AND [english]/lim AND [2011-2021]/py
5.	Limit by publication type	#4 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

6.		**'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'**
7.		'degradation'/exp OR degrad* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorbable OR adsorbable OR split OR splitting OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR movement OR shift* OR transfer* OR 'delamination'/exp OR delamina* OR leach* OR filtrate OR filter* OR seep* OR evaginat* OR subsidence
8.		Leachable* OR extractable*
9.		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat* OR fail*) NEAR/3 (graft? OR endograft? OR stentgraft? OR stent? OR suture OR catheter? OR microcatheter?)
10.		'mechanics'/exp
11.		'device material'/exp/mj
12.		'Biomedical and dental materials'/exp/mj
13.	Combine sets	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14.	**PTFE + Material Response**	**#5 AND #13**

Host Response

15.		**Host NEAR/2 (reaction* OR response*)**
16.		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
17.		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
18.		(immun*:ti OR autoimmun*:ti OR hypersens*:ti) NOT immunofluorescenc*:ti
19.		'inflammation'/exp OR inflamm*
20.		'foreign body' OR granuloma* OR 'foreign body'/exp OR (fibro*NEAR/2 capsule*)

21.		'adhesion'/exp OR 'tissue adhesion'/exp OR 'tissue response' OR 'bone response'
22.		(protrude* OR protrus*)
23.		'thrombosis'/exp OR 'stenosis, occlusion and obstruction'/exp OR 'stent complication'/exp OR restenosis OR thromb*
24.	Combine sets	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25.	**Combine sets** **PTFE + Material Response+ Host Response**	**#14 AND #24**
26.	**PTFE devices + Host response (excluding thrombosis)**	#3 AND #5 AND (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
27.	**Final set**	**#25 OR #26**

Example Embase Explosion

Mechanics/exp

- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance
- Compressive strength
- Dynamics
    - Compression
    - Computational fluid dynamics
    - Decompression
        - Explosive decompression
        - Rapid decompression
        - Slow decompression
    - Gravity
        - Gravitational stress
        - Microgravity
        - Weight
            - Body weight
                - Birth weight
                    - High birth weight
                    - Low birth weight
                        - Small for date infant
                        - Very low birth weight

        - Extremely low birth weight
    - Body weight change
        - Body weight fluctuation
        - Body weight gain
            - Gestational weight gain
        - Body weight loss
            - Emaciation
        - Body weight control
        - Fetus weight
        - Ideal body weight
        - Lean body weight
        - Live weight gain
    - Dry weight
    - Fresh weight
    - Molecular weight
    - Organ weight
        - Brain weight
        - Ear weight
        - Heart weight
        - Liver weight
        - Lung weight
        - Placenta weight
        - Spleen weight
        - Testis weight
        - Thyroid weight
        - Uterus weight
    - Seed weight
    - Tablet weight
    - Thrombus weight
- Weightlessness
- Hydrodynamics
    - Hypertonic solution
    - Hypotonic solution
    - Isotonic solution
    - Osmolality
        - Hyperosmolality
        - Hypoosmolality
        - Plasma osmolality
        - Serum osmolality
        - Urine osmolality
    - Osmolarity
        - Blood osmolarity
        - Hyperosmolarity
        - Hypoosmolarity
        - Plasma osmolarity
        - Serum osmolarity
        - Tear osmolarity
        - Urine osmolarity
    - Osmosis
        - Electroosmotic
        - Osmotic stress
            - Hyperosmotic stress
            - Hypoosmotic stress
- Photodynamics

        - Photoactivation
            - Photoreactivation
        - Photodegradation
        - Photoreactivity
            - Photocytotoxicity
            - Photosensitivity
            - Photosensitization
            - Phototaxis
            - Phototoxicity
        - Photostimulation
    - Proton motive force
    - Shock wave
        - High-energy shock wave
    - Stress strain relationship
    - Thermodynamics
        - Adiabaticity
        - Enthalpy
        - Entropy
- Elasticity
    - Viscoelasticity
    - Young modulus
- Force
- Friction
    - Orthodontic friction
- Hardness
- Kinetics
    - Adsorption kinetics
    - Flow kinetics
        - Electroosmotic flow
        - Flow rate
        - Gas flow
        - Laminar airflow
        - Laminar flow
        - Powder flow
            - Angle of repose
            - Hausner ration
        - Pulsatile flow
        - Shear flow
        - Thixotropy
        - Tube flow
        - Turbulent flow
        - Vortex motion
        - Water flow
    - Motion
        - Coriolis phenomenon
        - Rotation
        - Vibration
            - Hand arm vibration
            - High frequency oscillation
            - Oscillation
            - Oscillatory potential
            - Whole body vibration
    - Velocity
        - Acceleration

            - Deceleration
            - Processing speed
            - Wind speed
- Mass
    - Biomass
        - Fungal biomass
        - Immobilized biomass
        - Microbial biomass
    - Body mass
    - Bone mass
    - Dry mass
    - Fat free mass
    - Fat mass
    - Heart left ventricle mass
    - Kidney mass
- Materials testing
- Mechanical stress
    - Contact stress
    - Contraction stress
    - Shear stress
    - Surface stress
    - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
    - Quantum theory
- Rigidity
- Torque
- Viscosity
    - Blood viscosity
        - Plasma viscosity
    - Gelatinization
    - Shear rate
    - Shear strength
    - Shear mass
    - Sputum viscosity
- Viscoelasticity

Appendix C. Study Flow Diagram

I. 1,782 Citations identified by searches:

1. 1154 citations were not screened manually due to likely irrelevance (based on text mining, logistic regression, etc.)

2. 629 citations were screened for potential inclusion at title/abstract level (535 citations were selected by text mining in Distiller (30%); and 94 additional citations were selected - 89 citations by logistic regression (5%), 4 citations for including "random" or "systematic" in the title or abstract) 1 citation identified in the search for another material

a. 312 citations were excluded at the title/abstract level. Citations excluded at this level were off-topic, or not published in English, did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest.

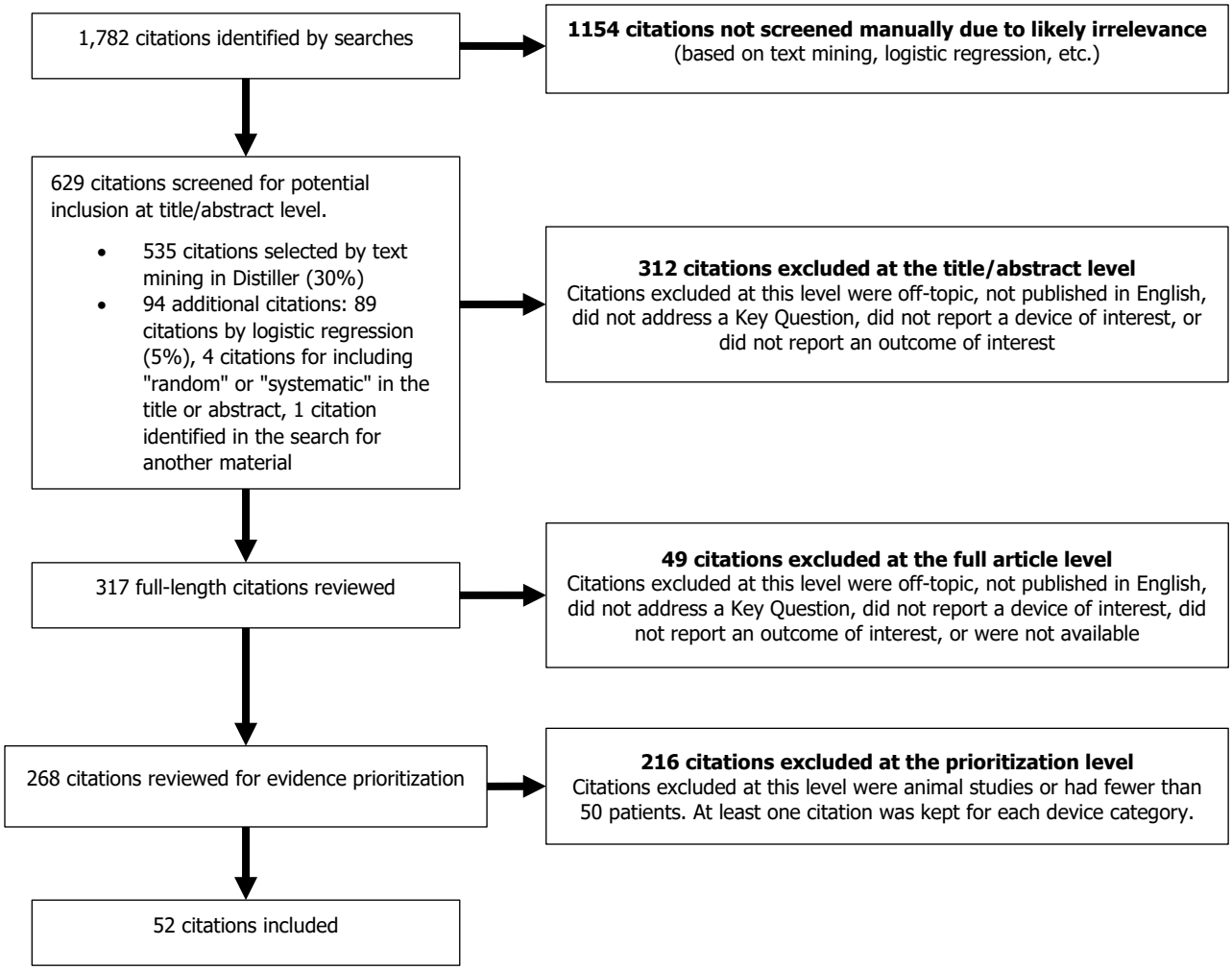
b. 317 full-length citations were reviewed:

i. 49 citations excluded at the full article level, Citations excluded at this level were off-topic, or not published in English, or did not address a Key Question, or did not report a device of interest, or did not report an outcome of interest, or were not available.

ii. 288 citations reviewed for evidence prioritization

1. 216 citations were excluded at the prioritization level. Citations excluded at this level were animal studies or had fewer than 50 patients. At least one citation was kept for each device category

2. 52 citations included.


1,782 citations identified by searches
1154 citations not screened manually due to likely irrelevance
(based on text mining, logistic regression, etc.)
629 citations screened for potential inclusion at title/abstract level.
535 citations selected by text mining in Distiller (30%)
94 additional citations: 89 citations by logistic regression (5%), 4 citations for including "random" or "systematic" in the title or abstract, 1 citation identified in the search for another material
312 citations excluded at the title/abstract level
Citations excluded at this level were off-topic, not published in English, did not address a Key Question, did not report a device of interest, or did not report an outcome of interest
317 full-length citations reviewed
49 citations excluded at the full article level
Citations excluded at this level were off-topic, not published in English, did not address a Key Question, did not report a device of interest, did not report an outcome of interest, or were not available
268 citations reviewed for evidence prioritization
216 citations excluded at the prioritization level
Citations excluded at this level were animal studies or had fewer than 50 patients. At least one citation was kept for each device category.
52 citations included

Appendix D. Evidence Tables

Table 8: PTFE as a Material - Health Effects (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Ovcharenko 2020[2]

Study Design: Non-randomized comparative study

Device or Material: GORE-TEX vs. Hastalex [graphene oxide in poly(carbonate-urea)urethane] vs. glutaraldehyde

Route: Subcutaneous pouch on dorsum

Dose: 0.5 x 0.5 cm sample of each material

Frequency/Duration: 5 animals sacrificed at 14 days, 10 animals sacrificed at 60 days

Response: Dense connective tissues, FBGCs, Calcification

Species (strain): Wistar young rats

Gender: NR, NR.

Number per group: 15

Observed adverse effects: At 2 weeks, a loose 69 µm collagen-based fibrous capsule was observed around the sample, indicating the end of the inflammatory process. Implantation sites demonstrated no FBGCs or lymph nodes at 2 weeks. At 2 months, dense connective tissues 78 µm thick with evident collagen fibers were observed. FBGCs were present in the fibrous capsule. Such FBGCs can potentially contribute to oxidative damage and destruction of implanted devices. There were visible calcific deposits at the tissue/implant interaction.

Timing of adverse effects: 2 months

Factors that predict response: NR

FBGC = foreign body giant cell; NR = not reported

Table 9: Catheters - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Kale 2020[4]

Study Design: RCT

Device or Material: NEOCAN 24G PTFE PIC vs. Vasofix Certo 24G PUR PIC

Contact Duration: PTFE: 56±33 hours, PUR: 66±46 hours

Dose: 1 catheter

Frequency/Duration: Single administration

Response: Extravasation

Patient characteristics (gender, mean age): NR, PTFE: 34±4 weeks, PUR: 35±4 weeks.

Number per group: 32 PTFE, 32 PUR

Observed adverse effects: No inflammation or blockage was observed. 28 out of 32 PTFE catheters were removed due to extravasation, but this was not different than PUR catheters (25 out of 32).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Lv 2020[3]

Study Design: Systematic review

Device or Material: Peripheral intravenous catheter

Contact Duration: NR

Dose: NR

Frequency/Duration: Single administration

Response: Phlebitis

Patient characteristics (gender, mean age): Overall 54% male, Overall mean: 57 yrs.

Number per group: 35 studies (9 RCT, 24 prospective, 2 retrospective) reporting on 20,697 PIVCs in 15,791 patients

Observed adverse effects: Anaysis concluded Teflon had a higher phlebitis incidence (33%, 95% CI 25–41) vs PUR Vialon (27%, 95% CI 21–32). 3 of the studies included in the review reported that Teflon catheter use was a risk factor for the development of phlebitis

Timing of adverse effects: NR

Factors that predict response: NR

CI= confidence interval; FBGC = foreign body giant cell; NR = not reported; PTFE = polytetrafluoroethylene; PUR = polyurethane; RCT = randomized controlled trial

Table 10: Filters - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Smouse 2013[6]

Study Design: Single-arm study

Device or Material: Crux Vena Cava Filter

Contact Duration: 180 days

Dose: 1 filter

Frequency/Duration: Single administration

Response: Thrombus in/near filter

Patient characteristics (gender, mean age): 58.4% male, 59.1±17.2 yrs.

Number per group: 125

Observed adverse effects: 9 cases of thrombus observed in or near the filter. No signs of filter migration or fracture were observed.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Gray 2018[5]

Study Design: Single-arm study

Device or Material: GORE Embolic Filter

Contact Duration: 30 days

Dose: 1 filter

Frequency/Duration: Single administration

Response: Death, Stroke, Myocardial infarction

Patient characteristics (gender, mean age): 61.2% male, mean 74.7 (51.3 - 92.6) years.

Number per group: 250

Observed adverse effects: The study reported 10 (4%) major adverse events (death, stroke, myocardial infarction). This was less than their goal of 12%. There were 2 deaths, 1 major stroke, 6 minor strokes, and 1 MI.

Timing of adverse effects: 1 death and the 6 minor strokes occurred within 2 days of carotid artery stenting (CAS). The MAEs occurred with 30 days of CAS.

Factors that predict response: NR

Source Citation: Smouse 2013[6]

Study Design: Single-arm study

Device or Material: Crux Vena Cava Filter

Contact Duration: 180 days

Dose: 1 filter

Frequency/Duration: Single administration

Response: Deep vein thrombosis, Pulmonary embolism

Patient characteristics (gender, mean age): 58.4% male, 59.1±17.2 yrs

Number per group: 125

Observed adverse effects: 13 cases of lower-limb DVT in 12 patients. 3 cases of definitive pulmonary embolism and 2 cases of suspected PE were reported.

Timing of adverse effects: The cases of PE occurred within 30 days of implantation.

Factors that predict response: NR

CAS= carotid artery stenting; DVT= deep vein thrombosis; MAE= major adverse event; MI= myocardial infarction; NR= not reported; PE= pulmonary embolism

Table 11: Vascular Grafts - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Drouven et al. 2019[14]

Study Design: Non-randomized comparative study

Device or Material: Basilic vein transposition vs. PTFE forearm loop graft as tertiary vascular access

Contact Duration: Mean follow-up 29 months

Dose: For the PTFE loop, a standard wall PTFE graft (Gore-Tex; W. L. Gore & Associates, Flagstaff, Ariz) with 6-mm diameter and 0.5-mm wall thickness was used.

Frequency/Duration: Single administration

Response: Aneurysm, Hematoma, Interventions required, Non-maturation, Occlusion, Primary assisted patency, Primary patency, Secondary patency, Stenosis, Thrombosis

Patient characteristics (gender, mean age): 69 males and 61 females; basilica vein 58.3 (SD 13.9) and PTFE 62.6 (SD 14.9) years

Number per group: Basilic vein 55 and PTFE 75

Observed adverse effects: A significantly higher 2-year primary assisted patency rate was found for the basilic vein group (72.7% (SE 6.5%) vs. 47.6% (SE 6.2%); p<.01). The 2-year primary patency rates and secondary patency rates were comparable between basilic vein and PTFE loop (25.1% (SE 6.6%) vs. 13.7% (SE 4.4%) [p=0.11] and 75.5% (SE 6.5%) vs. 73.9% (SE 5.3%) [p=0.17], respectively). Complications N and (PY^{-1}): Non-maturation: PTFE 0 (PY^{-1} 0.00) vs basilica vein 5 (PY^{-1} 0.04) p=0.008. Stenosis: PTFE 21 (PY^{-1} 0.11) vs. basilica vein 10 (PY^{-1} 0.07) p=0.073. Occlusion: PTFE 100 (PY^{-1} 0.54) v.s basilica vein 15 (PY^{-1} 0.11) p<0.001. Aneurysm: PTFE 3 (PY^{-1} 0.02) vs. basilica vein 1 (PY^{-1} 0.01) p=0.486. Hematoma: PTFE 0 (PY^{-1} 0.00) vs. basilica vein 2 (PY^{-1} 0.01) p=0.097

Timing of adverse effects: NR but mean follow-up was 29 months

Factors that predict response: Multivariate regression identified body mass index (HR 1.77; 95% CI 1.05–2.98; p=0.03) and age (HR 0.54; 95% CI 0.32–0.91; p=0.02) as predictors for failure regarding primary patency in PTFE loop patients. Previous catheter use (HR 0.29; 95% CI 0.12–0.70; p=0.006) and the presence of diabetes (HR 3.32; 95% CI 1.50-7.39; p=0.003) were independent predictors for failure regarding primary patency in basilic vein transposition patients. The incidence of total complications was significantly higher in the PTFE loop group with 0.70 PY^{-1} compared with 0.28 PY^{-1} in the basilic vein transposition group (p=0.001). In terms of intervention rate, a significantly higher percutaneous transluminal angioplasty rate and surgical revision rate were found in the PTFE loop group than in the basilic vein group (1.77 PY^{-1} vs. 1.05 PY^{-1} [p=0.022] and 0.20 PY^{-1} vs. 0.07 PY^{-1} [p=0.002], respectively).

Source Citation: Shakarchi et al. 2019[7]

Study Design: Systematic review

Device or Material: PTFE, Flixene, Acuseal, Polycarbonate, urethane, Avflo, Polyurethane

Vectra grafts

Contact Duration: 12 to 36 months

Dose: NR

Frequency/Duration: Single administration

Response: Access thrombosis, Cannulation time, Primary patency, Pseudoaneurysm, Secondary patency, Steal syndrome

Patient characteristics (gender, mean age): NR

Number per group: 19 studies total; number of patients for Flixene 230; Avflo 74; Acuseal 260; Vectra 762

Observed adverse effects: Flixene grafts (230 procedures in 5 studies): Primary patency rate at 12 months (95% CI): 43.3% (95% CI 31.6–55.4), Secondary patency rate at 12 months (95% CI): 73.4% (95% CI 63.0–82.7) Primary patency rate at 18 months range 21 to 34%, based on 2 studies. Secondary patency rate at 18 months range 51 to 57%, based on 2 studies Mean time to first cannulation (days) based on 3 studies: range 2 to 21 days. Avflo (4 studies and 74 procedures). Primary patency rate at 12 months (95% CI): 58.2% (95% CI 48.0–68.1). Secondary patency rate at 12 months (95% CI): 79.2% (95% CI 68.0–88.7). Primary patency rate at 24 months 56.3%, based on 1 study. Secondary patency rate at 24 months 81.8%, based on 1 study. Time to first cannulation was 7 days based on 1 study, and all patients cannulated within 48 hours: 2 studies. Acuseal (4 studies, 260 procedures). Primary patency rate at 12 months (95% CI): 43.6% (95% CI 30.7–56.9). Secondary patency rate at 12 months (95% CI): 70.5% (95% CI 49.7–87.8). Primary patency rate at 24 months was 0, based on 1 study. Secondary patency rate at 24 months was 35.1%, based on 1 study. Mean time to first cannulation (days) based on 3 studies: range 1.3 to 15 days. Vectra (based on 6 studies and 762 procedures). Primary patency rate at 12 months (95% CI): 63.7% (95% CI 53.4–73.4) based on 5 studies. Secondary patency rate at 12 months (95% CI): 85.8% (95% CI 82.9–88.4). Primary patency rate at 18 to 36 months range 15 to 63% based on 5 studies. Secondary patency rate at 18 to 36 months range 50 to 87%, based on 5 studies. Time to first cannulation range was 1 to 19 days based on 4 studies. Flixene, Access thrombosis: 11% to 29% based on 4 studies. Pseudoaneurysm: 0 to 6% based on 4 studies. Avflo, Access thrombosis: 16% to 42% based on 4 studies. Pseudoaneurysm: 0 based on 1 study. Acuseal, Access thrombosis: 17% to 41% based on 3 studies. Pseudoaneurysm: 0 to 15% based on 4 studies. Vectra, Access thrombosis: 23% to 37% based on 4 studies. Pseudoaneurysm: 0 to 17% based on 4 studies

Timing of adverse effects: Flixene ≤18 months; Avflo ≤24 months; Acuseal ≤24 months, Vectra ≤18 to 36 months follow-up

Factors that predict response: NR

Source Citation: Watanabe et al. 2019[8]

Study Design: Systematic review, Non-randomized comparative study conducted by study authors and a separate in-depth review of extrusions

Device or Material: Medialization laryngoplasty using **GORE-TEX** with or without arytenoid adduction

Contact Duration: NR

Dose: Case series: single 6 to 7 mm wide ribbon, SR: NR

Frequency/Duration: Single administration

Response: Displacement, Extrusion into the lumen, Inflammation requiring removal of the **GORE-TEX** implant

Patient characteristics (gender, mean age): Case series: 48 men and 20 women with a median age of 64 years (16 to 87 years).SR: 3/9 did not report gender; 176/310 patients were male; mean age NR. In-depth review of extrusions: 1 male, 6 female and 5 cases in which the gender was unknown.

Number per group: Case series conducted by authors: 68 cases. SR: 555 cases in 9 studies. In-depth review of extrusions: 12 cases

Observed adverse effects: Case series: One patient required emergent tracheostomy after developing cervical hematoma on postoperative day 1. After discharge, the patient repeatedly developed granulomas at the surgical site on his neck 3 months later. He developed laryngeal edema, and the GORE-TEX implant was

removed 6 months after surgery. One patient experienced unresolved edematous changes on the affected side of her larynx 1 month after the surgery. She then developed neck swelling. The GORE-TEX implant had extruded from the ventricle of the larynx 2 months after the surgery and required removal.

SR: The case series above is included in the 9 studies described here. 3/9 studies reported no complications associated with GORE-TEX. Of the 6/9 studies reporting complications associated with GORE-TEX, there were a total of 11 complications including 6 cases of extrusion into the lumen, 3 cases of persistent inflammation with granulation formation requiring removal of the GORE-TEX implant, and 2 cases of displacement. The 11 AEs were described in detail as follows: hyperthermia and granulation tissue (1 case), recalcitrant mucosal granulation and extrusion (1 case), rndolaryngeal extrusion (2 cases), persistent inflammation (1 case), extrusion (3 cases), implant displacement (2 cases), and inflammation and granulation (1 case)

Timing of adverse effects: Case series: median 19 months. Review of extrusions: 1 month to 10 years (median, 49 months)

Factors that predict response: Case series: The authors report "we found no specific factors, including age, sex, etiology, surgeon, operation time and intraoperative blood loss, associated with the occurrence of complications." SR: The authors report "Use of excessively large implants in women and occurrence of postoperative hematoma followed by infection are factors that may cause complications." "There was no significant difference in the incidence of GT extrusion between patients with a preserved perichondrium (2 in 286) and those without a preserved perichondrium (4 in 269), p = 0.44."

Source Citation: Cho et al. 2018[26]

Study Design: Single-arm study

Device or Material: Extra-cardiac Fontan procedure with 16 mm PTFE (**GORE-TEX** vascular graft; W.L. Gore & Associates, Inc., Flagstaff, AZ, USA) conduit vs. matched controls with conduit size of 19.2 ± 1.4mm (18 mm, n=34; 20 mm, n=23 and 22 mm, n=9)

Contact Duration: ≤16 years

Dose: 16 mm PTFE conduit vs. a larger conduit (mean 19.2±1.4 mm)

Frequency/Duration: Single administration

Response: Catheter intervention, Conduit-related events, Freedom from catheter-based intervention

Patient characteristics (gender, mean age): Mean age PTFE 16 mm 2.9±1.2 years and matched control group 3.1±1.2; gender NR

Number per group: PTFE 16 mm group 66 patients and 66 control patients matched for age and size

Observed adverse effects: There was a significant difference in conduit-related events between the groups (1 in 16-mm PTFE, 5 in matched controls; p=0.031). In a paired cohort from the 2 groups including patients who were followed up for more than 10 years (15 patients from each group), the body mass index was 51.0 ± 33.2% in 16 mm PTFE and 30.3 ± 34.2% in matched controls. The decreases in the conduit cross-sectional areas for the paired patients in 16 mm PTFE (n=20) and matched controls (n=20) were 14.9 ± 19.7% and 24.5 ± 15.5% (p=0.076), respectively. Final follow-up: There were no significant differences at the last follow-up catheterization between the 16 mm and matched control groups. There were also no differences in the inferior vena cava pressure or intraconduit pressure between the two groups.

Conduit change N: 16 mm group 1 (due to progressive valve regurgitation 16 years after the procedure) vs. matched controls 2 (due to conduit thrombosis and stenosis 2 months and 9 years after ECFP); Conduit thromboembolectomy N: 16 mm group 0 vs. matched controls 1; atrioventricular valve repair N: 16 mm group 1 vs. matched controls 2; atrioventricular valve replacement N: 16 mm group 1 vs. matched controls 0; aortic valve replacement N: 16 mm group 1 vs, matched controls 0; dub-aortic muscle resection N: 16 mm group 0 vs. matched controls 1; pulmonary artery angioplasty N: 16 mm group 0 vs. matched control 4;

pulmonary vein angioplasty N: 16 mm group 1 vs. matched control 1; Catheter intervention N: 16 mm group 11 vs. matched control 6, p=0.369; Collateral vessels closure N: 16 mm group 6 vs. matched control 6; Balloon pulmonary angioplasty N: 16 mm 5 vs. matched control 0; conduit-related events N: 16 mm group 1 vs. matched control 5, p=0.031;

Timing of adverse effects: Mean follow-up PTFE 7.8 ± 6.0 years and matched control 9.1 ± 4.9 years

Factors that predict response: NR

Source Citation: Goja et al.2018[16]

Study Design: Non-randomized comparative study

Device or Material: AS reconstruction using nonringed ePTFE grafts (GORE-TEX, W.L. Gore & Associates, Inc., Newark, DE, USA) vs. venous extension grafts

Contact Duration: ≤2 year

Dose: ≤5 mm

Frequency/Duration: Single administration

Response: Acute cellular rejection, Dysfunction (graft), Bile leak, Biliary stricture, Bleeding, Graft loss, Patency, Re-exploration, Small-for-size syndrome, Thrombosis, Vascular complications, allograft

Patient characteristics (gender, mean age): Mean age of patients was 48 ± 10.21 years; 366 male and 71 female.

Number per group: V graft 200 patients and ePTFE in 237 patients

Observed adverse effects: The MHV graft patency rate at 7 and 14 days was 100% in each group. Similarly, the patency rate for V vs. ePTFE at 1 month (99.5% vs. 97.5% p=0.09), 3 months (98.5% vs. 95.8% p=0.09), and 12 months (96% vs. 92.8% p=0.15) was comparable between the groups. No patient was re-explored for graft blockage. There was no complication attributable to ePTFE in this cohort. There was no difference in bile leak, biliary stricture, vascular complications, acute cellular rejection, re-exploration, small-for-size syndrome, or early allograft dysfunction.

Timing of adverse effects: 30-day, 90-day, and 1-year for survival; Graft patency was checked by Doppler ultrasonography intraoperatively, then once a day for the first week and weekly till hospital discharge. Follow-up USG Doppler was performed at 3, 6, and 12 months following transplantation. All the recipients were followed up twice a week for a month, then weekly for 3 months, fortnightly for 6 months, monthly for 24 months, and once in 2 months after 2 years.

Factors that predict response: There was no significant difference in graft patency rate at the different points of time in each type of RL graft harvested between V and ePTFE groups. Although 7- and 14-day patencies were similar between V and an ePTFE group among three types of RL graft, 12-month patency was low in non-MHV (V 90%, ePTFE 86.7%) as compared to MHV (V 97.4%, ePTFE 95.2%) grafts reflecting the increased tendency of blockage in multiple smaller tributaries.

Source Citation: Kaisar et al. 2018[17]

Study Design: Non-randomized comparative study

Device or Material: PROPATEN- heparin-bonded PTFE vascular graft with distal anastomotic patch versus autogenous saphenous vein graft in tibial artery bypass

Contact Duration: ≤4 years

Dose: 6 mm PROPATEN graft

Frequency/Duration: Single administration

Response: Hematoma, Interventions, Primary patency, Occlusion, Secondary patency

Patient characteristics (gender, mean age): Mean age PROPATEN 73 (SD 11.6) vs. vein group 75 (SD 13.4) years; 69 males and 39 females.

Number per group: 62 revascularizations in 59 patients in the PROPATEN group and 46 procedures in 44 patients in the vein group.

Observed adverse effects: Primary patency rates for 1-, 2-, 3-, and 4-year follow-up between the PROPATEN and vein groups (85%, 71%, 64%, and 57%, vs. 87%, 78%, 67%, and 61% respectively; p=0.97). Both groups had comparable secondary patency rates yearly over the same 4-year period (PROPATEN group: 84%, 76%, 74%, and 67%, respectively; the vein group: 88%, 79%, 76%, and 72%, respectively; p=0.94). There was no difference in the 30-day postoperative complication rates between the PROPATEN and vein group, which were 5% and 7%, respectively (NS). In the PROPATEN group, there were 2 wound complications and 1 groin hematoma that required surgical evacuation. In the vein group, 2 patients developed wound dehiscence from the saphenous vein harvest site while 1 patient developed postoperative bleeding that required surgical repair to achieve hemostasis. During the follow-up period, graft occlusion in the PROPATEN and the vein group occurred in 17 and 15 cases, respectively. In 13 of these PROPATEN graft occlusion cases, endovascular interventions with thrombolytic therapy were successful in restoring the graft flow that revealed stenosis in the distal anastomosis. Percutaneous balloon angioplasty was performed successfully in 7 of these cases to maintain the graft flow. A similar effort of endovascular interventions was performed in 6 vein graft occlusion cases of which it was successful only in 3 cases.

Timing of adverse effects: Postoperative ultrasound surveillance along with ankle-brachial index was performed at 1, 3, 6, 12 months, and every 6 months thereafter. Patency and limb salvage rates were reported yearly for up to 4 years. Postoperative complications were reported for 30-days postoperation.

Factors that predict response: Univariate analysis of primary patency for these bypass grafts showed that foot ulcers, active tobacco user, and poor run-off score of 0–1 were associated with this outcome.

Source Citation: Nguyen et al. 2018[15]

Study Design: Retrospective comparative study

Device or Material: PTFE grafts and femoral vein as conduits for femorofemoral crossover grafts

Contact Duration: Median follow-up was 9.8 months (range 0e107)

Dose: NR

Frequency/Duration: Single administration

Response: Blood transfusion, Primary assisted patency, Primary patency, Secondary patency, Wound complication

Patient characteristics (gender, mean age): 51 females and 68 males; mean age vein 65.5 (SD 8.5) and PTFE 66.5 (SD 10.8) years.

Number per group: 89 PTFE, 30 vein (18 were autogenous femoral veins, 12 were cryopreserved)

Observed adverse effects: The 30-day complication rate was 38.7% and was not different between groups (36% for PTFE, 44.4% for autologous vein grafts and 50% for cryovein, p=0.33) with wound complications being most frequent (18% PTFE, 27.8% autologous vein, 16.7% cryovein, p=0.25). Patients receiving vein grafts were more likely to receive blood transfusion (34.8% PTFE vs. 70% vein, p=0.001). 30-day complications: hematoma vein group 0% n=0 PTFE 4.5% n=4 p=0.57; seroma vein group 6.7% n=2 PTFE 5.6% n=5 p=1.00; renal insufficiency vein group 6.7% n=2 PTFE 9% n=8 p=1.00; hemodialysis vein group 0% n=0 PTFE 0% n=0 p=1.00; pseudoaneurysm vein group 3.3% n=1 PTFE 2.2% n=2 p=1.00; Primary patency rates at 1, 2, and 3 years were 83.7 %, 73.7% and 69.8%, respectively, for PTFE bypasses, and 100% for all time points for venous grafts, respectively (p=0.03). Primary-assisted and secondary patency rates were not significantly different between the 2 groups (p=0.16).

Timing of adverse effects: Intraoperative, 30 days and 1-, 2-, and 3-years; femorofemoral bypasses were evaluated with duplex ultrasound every 3 months for the first year and then every 6 months for the second year. If there were no complications or concerning ultrasound findings suggesting significant stenosis or impending graft failure, then patients were followed up annually with surveillance ultrasound.

Factors that predict response: A subgroup analysis of isolated femorofemoral bypasses was performed and showed no significant differences in primary patency at 1, 2, and 3 years (PTFE 86.8%, 74%, and 74% vs. vein 100% for all time points, respectively; p=0.40). Primary-assisted patencies at 1 and 2 years were significantly higher for bypasses created with femoral vein (100% for both time points) versus those created with PTFE graft (87% for both time points) (p=0.02). Secondary patency of isolated femorofemoral bypasses were not significantly different between veins and PTFE grafts (p=1.00). Survival at 1, 2, and 3 years (PTFE 79.2%, 64.5% and 54.8% vs. vein 86.7%, 86.7% and 65%, respectively; p=0.40) and amputation-free survival at 1, 2, and 3 years (PTFE 93% at all-time points vs. vein 87% at all-time points; p=0.86) between grafts created with prosthetic PTFE graft and those created with femoral vein were not statistically different. For axillobifemoral bypasses, a subgroup analysis was performed and showed no differences in patency rates (primary, p=0.12], primary-assisted [p=0.36], or secondary patencies [p=1.00] at 1, 2, or 3 years, p=1.00). However, survival was significantly higher in patients who received a PTFE conduit for the femorofemoral component of an axillobifemoral graft as compared with patients who received a femoral vein conduit for the femorofemoral component. Survival at 1, 2, and 3 years was 93.8%, 93.8%, and 93.8%, respectively, for patients with a PTFE femorofemoral component and 58%, 46%, and 46%, respectively, for patients with femoral vein (p=0.001). Amputation-free survival at 1, 2, and 3 years was not significantly different in patients who received vein grafts for the femorofemoral component as compared with those who received PTFE grafts for the femorofemoral component (p=0.21).

Source Citation: Veraldi et al. 2018[18]

Study Design: Non-randomized comparative study

Device or Material: Percutaneous transluminal angioplasty (PTA) ± bare metal stent (BMS) vs heparin-bonded ePTFE graft (PROPATEN-GORE) + Linton patch in patient affected by symptomatic femoropopliteal TASC II-D lesions

Contact Duration: Mean follow-up was 26.7 months

Dose: 6 or 7 mm PROPATEN-GORE graft was used as conduit

Frequency/Duration: Single administration

Response: Bleeding, Hematoma, Occlusion, Primary assisted patency, Primary Patency, Re-intervention, Restenosis, Secondary patency, technical success

Patient characteristics (gender, mean age): Mean age PTA/BMS 76 years and PTFE 72 years; sex reported by limb, 61 male and 19 female

Number per group: 68 patients total (80 limbs); PTA/BMS 40 limbs and PTFE 40 limbs

Observed adverse effects: Primary patency at 6, 12, and 24 months of PTA/BMS versus PTFE group was 76.9% vs. 97.5% (p=0.007), 65.7% vs. 89.1% (p=0.05), and 52.6% vs. 78.1% (p=0.005), respectively. Assisted primary patency was 76.9% vs. 97.5% (p=0.007), 68.5% vs. 91.8% (p=0.02), and 57.8% vs. 87.5% (p=0.001), respectively. Secondary patency was 94.8% vs. 97.5% (p=NS), 85.7% vs. 97.2% (p=NS), 73.6% vs. 93.7% (p=0.004), respectively. Rate of reintervention at 24 months was 45% in PTA/BMS vs. 20% in PTFE group (p=0.03). In PTA/BMS, technical success was obtained in 38 limbs (95%): it was impossible to cross the lesion in 2 cases, and a surgical revascularization with bypass was necessary. After the procedure, 3 limbs developed perioperative complications: 1 patient developed a retroperitoneal hematoma and 2 presented local bleeding at the site of femoral access. All complications were conservatively treated, and none of them required a reoperation before discharge.

In the PTFE group, technical success was 100%. Five limbs (12.5%) developed local complications: 2 cases of arterial bleeding requiring surgical hemostasis, 2 lymphatic fistulas (conservative treatment), and 1 skin necrosis requiring surgical debridement. In-hospital complications: PTA/BMS 3 (7.5%) vs PTFE 5 (12.5%) p=NS; Reintervention after discharge PTA/BMS 18 (45%) vs PTFE 8 (20%) p=0.03. During follow-up, 26 limbs (32.5%) required a reintervention for significant stenosis or symptomatic occlusion (18 patients, 45% in group PTA/BMS vs. 8 patients, 20% PTFE group, p=0.03).

In group PTA/BMS 14 limbs underwent to re-PTA, 2 of which required subsequent open revascularization for recurrence of occlusion. Four (10%) limbs developed symptomatic occlusion and were treated with a surgical revascularization without any other endovascular attempts. Two PTA procedures were planned following evidence of significant distal stenosis, and 1 target limb underwent to surgical correction of a proximal anastomotic aneurysm.

Timing of adverse effects: Patients were followed with a clinical assessment and duplex at 1, 6, and 12 months after procedure and then annually. A closer follow-up was performed in case of any complication.

Factors that predict response: Univariate analysis showed critical limb ischemia and poor runoff to be independent risk factors for significant restenosis/occlusion of target artery and reintervention.

Source Citation: Uhl et al. 2017[19]

Study Design: Non-randomized comparative study

Device or Material: Autologous vein vs. heparin bonded ePTFE for below knee femoropopliteal bypasses in patients with CLI in whom endovascular therapy was not possible or failed

Contact Duration: Mean follow-up was 34 months

Dose: HePTFE (6 mm ring enforced PROPATEN-GORE)

Frequency/Duration: Single administration

Response: Occlusion, Primary patency, Primary assisted, Patency, Restenosis, Revascularization Secondary patency

Patient characteristics (gender, mean age): Mean age: PTFE 73.0 (SD 10) and autologous vein 70.5 (SD 9), 90 male and 61 female

Number per group: Autologous vein 76 cases and heparin-bonded ePTFE 75 cases

Observed adverse effects: Early graft occlusion occurred in 9 cases (vein group 6.6% vs. HePTFE group 5.3%; p=0.508). No early occluded vein graft resulted in a major amputation within 30 days. Except for the 2 patients with the early occluded HePTFE grafts who underwent major amputation for the abovementioned reasons, all other early occluded grafts underwent thrombectomy within the first 24 hours. For 1-, 3-, and 5-years, primary patency in the vein group was 75.3%, 62.2%, and 55.5%; in the HePTFE group it was 73.6%, 51.7%, and 51.7% after the same time intervals. There was no significant difference after 5 years (p=0.897). After 1 year, primary assisted patency was 79.1% in the vein group and 75.0% in the HePTFE group, after 3 years it was 72.8% in the vein group and 54.9% in the HePTFE group, and after 5 years it was 66.8% in the vein group and 54.9% in the HePTFE group. Primary assisted patency rates in the 2 graft groups 5 years postoperatively again showed no significant difference (p=0.270). Comparing the 2 groups, vein and PTFE, the secondary patency was 91.1% vs. 82.7% after 1 year, 81.7% vs. 69.0% after 3 years, and 74.6% vs. 55.6% after 5 years, again without significant difference after 5 years (p=0.119) Restenosis: An intervention was performed in 15 cases to avoid a graft occlusion due to a stenosis (3 in the HePTFE group, 12 in the vein group).

Timing of adverse effects: ≤5 years for survival; Completion angiography was performed before leaving the operating room to exclude technical failure. Duplex scans and clinical examinations regarding wound healing and clinical symptoms were done before discharge from hospital and 6 months postoperatively. If the 6-month examination was satisfactory patients were checked at intervals of 12 months. For patency and limb salvage AEs were reported at 1-, 3-, and 5-years.

Factors that predict response: In subgroup analysis regarding 1-, 2-, and 3- vessel runoff, no significant difference was found in primary, primary assisted, or secondary patency; limb salvage; or survival between the 2 groups after 1 year. When comparing patients with previous endovascular treatment with patients without previous revascularization procedures, no significant difference was found regarding primary and secondary patency, limb salvage, and survival. In the multivariate analysis for secondary patency, smoking (p=0.01, 95% CI 1.2–5.5, HR 2.6) and prosthetic graft material (p=0.03, 95% CI 1.1–4.8, HR 2.3) were associated with a higher risk of graft failure, and prosthetic graft material was found to have an impact on limb salvage (p=0.04, 95% CI 1.1–8.8, HR 3.1).

Source Citation: Thorat et al. 2016[20]

Study Design: Non-randomized comparative study

Device or Material: Inferior right hepatic vein reconstruction using PTFE vs. direct IRHV-to-IVC anastomosis

Contact Duration: ≤2 months

Dose: PTFE graft: Liver allografts with MHV included requiring single ePTFE vascular graft for MHV reconstruction to form a common outflow channel (n=32). Bridging conduit plasty: Liver allografts without MHV requiring 2 ePTFE vascular grafts for backtable MHV reconstruction and IRHV reconstruction to facilitate second IRHV-to-IVC anastomosis (n=20

Frequency/Duration: Single administration

Response: Graft migration, Graft removal, Hepatic venous stenosis, Patency

Patient characteristics (gender, mean age): PTFE with MHV subgroup: 20 males and 12 females with a mean age of 54 years; PTFE bridging conduit plasty: 16 males and 4 females with an average age of 51±10 years; direct IRHV-IVC: males 30 and females 17 with a mean age 54±6

Number per group: ePTFE 52 patients total and direct IRHV-to-IVC anastomosis comparator 47 patients

Observed adverse effects: There were no thrombotic complications in either group of recipients; 4.2% of the recipients from direct IRHV-to-IVC anastomosis group developed hepatic venous stenosis but with no clinical deterioration 6 months postsurgery; and 1 patient from the PTFE group A developed ePTFE graft migration in the second portion of the duodenum that required surgical exploration and graft removal in the third postoperative month. No acute obstruction of ePTFE graft occurred in any of the recipients. All the recipients in the cohort recovered well in the postoperative period, with satisfactory liver functions. The patency rate of the ePTFE grafts used in studied recipients was 100% for the first 2 months.

Timing of adverse effects: Doppler ultrasonography was performed on first postoperative day, then every alternate day during the first week, and then once per week until the patient was discharged. CT scans were performed for patients with Doppler ultrasound showing abnormalities of outflow with high serum concentrations of liver enzymes (>300 to 400 IU/L) during the immediate posttransplant period. Patency was reported at the 2 month postoperative visit.

Factors that predict response: NR

Source Citation: AI Shakarchi et al. 2015[9]

Study Design: Systematic review

Device or Material: Reliable Outflow (HeRO) graft (Cryolife Inc company; Eden Prairie, MN, USA) in complex hemodialysis patients

Contact Duration: 7 to 18.5 months

Dose: NR

Frequency/Duration: Single administration

Response: Steal syndrome

Patient characteristics (gender, mean age): No difference in rate of male versus female; mean age NR

Number per group: 8 studies with 409 patients were included

Observed adverse effects: Primary and secondary pooled patency rates in this complex cohort of dialysis patients were 21.9% (9.6 to 37.2%) and 59.4% (39.4 to 78%).The rate of interventions required to maintain HeRO patency ranged between 1.5 and 3 procedures per year.

Timing of adverse effects: Through 7 to 18.5 months' follow-up period

Factors that predict response: NR

Source Citation: Anaya-Ayala et al. 2015[21]

Study Design: Non-randomized comparative study

Device or Material: Hybrid graft vs. standard PTFE graft for hemodialysis access

Contact Duration: Median follow-up was 21 months

Dose: NR

Frequency/Duration: Single administration

Response: Primary assisted patency, Primary patency, Reintervention, Secondary patency, technical success

Patient characteristics (gender, mean age): Mean age Hybrid graft group 65±14 years and PTFE 63±12 years; 33 males and 27 females

Number per group: Hybrid graft 25 patients and PTFE 35 patientsObserved adverse effects: Technical success was achieved in all cases, and all grafts were usable for hemodialysis. Estimated primary patency (24% vs. 18%, p>0.05), assisted primary patency (34% vs 28%; p>0.05), and secondary patency rates (40% vs 38%, p≥0.05) at 24 months were equivalent for Hybrid vs. PTFE grafts, respectively. Primary patency, assisted primary patency, and secondary patency rates at 12 months for the Hybrid graft patients vs. the standard PTFE patients were 66%±8% vs. 45%±8% (p=0.04), 69%±7% vs. 50%±7% (p=0.02), and 69%±7% vs 66%±7% (p>0.05), respectively. Six of 25 patients had graft occlusions and required open thrombectomy with a fistulogram of the Hybrid graft at a median of 2 months (range 1–8). Three did not require additional interventions, as no cause was determined. One patient required dilation of the innominate vein, and 1 patient required both dilation and stenting of the axillary and innominate veins. The final patient required surgical revision of the arterial anastomosis. None of these patients required a central venous line. For PTFE, 11/35 patients required open thrombectomy of the graft at a median of 2 months (range 1–8), with 5 needing additional endovascular interventions. Three patients required dilation of the innominate vein, and 2 patients had both dilation and stenting of the axillary and innominate veins.

Timing of adverse effects: 24 months for patient survival, thrombectomy needed at a median of 2 months post operation.

Factors that predict response: NR

Source Citation: Donati et al. 2015[1]

Study Design: Non-randomized comparative study

Device or Material: AVG made of PTFE GORE-TEX, W. L. Gore & Associates, Flagstaff, AZ, USA) Grafts vs Tunneled Cuffed Catheters for Hemodialysis

Contact Duration: ≤24-month follow-up

Dose: 19 PTFE grafts had an internal diameter of 6 mm, and 3 PTFE grafts had an internal diameter of 7 mm. 9 grafts had a conic feature, 5 of them had 6 mm diameter in the venous side and 4 mm diameter in the arterial side, 4 had a 7 mm diameter on the venous side and 4 mm diameter in the arterial side. In 19 cases out of 31 (61.3%), the PTFE grafts were placed in the arm

Frequency/Duration: Single administration

Response: Graft survival, Thrombosis

Patient characteristics (gender, mean age): 48 males and 39 females; PTFE mean age 63.8 ± 14.6 years and TCC mean age 73.5 ± 11.3 years

Number per group: TCC 56 patients and PTFE 31 patients

Observed adverse effects: Seventeen out of 31 patients (54.8%) with PTFE graft and 25/56 patients with TCC (44.6%) experienced a loss of the vascular access during a 1-year follow-up (p=NS). During a 24-month follow-up, loss of the vascular access was observed in 22/31 cases (71%) in the PTFE graft group and in 33/56 cases (58.9%) in the TCC group. Median survival of PTFE grafts at 24 months was 8.7±3.4 months, whereas TCC survival was 14.1±3.1 months (p=ns).

Vascular access lasted a median of 5.4 months longer in the TCC group than in the PTFE group, but the difference did not reach statistical significance (log-rank 1.34, p=0.25). Vascular access thrombosis caused vascular access loss in 20/31 cases (64.5%) in patients with a PTFE graft and in 4/56 cases (7.1%) in patients with TCC (P <0.001). Vascular access loss was due to infection in 4/31 cases (12.9%) in the PTFE group and in 9/56 cases (16.1%) in the TCC group (p=NS). The mean time interval between vascular access placement and the onset of these major complications was 7.5±7.9 months in the PTFE group and 13.0±14.9 months in the TCC group (p=NS). Vascular access infection occurred after a mean time of 9.4±7.2 months after vascular access placement in the PTFE group and after 16.4±15.6 months in the TCC group (p=NS). The time between vascular access placement and the diagnosis of thrombosis was 7.1±8.1 months in the PTFE group and after 1.8 ± 1.2 months in the TCC group (p=NS). The overall infectious and thrombotic complications of vascular access during the follow-up (any complication) were more frequent in the PTFE graft group compared with the TCC group: 13/31 (41.9%) in the PTFE group versus 7/56 (12.5%) in the TCC group (p<0.001).

Timing of adverse effects: Patients were monitored 3 times a week for adverse events during their hemodialysis sessions. Final follow-up was at 24 months.

Factors that predict response: Cox regression analysis adjusted for age, gender, type of vascular access, number of previously created arterial venous fistulae, diabetes, atrial fibrillation, and cigarette smoking confirmed that the survival of the vascular assess was similar between the TCC and the PTFE group at 12 months follow-up. However, in this analysis, diabetes (p=0.02) and all thrombotic and infectious complications of vascular access (p=0.01) proved to be significant independent predictors of access survival. In particular after 12 months, nondiabetic patients experienced vascular access survival 2.2 times higher than diabetic patients. Vascular access survived in 62.1% of nondiabetic patients, whereas it survived in 44.4% of diabetic patients during a 12-month follow-up. Moreover, patients experiencing any infectious or thrombotic complications had a 2.7 times higher risk of vascular access failure than those not experiencing complications. At the 24-month follow-up, only diabetes remained as a risk factor for vascular access survival. The absence of diabetes was significantly associated with an improvement in vascular access survival (p=0.02). Patients without diabetes had a 1.9 times higher probability of vascular access survival than that of diabetic patients independent of the type of vascular access. Vascular access survival was 27.8% in diabetic patients and 43.1% in nondiabetic patients.

Source Citation: Shemesh et al. 2015[27]

Study Design: Single-arm study

Device or Material: Standard ePTFE graft or a heparin-bonded ePTFE (PROPATEN) graft for hemodialysis access

Contact Duration: NR

Dose: Tapered 4- to 7-mm stretch ePTFE (W. L. Gore & Associates)

Frequency/Duration: Single administration

Response: Assisted primary patency, Bleeding complications, Cannulation time, Occlusion, Primary patency, Secondary patency, Thrombosis, Thrombolytic treatment

Patient characteristics (gender, mean age): 77 men and 83 women; mean age PROPATEN 69.9±10.2, standard 67.8±12 years

Number per group: 80 patients per group

Observed adverse effects: Primary patency was 35% and 14% for heparin-bonded grafts and 29% and 12% for standard ePTFE grafts at 6 and 12 months, respectively (p=0.48). Assisted primary patency was 54%, 41%, and 27% for heparin-bonded grafts and 41%, 30%, and 23% for standard grafts at 12, 24, and 36 months, respectively (p=0.12) by log-rank, p=0.04 by Gehan-Breslow-Wilcoxon. Secondary patency was 83%, 83%, and 81% for heparin-bonded grafts and 81%, 73%, and 68% for standard grafts at 12, 24, and 36 months, respectively (p=0.33).

All grafts were ready for cannulation between 2 and 4 weeks postoperatively with no difference between the groups. Of 80 standard grafts, 24 were eventually abandoned vs. 17 heparin-bonded grafts (p=0.188). Bleeding complications and intervention rates were similar in both groups. Mean time to first thrombosis was 9.7±10 months in the heparin-bonded group and 7.8±10.6 months in the standard group (p=0.17). An anatomic cause for occlusion in the first month could be found in 5 (83%) of the 6 heparin-bonded grafts compared with only 8 (50%) of the 16 standard grafts (p=0.18). There were no differences between upper and lower arm access and between the 2 graft types in the upper arm and the 2 graft types in the lower arm. Although the number of thrombolytic treatments was lower by 18% and the time to first thrombosis was longer by 24% in the heparin-bonded group, these differences did not reach statistical significance. 50/80 heparin-bonded grafts thrombosed during the follow-up period and required 119 thrombolytic treatments (range 0-8) compared with 57/80 standard grafts, which required 145 thrombolytic treatments (range 0-8) (p=0.16). 17 grafts were abandoned in the heparin-bonded group vs. 24 in the standard group (p=0.188).

Timing of adverse effects: Through median study follow-up period 23.5 months

Factors that predict response: There were significantly fewer thromboses in heparin-bonded grafts during the first month (8% vs. 20%, p=0.025) and first 5 months (p=0.02).

Source Citation: Attia et al. 2014[22]

Study Design: Non-randomized comparative study

Device or Material: Femoropopiteal bypass surgery for lower limb ischemia with PTFE vs. saphenous vein graft

Contact Duration: Mean and median follow-up period was 12 and 18 months, respectively

Dose: NR

Frequency/Duration: Single administration

Response: Patency

Patient characteristics (gender, mean age): 35 males and 15 females; median age 62 years (range 44 to 70)

Number per group: PTFE 18 patients and saphenous vein graft 32 patients

Observed adverse effects: Use of a prosthetic graft and construction of an intragenicular anastomosis (12 cases) was associated with lower graft patency rates, but statistical significance was not reached. According to study authors "The reversed saphenous vein is the preferred conduit in the present study. However, when the different surgical subgroup are examined separated femoro-distal bypass with vein graft is associated with increased patency rate than femoro distal bypass with synthetic graft."

Timing of adverse effects: Patients were assessed 6 weeks postoperation and at 3, 6, 9, 12, and 18 months.

Factors that predict response: NR for the PTFE patients. The authors looked at risk factors across all 50 patients combined, regardless of graft material.

Source Citation: Rychlik et al. 2014[10]

Study Design: Systematic review

Device or Material: Dacron versus PTFE grafts for above-knee femoropopliteal artery bypass

Contact Duration: ≤10 years

Dose: 5 to 8 mm grafts

Frequency/Duration: Single administration

Response: Antiplatelet/anticoagulation use, Primary patency, Secondary patency

Patient characteristics (gender, mean age): Mean age 66 years, gender NR

Number per group: 8 publications reporting on 6 RCTs with 601 Dacron and 591 PTFE

Observed adverse effects: Although primary and secondary patency rates at 12 months were not significantly different (RR 0.78; p=.08, and RR 0.84; p=0.52), 24-, 36-, and 60-month primary patency rates were significantly better with Dacron compared with PTFE grafts (RR 0.79; p=0.003; RR 0.80; p=0.03; RR 0.85; p=0.02). Statistical analysis also supported higher secondary patency rates for Dacron at 24 months (RR 0.75; p=0.02) and 60 months (RR 0.76-0.77; p=0.03-0.27). Although primary patency was similar between grafts (28% vs. 28%; p=0.12), secondary patencies were better with Dacron at 10 years (49% vs. 35%; p=0.01).

Timing of adverse effects: ≤10 years

Factors that predict response: There was no meta-analysis of this although individual RCTs identified some factors. One study that favored Dracon found that "in patients with only 1 patent crural vessel, the authors noticed decreased patency of both grafts and favored the use of PTFE graft". A second study that favored Dracon found "that the number of outflow vessels had a significant impact on the graft patency; 67% of patients with more than one crural vessel had patent graft (p=0.01). Another study that found no difference between PTFE and Dracon reported "a small graft size (5-6 mm) was a significant predictor of graft failure (p=0.0006). In another study that did not find a difference between Dracon and PTFE authors reported that "multivariate analysis revealed that below-knee anastomosis was the independent predicting factor of primary graft failure (RR 1.7; CI 1.05–2.8). Impaired secondary patency was associated with a below-knee bypass RR of 3.3 (CI 1.8–6.3) and distal gangrene RR of 2.0 (CI 1.01–3.8; p=0.048). Major amputation was predicted by infragenicular bypass, tissue necrosis, and poor runoff."

Source Citation: Van der Slegt 2014[23]

Study Design: Non-randomized comparative study

Device or Material: Precuffed ePTFE grafts compared with autologous saphenous vein (ASV) grafts used in patients with peripheral arterial disease

Contact Duration: ≤5 years

Dose: NR

Frequency/Duration: Single administration

Response: Bladder retention, Compartment syndrome , Decubitus ulcer, Hemorrhage, Primary patency, Primary assisted patency, Secondary patency, Seroma, Wound necrosis

Patient characteristics (gender, mean age): Mean age (range) PTFE 73.0 (41.0-92.7) and ASV 70.1 (36.8-96.5) years; 150 female and 317 male

Number per group: 169 precuffed ePTFE grafts and 298 ASV grafts

Observed adverse effects: **Primary patency rates** at 1, 2, and 5 years were supragenicular ePTFE 56%, 42%, 25% and for ASV 68%, 60%, and 60%, respectively ($p<0.05$); infragenicular PTFE 34%, 18% and 8% vs. ASV 65%, 60%, and 54%, respectively ($p<0.05$); femoro-crural PTFE 24%, 24%, 9% vs. ASV 39%, 39%, and 18%, respectively ($p\geq0.05$).

Primary assisted patency rates at 1, 2, and 5 years were supragenicular ePTFE 59%, 45%, 27% and for ASV 87%, 82%, and 82%, respectively ($p<0.05$); infragenicular PTFE 36%, 22%, and 11% vs. ASV 79%, 77%, and 74%, respectively ($p<0.05$); femoro-crural PTFE 24%, 24%, 9% vs. ASV 45%, 43%, and 30%, respectively ($p<0.05$).

Secondary patency rates of ePTFE vs. ASV at 1 and 5 years, respectively, were as follows: for 134 supragenicular femoropopliteal bypasses, 60% and 27% vs 89% and 85% ($p<.05$); for 190 infragenicular femoropopliteal bypasses, 40% and 25% vs. 86% and 79% ($p<.05$); and for 84 femoro-crural bypasses, 30% and 14% vs. 50% and 50% ($p<.05$).

Minor events PTFE vs. ASV: bladder retention 2 (1%) vs. 2 (1%) p=.62, decubitus 0 vs. 4 (1%) (p=0.30) Surgical events PTFE vs. ASV: wound necrosis 3 (2%) vs. 2 (1%) (p=0.36), seroma 4 (2%) vs. 3 (1%) (p=0.26); hemorrhage 11 (7%) vs. 15 (5%) (p=0.53), compartment syndrome 2 (1%) vs. 0 (p=0.13)

Timing of adverse effects: Mean follow-up PTFE 28.8 months and ASV 36.1 months; adverse events per procedure were recorded until 1 month after discharge of the primary procedure. Follow-up after ASV bypass surgery included routine duplex ultrasound and ABI at 3 months, 6 months, 1 year, and 2 years after the initial procedure, followed by ABI every subsequent 2 years. Follow-up after ePTFE bypass surgery was restricted to duplex ultrasound and ABI examination at 3 months, 1 year, and 2 years after the initial procedure. ABI was measured every subsequent 2 years. All other interim duplex ultrasound examinations were performed after suspicion of graft-related problems.

Factors that predict response: NR

Source Citation: Moulakakis et al. 2013[24]

Study Design: Non-randomized comparative study

Device or Material: Anaconda (Sulzer Vascutek, Bad Soden, Germany); Zenith (Cook Inc, Bloomington, Ind); Excluder (W. L. Gore and Assoc, Flagstaff, Ariz); and Endurant (Medtronic, Minneapolis, Minn)

Contact Duration: ≤30 day follow-up

Dose: NR

Frequency/Duration: Single administration

Response: Endoleaks, Hematoma

Patient characteristics (gender, mean age): Mean (SE) age years: Anaconda 73.11 (0.86), Zenith 73.08 (1.06), Excluder 70.87 (1.34), Endurant 74.17 (1.55); 81 males and 6 females

Number per group: Anaconda 28 patients, Zenith 26 patients, Excluder 23 patients, and Endurant 10 patients

Observed adverse effects: Endografts were successfully implanted in all patients. There were no open conversions, no deaths, and no major perioperative complications. There was no postoperative increase in troponin levels. Minor complications included local hematomas in femoral incisions in 3 patients (1 each in Anaconda, Zenith, and Excluder), who were treated conservatively. At 1-month follow-up, endoleaks were recorded in 12 (13.8%) patients (Anaconda n=5, 17.9%; Zenith n=3, 11.5%; Excluder n=3 patients, 13.0%; Enduran, 1 patient, 10%). No statistically significant differences were recorded for the presence of endoleak with regard to the endograft type. IL-10: the Anaconda group showed the highest mean value at 24 hours and differed significantly from the Excluder (p<.001) and Endurant (p=0.04) groups. The Zenith group also showed higher mean values than the Excluder (p=0.01). Comparisons among the groups of endograft types at 48 hours showed that mean values in patients treated with Anaconda endografts were higher compared with Endurant (p<0.001) and Excluder (p<0.001) endografts, whereas mean values in patients treated with Zenith endografts were significantly higher compared with Endurant (p<0.001) and Excluder (p<0.001) endografts. Patients treated with Anaconda endografts showed the highest IL-6 mean values at 24 hours postoperatively. Statistically significant differences were observed among patients treated with the Anaconda vs. the Excluder (p<0.001), Anaconda vs. Endurant (p=0.04), and Zenith vs. Excluder (p=0.01). Comparisons at 48 hours showed significant differences for Anaconda vs. Excluder (p<0.001), Anaconda vs. Endurant (p<0.001), Zenith vs. Excluder (p<0.001), and Zenith vs. Endurant (p<0.001). With regard to IL-8, although patients treated with Anaconda endografts showed the highest mean values at 24 hours and 48 hours postoperatively, no statistical differences were observed among the patients treated with different types of endografts. Patients in the Excluder group showed statistically lower mean values at 24 hours and 48 hours postoperatively.

For white blood cells (WBC), higher mean values were recorded after 24 hours in patients treated with the Anaconda endograft compared with the Excluder (p<0.001) and Zenith (p<0.001) endografts and the Endurant endograft compared with the Excluder (p=0.001) and Zenith (p=0.01) endografts. After 48 hours, statistically significant differences were observed among Anaconda vs. Excluder (p<0.001), Anaconda vs. Zenith (p<0.001), Anaconda vs. Endurant (p<.001), Endurant vs. Excluder (p=0.004), and Zenith vs.Excluder (p=0.02) groups.

Timing of adverse effects: Operative outcomes were recorded. Temperature, WBC count, platelet count, and serum concentrations of cytokines (IL-6, IL-8, and IL-10) were measured preoperatively, 24 hours postoperatively, and 48 hours postoperatively. Final follow-up was 30 days.

Factors that predict response: NR

Source Citation: Dorigo et al. 2012[25]

Study Design: Registry data

Device or Material: Heparin-bonded ePTFE graft (PROPATEN Gore- Tex, W.L. Gore & Associates Inc, Flagstaff, AZ, USA) and autologous saphenous vein in below-knee femoropopliteal bypasses

Contact Duration: 28.5±22.1 months

Dose: NR

Frequency/Duration: Single administration

Response: Adjunctive procedures, Antiplatelet/anticoagulation therapy, Primary patency, Secondary patency, Thrombosis

Patient characteristics (gender, mean age): 224 women and 726 male; median age PROPATEN 72.7 years and ASV 72.4 years

Number per group: PROPATEN 556 patients, and ASV group 394 patients

Observed adverse effects: Patients in HePTFE group more frequently had adjunctive procedures performed at distal anastomotic sites in order to improve run-off status. Postoperative and long-term medical treatment

consisted of single antiplatelet therapy in 40% of HePTFE group and in 39% (p=NS) in ASV group, double antiplatelet therapy in 17% of HePTFE group and 21% (p=NS) in ASV group and of oral anticoagulants in 43% of the HePTFE group and 40% (p=NS) in ASV group, the regimen for anti-coagulation or anti-platelet being determined on the basis of surgeon's preference. Primary patency rate at 48 months was significantly better in ASV group (61%) than in HePTFE group (44.5%; p=0.004). In below-knee bypasses, the corresponding figures were 45.2% in HePTFE group (SE 0.03) and 69% in ASV group (SE 0.04; p<0.001); in tibial bypasses, they were 39% (SE 0.07) and 53% (SE 0.04; p=0.04).

The rates of secondary patency at 48 months were 57% in HePTFE group (SE 0.03) and 67.5% in ASV group (SE 0.03), without significant differences between the two groups (p=0.1).

Early postoperative results: early graft thrombosis occurred in 55 patients (35 in HePTFE group and 20 in ASV group), with cumulative 30-day graft patency rates of 94 % and 95%, respectively (p=0.3).

Long-term follow-up: during follow-up, 263 new graft thromboses (173 in HePTFE group and 90 in ASV group) occurred. In 33 cases (8 in HePTFE group and 25 in ASV group) significant stenoses at anastomotic sites or at saphenous valves without graft thrombosis were detected; in 16 cases percutaneous transluminal angioplasty of the distal anastomosis or of the residual valves was performed, while in 13 patients endarterectomy of the common femoral artery with patching of the proximal anastomosis was required. Four patients were medically managed without developing graft occlusion.

Timing of adverse effects: Mean duration of follow-up was 28.5±22.1 months, Follow-up was performed within the third postoperative month, at 12 months and then yearly.

Factors that predict response: At univariate analysis, female gender, secondary intervention, distal tibial anastomosis, adjunctive distal procedures, poor run-off score, and kind of graft were found to significantly affect long-term primary patency; at multivariate analysis female gender, secondary intervention and kind of graft maintained their significance. For secondary patency, female gender, secondary intervention, distal tibial anastomosis, critical limb ischemia, adjunctive distal procedures, and poor run-off score were found to significantly affect it at univariate analysis, while at multivariate analysis only secondary interventions-maintained significance.

Source Citation: Kakkos et al. 2011[13]

Study Design: Non-randomized comparative study

Device or Material: Polyurethane Vectra vascular access grafts (C R Bard, Inc.) and PTFE carbon-impregnated IMPRA Carboflo vascular grafts (C R Bard, Inc.)

Contact Duration: ≤3 years

Dose: NR

Frequency/Duration: Single administration

Response: Assisted primary patency Functional secondary patency, Graft ligation/removal, Primary patency Pseudoaneurysm, Secondary patency, Thrombosis, Steal syndrome, Venous hypertension

Patient characteristics (gender, mean age): 167 women and 157 men; median (interquartile range) age was 63 (53–75) years

Number per group: 239 polyurethane and 125 carbon-impregnated PTFE vascular access grafts were placed in 324 consecutive patients.

Observed adverse effects: Twenty-nine grafts developed early postoperative complications including non-salvageable perioperative thrombosis in 19 (5.2%) patients and venous hypertension, steal syndrome, or infection in the remaining 10 (2.7%) patients, necessitating graft ligation or removal.

During follow-up, 36 patients (9.9%) developed a pseudoaneurysm, either anastomotic (1.6%: infected n=4, noninfected n=2) or at the needle-stick site (7.1%: infected n=4, non-infected n=26). Nineteen

additional patients (5.2%) developed graft infection requiring excision. Infected graft salvage was possible only in 2 patients (7%). Cumulative graft pseudoaneurysm formation (at needlestick site) rates at 3 years were not significantly different between Vectra and PTFE Carboflo grafts (17% vs. 23%; p=0.72). Both noninfected anastomotic aneurysms were surgically managed; 1 of them required graft ligation following unsuccessful management with a stent graft, while the second one was salvaged. Non-infected pseudoaneurysms at the needle-stick site (n=26) were mostly managed conservatively. In 5 cases (3 Vectra and 2 PTFE Carboflo grafts), a stent graft (Fluency, C R Bard, Inc.) was placed.

One of them was complicated by endoleak treated with placement of an additional stent graft, both removed later because of infection. Another was complicated by early occlusion. One pseudoaneurysm was seen in association with occlusion of the graft that was abandoned. The remaining 20 pseudoaneurysms were managed expectantly. There was a significant trend for better primary patency of Vectra compared with PTFE Carboflo grafts (15% vs. 11%, respectively, at 3 years; p=0.004). This difference in patency was 12% for primary assisted patency (39% vs. 27%, respectively, at 3 years; p<0.001) and secondary patency (69% vs. 57%, respectively, at 3 years; p=0.012) and 15% for functional secondary patency (61% vs. 46%, respectively, at 3 years; p=0.002).

Timing of adverse effects: ≤3 years

Factors that predict response: Straight upper arm Vectra grafts had the best secondary patency compared with their PTFE counterparts and loop (Vectra and PTFE) grafts (p=0.001); however, loop configuration was the single predictor of worse secondary patency on multivariate analysis (p=0.009; RR 1.7).

Source Citation: Kennealey et al. 2011[11]

Study Design: RCT

Device or Material: Standard cuffed ePTFE graft (Venaflo, Bard Peripheral Vascular, Tempe, Ariz) vs. the bovine carotid artery (BCA) graft (Artegraft, North Brunswick, NJ) for permanent hemodialysis access

Contact Duration: Mean 33 months

Dose: NR

Frequency/Duration: Single administration

Response: Angioplasty, assisted primary patency, Interventions needed, Primary patency, Pseudoaneurysm, Secondary patency, Steal syndrome, Survival of the graft, Thrombosis

Patient characteristics (gender, mean age): 27 male and 26 female, mean age BCA 63±13 years and ePTFE 59±16 years

Number per group: 26 patients in the BCA group and 27 patients in the ePTFE group

Observed adverse effects: Although there was no significant difference in secondary patency rates, primary and assisted primary patency rates were significantly higher in BCA than in the ePTFE grafts (60.5% vs.10.1% and 60.5% vs.20.8% at 1 year, respectively). The BCA graft survival advantage was most profound in the upper arm grafts with significantly higher primary and assisted patency rates (p<0.0001 and p<0.0005, respectively). The total number of interventions (upper arm grafts) and total number of angioplasties (overall and upper arm) required to maintain patency were significantly fewer in the BCA group. Graft thrombosis occurred 0.34±0.09 times per patient year in the BCA group compared to 0.77±0.16 times per patient year in the ePTFE group (p=0.01). In the BCA group, 4 patients underwent 7 interventions before the first episode of thrombosis, which was not significantly different from the ePTFE group (5 patients underwent 6 interventions). Total number of interventions per patient year needed to prolong patency was 1.45±0.19 in the BCA group and 1.99±0.25 in the ePTFE group (p=0.09). The most common intervention used to achieve this secondary patency was percutaneous angioplasty. There were 1.19±0.18 angioplasties per patient year compared to 1.86±0.24 (p=0.02) in the BCA and ePTFE groups, respectively.

The most common complication was graft thrombosis, which occurred 0.77±0.16 times per patient year in the ePTFE group compared to 0.34± 0.09 times per patient year in the BCA group (p=0.01). Thrombosis BCA 0.34±0.09 ePTFE 0.77±0.16 (p=0.01); pseudoaneurysm BCA 0 ePTFE 0.06±0.05 (p=0.07); steal syndrome BCA 0.03±0.03 ePTFE 0.03±0.03 (p=0.88)

Timing of adverse effects: Mean follow-up was 33 months, assessments were conducted every 4 months through month 40 and at year 1 and year 2.

Factors that predict response: The BCA graft survival advantage was most profound in the upper arm grafts with significantly higher primary and assisted patency rates (p<0.0001 and p<00005, respectively). There was no statistically significant difference in the rate of thrombosis, pseudoaneurysm formation, or arterial steal syndrome between the BCA and ePTFE groups within either graft location subset

Source Citation: Mousavi et al. 2011[12]

Study Design: RCT

Device or Material: Frozen saphenous vein vs. synthetic **GORE-TEX** vascular graft for A–V fistula

Contact Duration: ≤12 months

Dose: NR

Frequency/Duration: Single administration

Response: Auscultatable murmurs, Death, Renal insufficiency, Graft survival, Thrill sensation, Thrombosis

Patient characteristics (gender, mean age): 32 male, 28 female; Patients were 30 to 74 years old in the saphenous vein group (51.53±12.46) and 31 to 75 years old in the GORE-TEX group (51.6±11.68)

Number per group: 30 per group

Observed adverse effects: At the end of the follow-up period, 70.50% of the saphenous vein group and 72% of the GORE-TEX group were still being dialyzed from their shunts, which showed no significant difference. Flowmetry showed that at the end of the year, 41.66% of the GORE-TEX group had good flow, 41.66% had moderate flow, and 16.66% had poor flow. In the saphenous vein group, 40% had good flow, 50% had moderate flow, and 10% had poor flow, which did not show significant differences. One patient died from complications of renal insufficiency. 75% of the saphenous vein group and 76.66% of the GORE-TEX group had auscultatable murmurs on their shunts which showed no significant difference. There was no significant difference in thrill sensation between the 2 groups in any of the follow-up visits, and 71.42% of the saphenous vein group and 73.33% of the GORE-TEX group had sensible thrill on their fistulas at the end of the year. The overall thrombosis rate of the fistulas at the end of the follow-up period was 25% in the saphenous vein group and 20% in the GORE-TEX group, which were not statistically meaningful.

Timing of adverse effects: ≤12 months

Factors that predict response: NR

Source Citation: Drouven et al. 2019[14]

Study Design: Non-randomized comparative study

Device or Material: Basilic vein transposition vs. PTFE forearm loop graft as tertiary vascular access

Contact Duration: Mean follow-up 29 months

Dose: For the PTFE loop, a standard wall PTFE graft (Gore-Tex; W. L. Gore & Associates, Flagstaff, Ariz) with 6 mm diameter and 0.5 mm wall thickness was used.

Frequency/Duration: Single administration

Response: Steal syndrome and distal ischemia, Venous hypertension

Patient characteristics (gender, mean age): 69 males and 61 females; basilica vein 58.3 (SD 13.9) and PTFE 62.6 (SD 14.9) years

Number per group: Basilic vein 55 and PTFE 75

Observed adverse effects: Venous hypertension: PTFE 0 (PY^{-1} 0.00) vs. basilica vein 4 (PY^{-1} 0.03; p=0.242) Steal syndrome and distal ischemia: PTFE 1 (PY^{-1} 0.01) vs. basilica vein 1 (PY^{-1} 0.01; p=0.831)

Timing of adverse effects: NR but mean follow-up was 29 months

Factors that predict response: Multivariate regression identified body mass index (HR 1.77; 95% CI 1.05–2.98; p=0.03) and age (HR 0.54; 95% CI 0.32–0.91; p=0.02) as predictors for failure regarding primary patency in PTFE loop patients. Previous catheter use (HR 0.29; 95% CI 0.12–0.70; p=0.006) and the presence of diabetes (HR 3.32; 95% CI 1.50–7.39; p=0.003) were independent predictors for failure regarding primary patency in basilic vein transposition patients. The incidence rate of total complications was significantly higher in the PTFE loop group with 0.70 PY^{-1} compared with 0.28 PY^{-1} in the basilic vein transposition group (p=0.001). In terms of intervention rate, a significantly higher percutaneous transluminal angioplasty rate and surgical revision rate were found in the PTFE loop group than in the basilic vein group (1.77 PY^{-1} vs. 1.05 PY^{-1}; p=0.022 and 0.20 PY^{-1} vs. 0.07 PY^{-1}; p=0.002, respectively).

Source Citation: Shakarchi et al. 2019[7]

Study Design: Systematic review

Device or Material: PTFE Flixene, Acuseal Polycarbonate urethane, Avflo Polyurethane Vectra grafts

Contact Duration: 12 to 36 months

Dose: NR

Frequency/Duration: Single administration

Response: Steal syndrome

Patient characteristics (gender, mean age): NR

Number per group: 19 studies total; number of patients for Flixene 230; Avflo 74; Acuseal 260; Vectra 762

Observed adverse effects: Flixene Steal syndrome: 0 to 8% based on 3 studies, Avflo Steal syndrome: NR, Acuseal

Steal syndrome: 0 to 11% based on 3 studies Vectra, Steal syndrome: 0 to 3.5% based on 4 studies

Timing of adverse effects: Flixene ≤18 months; Avflo ≤24 months; Acuseal ≤24 months, Vectra ≤18 to 36 months follow-up

Factors that predict response: NR

Source Citation: Cho et al. 2018[26]

Study Design: Single-arm study

Device or Material: Extra-cardiac Fontan procedure with 16 mm PTFE (**GORE-TEX** vascular graft; W.L. Gore & Associates, Inc., Flagstaff, AZ, USA) conduit vs. matched controls with conduit size of 19.2±1.4mm (18 mm, n=34; 20 mm, n=23 and 22 mm, n=9)

Contact Duration: ≤16 years

Dose: 16 mm PTFE conduit vs. a larger conduit (mean 19.2±1.4 mm)

Frequency/Duration: Single administration

Response: Cirrhosis, Coarse liver parenchyma, Mortality, Protein-losing enteropathy, Reoperation, Thromboembolism

Patient characteristics (gender, mean age): Mean age PTFE 16 mm 2.9±1.2 years and matched control group 3.1±1.2; gender NR

Number per group: PTFE 16-mm group 66 patients and 66 control patients matched for age and size Observed adverse effects: There was no significant difference in mortality between the groups (p=0.109). The freedom from reoperation was 94.0±3.4% in 16 mm PTFE and for matched controls 79.3±5.7% after 10 years (p=0.070). Late-occurring morbidities included protein-losing enteropathy (2 in 16 mm PTFE, 4 in matched controls; p=0.491) and thromboembolism (0 in 16 mm PTFE, 4 in matched controls; p=0.206). Protein-losing enteropathy N: 16 mm group 2 vs. matched controls 4 (p=0.491); thromboembolism N: 16-mm group 0 vs. matched controls 4, p=0.206; reoperation N: 16 mm group 4 vs. matched controls 11 (p=0.070); mortality N: 16 mm group 1 vs. matched control 6 (p=0.109); early mortality 16 mm 0 matched control 3 (due to heart failures after ECFP); late mortality 16 mm 1 (due to recurrent pulmonary vein stenosis and heart failure 1 year after the procedure) vs. matched control 3 (due to septic shock after mediastinitis). Freedom from catheter-based intervention was present for 89.3±4.8% (16 mm PTFE) and 93.3±3.8% (matched controls) over 10 years (p=0.369), respectively. Coarse liver parenchyma was detected in 9 of 23 (39.1%) patients from the 16 mm PTFE group and in 7 of 18 (38.8%) patients from the matched control group upon ultrasonography. Among patients with >10 years of follow-up, 6 patients with liver cirrhosis were detected (16 mm: 3 of 23, 13%, matched control: 3 of 18, 16.6%), and coarse parenchyma was detected in 9 (39.1%) and 7 (38.3%) patients in 16 mm and matched control groups, respectively.

Timing of adverse effects: Mean follow-up PTFE 7.8±6.0 years and matched control 9.1±4.9 years

Factors that predict response: NR

Source Citation: Goja et al.2018[16]

Study Design: Non-randomized comparative study

Device or Material: AS reconstruction using nonringed ePTFE grafts (GORE-TEX, W.L. Gore & Associates, Inc., Newark, DE, USA) vs. venous extension grafts

Contact Duration: ≤2 year

Dose: ≤5 mm

Frequency/Duration: Single administration

Response: Hospital LOS, ICU LOS, Sepsis, Survival

Patient characteristics (gender, mean age): Mean age of patients was 48 ± 10.21 years; 366 male and 71 female

Number per group: Venous extension graft 200 patients, and ePTFE in 237 patients

Observed adverse effects: Sepsis: venous extension group 19 (9.5%) vs. PTFE 17 (7.1%) (p=0.4). There was no significant difference in ICU stay, hospital stay, 30-day (V 92%, ePTFE 94.5%; p=0.34), 90-day (V 90%, ePTFE 90.7%, p=0.87) and one-year (V 87.5%, ePTFE 89%; p=0.66) patient survival between the groups.

Timing of adverse effects: 30-day, 90-day and 1-year for survival: graft patency was checked by Doppler ultrasonography intraoperatively, then once a day for the first week and weekly till hospital discharge. Follow-up USG Doppler was performed at 3, 6, and 12 months following transplantation. All the recipients were followed up twice a week for a month, then weekly for 3 months, fortnightly for 6 months, monthly for 24 months, and once every 2 months after 2 years.

Factors that predict response: NR

Source Citation: Kaisar et al. 2018[17]

Study Design: Non-randomized comparative study

Device or Material: PROPATEN heparin-bonded PTFE vascular graft with distal anastomotic patch versus autogenous saphenous vein graft in tibial artery bypass

Contact Duration: ≤4 years

Dose: 6 mm PROPATEN graft

Frequency/Duration: Single administration

Response: Hospital LOS, Limb salvage

Patient characteristics (gender, mean age): Mean age PROPATEN 73 (SD 11.6) vs. vein group 75 (SD 13.4) years; 69 males and 39 females

Number per group: 62 revascularizations in 59 patients in the PROPATEN group and 46 procedures in 44 patients in the vein group

Observed adverse effects: The limb salvage rates were equivalent between the PROPATEN and vein group at 4 years (84% vs. 92%; p=0.89). Length of hospitalization, days (SD): PROPATEN 5.2 (SD 2.3) Vein group 7.5 (SD 3.6) (p=0.08).

Timing of adverse effects: Postoperative ultrasound surveillance along with ABI was performed at 1, 3, 6, 12 months, and every 6 months thereafter. Patency and limb salvage rates were reported yearly for up to 4 years. Postoperative complications were reported for 30-days postoperation.

Factors that predict response: Univariate analysis of primary patency for these bypass grafts showed that foot ulcers, active tobacco user, and poor run-off score of 0–1 were associated with this outcome. Multivariate analysis showed active tobacco usage and poor run-off score as predictors for graft occlusion.

Source Citation: Nguyen et al. 2018[15]

Study Design: Retrospective comparative study

Device or Material: PTFE grafts and femoral vein as conduits for femorofemoral crossover grafts

Contact Duration: Median follow-up was 9.8 months (range 0e107

Dose: NR

Frequency/Duration: Single administration

Response: Blood transfusion, Primary assisted patency, Primary patency, Secondary patency, Wound complication

Patient characteristics (gender, mean age): 51 females and 68 males; mean age vein 65.5 (SD 8.5) and PTFE 66.5 (SD 10.8) years

Number per group: 89 PTFE, 30 vein (18 were autogenous femoral veins, 12 were cryopreserved) Observed adverse effects: The 30-day complication rate was 38.7% and was not different between groups (36% for PTFE, 44.4% for autologous vein grafts and 50% for cryovein, p=0.33) with wound complications being most frequent (18% PTFE, 27.8% autologous vein, 16.7% cryovein, p=0.25). Patients receiving vein grafts were more likely to receive blood transfusion (34.8% PTFE vs. 70% vein, p=0.001). 30-day complications: hematoma vein group 0% n=0 PTFE 4.5% n=4 p=0.57; seroma vein group 6.7% n=2 PTFE 5.6% n=5 p=1.00; renal insufficiency vein group 6.7% n=2 PTFE 9% n=8 p=1.00; hemodialysis vein group 0% n=0 PTFE 0% n=0 p=1.00; pseudoaneurysm vein group 3.3% n=1 PTFE 2.2% n=2 p=1.00; Primary patency rates at 1, 2, and 3 years were 83.7 %, 73.7% and 69.8%, respectively, for PTFE bypasses, and 100% for all time points for venous grafts, respectively (p=0.03). Primary-assisted and secondary patency rates were not significantly different between the 2 groups (p=0.16).

Timing of adverse effects: Intraoperative, 30 days and 1-, 2-, and 3-years; femorofemoral bypasses were evaluated with duplex ultrasound every 3 months for the first year and then every 6 months for the second year. If there were no complications or concerning ultrasound findings suggesting significant stenosis or impending graft failure, then patients were followed up annually with surveillance ultrasound.

Factors that predict response: A subgroup analysis of isolated femorofemoral bypasses was performed and showed no significant differences in primary patency at 1, 2, and 3 years (PTFE 86.8%, 74%, and 74% vs. vein 100% for all time points, respectively; p=0.40). Primary-assisted patencies at 1 and 2 years were significantly higher for bypasses created with femoral vein (100% for both time points) versus those created with PTFE graft (87% for both time points) (p=0.02). Secondary patency of isolated femorofemoral bypasses were not significantly different between veins and PTFE grafts (p=1.00). Survival at 1, 2, and 3 years (PTFE 79.2%, 64.5% and 54.8% vs. vein 86.7%, 86.7% and 65%, respectively; p=0.40) and amputation-free survival at 1, 2, and 3 years (PTFE 93% at all-time points vs. vein 87% at all-time points; p=0.86) between grafts created with prosthetic PTFE graft and those created with femoral vein were not statistically different. For axillobifemoral bypasses, a subgroup analysis was performed and showed no differences in patency rates (primary, p=0.12], primary-assisted [p=0.36], or secondary patencies [p=1.00] at 1, 2, or 3 years, p=1.00). However, survival was significantly higher in patients who received a PTFE conduit for the femorofemoral component of an axillobifemoral graft as compared with patients who received a femoral vein conduit for the femorofemoral component. Survival at 1, 2, and 3 years was 93.8%, 93.8%, and 93.8%, respectively, for patients with a PTFE femorofemoral component and 58%, 46%, and 46%, respectively, for patients with femoral vein (p=0.001). Amputation-free survival at 1, 2, and 3 years was not significantly different in patients who received vein grafts for the femorofemoral component as compared with those who received PTFE grafts for the femorofemoral component (p=0.21).

Source Citation: Veraldi et al. 2018[18]

Study Design: Non-randomized comparative study

Device or Material: Percutaneous transluminal angioplasty (PTA) ± bare metal stent (BMS) vs heparin-bonded ePTFE graft (PROPATEN-GORE) + Linton patch in patient affected by symptomatic femoropopliteal TASC II-D lesions

Contact Duration: Mean follow-up was 26.7 months

Dose: 6 or 7 mm PROPATEN-GORE graft was used as conduit

Frequency/Duration: Single administration

Response: Bleeding, Hematoma, Occlusion, Primary assisted patency, Primary Patency, Re-intervention, Restenosis, Secondary patency, technical success

Patient characteristics (gender, mean age): Mean age PTA/BMS 76 years and PTFE 72 years; sex reported by limb, 61 male and 19 female

Number per group: 68 patients total (80 limbs); PTA/BMS 40 limbs and PTFE 40 limbs

Observed adverse effects: Primary patency at 6, 12, and 24 months of PTA/BMS versus PTFE group was 76.9% vs. 97.5% (p=0.007), 65.7% vs. 89.1% (p=0.05), and 52.6% vs. 78.1% (p=0.005), respectively. Assisted primary patency was 76.9% vs. 97.5% (p=0.007), 68.5% vs. 91.8% (p=0.02), and 57.8% vs. 87.5% (p=0.001), respectively. Secondary patency was 94.8% vs. 97.5% (p=NS), 85.7% vs. 97.2% (p=NS), 73.6% vs. 93.7% (p=0.004), respectively. Rate of reintervention at 24 months was 45% in PTA/BMS vs. 20% in PTFE group (p=0.03). In PTA/BMS, technical success was obtained in 38 limbs (95%): it was impossible to cross the lesion in 2 cases, and a surgical revascularization with bypass was necessary. After the procedure, 3 limbs developed perioperative complications: 1 patient developed a retroperitoneal hematoma and 2 presented local bleeding at the site of femoral access. All complications were conservatively treated, and none of them required a reoperation before discharge.

In the PTFE group, technical success was 100%. Five limbs (12.5%) developed local complications: 2 cases of arterial bleeding requiring surgical hemostasis, 2 lymphatic fistulas (conservative treatment), and 1 skin necrosis requiring surgical debridement. In-hospital complications: PTA/BMS 3 (7.5%) vs PTFE 5 (12.5%) p=NS; Reintervention after discharge PTA/BMS 18 (45%) vs PTFE 8 (20%) p=0.03. During follow-up, 26 limbs (32.5%) required a reintervention for significant stenosis or symptomatic occlusion (18 patients, 45% in group PTA/BMS vs. 8 patients, 20% PTFE group, p=0.03).

In group PTA/BMS 14 limbs underwent to re-PTA, 2 of which required subsequent open revascularization for recurrence of occlusion. Four (10%) limbs developed symptomatic occlusion and were treated with a surgical revascularization without any other endovascular attempts. Two PTA procedures were planned following evidence of significant distal stenosis, and 1 target limb underwent to surgical correction of a proximal anastomotic aneurysm.

Timing of adverse effects: Patients were followed with a clinical assessment and duplex at 1, 6, and 12 months after procedure and then annually. A closer follow-up was performed in case of any complication.

Factors that predict response: Univariate analysis showed critical limb ischemia and poor runoff to be independent risk factors for significant restenosis/occlusion of target artery and reintervention.

Source Citation: Uhl et al. 2017[19]

Study Design: Non-randomized comparative study

Device or Material: Autologous vein vs. heparin bonded ePTFE for below knee femoropopliteal bypasses in patients with CLI in whom endovascular therapy was not possible or failed

Contact Duration: Mean follow-up was 34 months

Dose: HePTFE (6 mm ring enforced PROPATEN-GORE)

Frequency/Duration: Single administration

Response: Occlusion, Primary patency, Primary assisted, Patency, Restenosis, Revascularization Secondary patency

Patient characteristics (gender, mean age): Mean age: PTFE 73.0 (SD 10) and autologous vein 70.5 (SD 9), 90 male and 61 female

Number per group: Autologous vein 76 cases and heparin-bonded ePTFE 75 cases

Observed adverse effects: Early graft occlusion occurred in 9 cases (vein group 6.6% vs. HePTFE group 5.3%; p=0.508). No early occluded vein graft resulted in a major amputation within 30 days. Except for the 2 patients with the early occluded HePTFE grafts who underwent major amputation for the abovementioned reasons, all other early occluded grafts underwent thrombectomy within the first 24 hours. For 1-, 3-, and 5-years, primary patency in the vein group was 75.3%, 62.2%, and 55.5%; in the HePTFE group it was 73.6%, 51.7%, and 51.7% after the same time intervals. There was no significant difference after 5 years (p=0.897). After 1 year, primary assisted patency was 79.1% in the vein group and 75.0% in the HePTFE group, after 3 years it was 72.8% in the vein group and 54.9% in the HePTFE group, and after 5 years it was 66.8% in the vein group and 54.9% in the HePTFE group. Primary assisted patency rates in the 2 graft groups 5 years postoperatively again showed no significant difference (p=0.270). Comparing the 2 groups, vein and PTFE, the secondary patency was 91.1% vs. 82.7% after 1 year, 81.7% vs. 69.0% after 3 years, and 74.6% vs. 55.6% after 5 years, again without significant difference after 5 years (p=0.119) Restenosis: An intervention was performed in 15 cases to avoid a graft occlusion due to a stenosis (3 in the HePTFE group, 12 in the vein group).

Timing of adverse effects: ≤5 years for survival; Completion angiography was performed before leaving the operating room to exclude technical failure. Duplex scans and clinical examinations regarding wound healing and clinical symptoms were done before discharge from hospital and 6 months postoperatively. If the 6-month examination was satisfactory patients were checked at intervals of 12 months. For patency and limb salvage AEs were reported at 1-, 3-, and 5-years.

Factors that predict response: In subgroup analysis regarding 1-, 2-, and 3- vessel runoff, no significant difference was found in primary, primary assisted, or secondary patency; limb salvage; or survival between the 2 groups after 1 year. When comparing patients with previous endovascular treatment with patients without previous revascularization procedures, no significant difference was found regarding primary and secondary patency, limb salvage, and survival. In the multivariate analysis for secondary patency, smoking (p=0.01, 95% CI 1.2–5.5, HR 2.6) and prosthetic graft material (p=0.03, 95% CI 1.1–4.8, HR 2.3) were associated with a higher risk of graft failure, and prosthetic graft material was found to have an impact on limb salvage (p=0.04, 95% CI 1.1–8.8, HR 3.1).

Source Citation: Thorat et al. 2016[20]

Study Design: Non-randomized comparative study

Device or Material: Inferior right hepatic vein reconstruction using PTFE vs. direct IRHV-to-IVC anastomosis

Contact Duration: ≤2 months

Dose: PTFE graft: Liver allografts with MHV included requiring single ePTFE vascular graft for MHV reconstruction to form a common outflow channel (n=32). Bridging conduit plasty: Liver allografts without MHV requiring 2 ePTFE vascular grafts for backtable MHV reconstruction and IRHV reconstruction to facilitate second IRHV-to-IVC anastomosis (n=20)

Frequency/Duration: Single administration

Response: Graft migration, Graft removal, Hepatic venous stenosis, Patency

Patient characteristics (gender, mean age): PTFE with MHV subgroup: 20 males and 12 females with a mean age of 54 years; PTFE bridging conduit plasty: 16 males and 4 females with an average age of 51±10 years; direct IRHV-IVC: males 30 and females 17 with a mean age 54±6

Number per group: ePTFE 52 patients total and direct IRHV-to-IVC anastomosis comparator 47 patients

Observed adverse effects: There were no thrombotic complications in either group of recipients; 4.2% of the recipients from direct IRHV-to-IVC anastomosis group developed hepatic venous stenosis but with no clinical deterioration 6 months post-surgery; and 1 patient from the PTFE group A developed ePTFE graft migration in the second portion of the duodenum that required surgical exploration and graft removal in the third postoperative month. No acute obstruction of ePTFE graft occurred in any of the recipients. All the recipients in the cohort recovered well in the postoperative period, with satisfactory liver functions. The patency rate of the ePTFE grafts used in studied recipients was 100% for the first 2 months.

Timing of adverse effects: Doppler ultrasonography was performed on first postoperative day, then every alternate day during the first week, and then once per week until the patient was discharged. CT scans were performed for patients with Doppler ultrasound showing abnormalities of outflow with high serum concentrations of liver enzymes (>300 to 400 IU/L) during the immediate posttransplant period. Patency was reported at the 2-month postoperative visit.

Factors that predict response: NR

Source Citation: AI Shakarchi et al. 2015[9]

Study Design: Systematic review

Device or Material: Hemodialysis Reliable Outflow (HeRO) graft (Cryolife Inc company; Eden Prairie, MN, USA) in complex hemodialysis patients

Contact Duration: 7 to 18.5 months

Dose: NR

Frequency/Duration: Single administration

Response: Steal syndrome

Patient characteristics (gender, mean age): No difference in rate of male versus female; mean age NR

Number per group: 8 studies with 409 patients were included

Observed adverse effects: Primary and secondary pooled patency rates in this complex cohort of dialysis patients were 21.9% (9.6 to 37.2%) and 59.4% (39.4 to 78%). The rate of interventions required to maintain HeRO patency ranged between 1.5 and 3 procedures per year.

Timing of adverse effects: Through 7 to 18.5 months' follow-up period

Factors that predict response: NR

Source Citation: Anaya-Ayala et al. 2015[21]

Study Design: Non-randomized comparative study

Device or Material: Hybrid graft vs. standard PTFE graft for hemodialysis access

Contact Duration: Median follow-up was 21 months

Dose: NR

Frequency/Duration: Single administration

Response: Primary assisted patency, Primary patency, Reintervention, Secondary patency, Technical success

Patient characteristics (gender, mean age):

Number per group: Mean age Hybrid graft group 65±14 years and PTFE 63±12 years; 33 males and 27 females

Observed adverse effects: Hybrid graft 25 patients and PTFE 35 patients

Timing of adverse effects: Technical success was achieved in all cases, and all grafts were usable for hemodialysis. Estimated primary patency (24% vs. 18%, p>0.05), assisted primary patency (34% vs 28%; p>0.05), and secondary patency rates (40% vs 38%, p≥0.05) at 24 months were equivalent for Hybrid vs. PTFE grafts, respectively. Primary patency, assisted primary patency, and secondary patency rates at 12 months for the Hybrid graft patients vs. the standard PTFE patients were 66%±8% vs. 45%±8% (p=0.04), 69%±7% vs. 50%±7% (p=0.02), and 69%±7% vs 66%±7% (p>0.05), respectively. Six of 25 patients had graft occlusions and required open thrombectomy with a fistulogram of the Hybrid graft at a median of 2 months (range 1–8). Three did not require additional interventions, as no cause was determined. One patient required dilation of the innominate vein, and 1 patient required both dilation and stenting of the axillary and innominate veins. The final patient required surgical revision of the arterial anastomosis. None of these patients required a central venous line. For PTFE, 11/35 patients required open thrombectomy of the graft at a median of 2 months (range 1–8), with 5 needing additional endovascular interventions. Three patients required dilation of the innominate vein, and 2 patients had both dilation and stenting of the axillary and innominate veins.

Factors that predict response: 24 months for patient survival, thrombectomy needed at a median of 2 months postoperation.

Source Citation: Donati et al. 2015[1]

Study Design: Non-randomized comparative study

Device or Material: AVG made of PTFE GORE-TEX, W. L. Gore & Associates, Flagstaff, AZ, USA) Grafts vs Tunneled Cuffed Catheters for Hemodialysis

Contact Duration: ≤24 month follow-up

Dose: 19 PTFE grafts had an internal diameter of 6 mm, and 3 PTFE grafts had an internal diameter of 7 mm. 9 grafts had a conic feature, 5 of them had 6 mm diameter in the venous side and 4 mm diameter in the arterial side, 4 had a 7 mm diameter on the venous side and 4 mm diameter in the arterial side. In 19 cases out of 31 (61.3%), the PTFE grafts were placed in the arm

Frequency/Duration: Single administration

Response: Graft survival, Thrombosis

Patient characteristics (gender, mean age): 48 males and 39 females; PTFE mean age 63.8 ± 14.6 years and TCC mean age 73.5 ± 11.3 years

Number per group: TCC 56 patients and PTFE 31 patients

Observed adverse effects: Seventeen out of 31 patients (54.8%) with PTFE graft and 25/56 patients with TCC (44.6%) experienced a loss of the vascular access during a 1-year follow-up (p=NS). During a 24-month follow-up, loss of the vascular access was observed in 22/31 cases (71%) in the PTFE graft group and in 33/56 cases (58.9%) in the TCC group. Median survival of PTFE grafts at 24 months was 8.7±3.4 months, whereas TCC survival was 14.1±3.1 months (p=ns).

Vascular access lasted a median of 5.4 months longer in the TCC group than in the PTFE group, but the difference did not reach statistical significance (log-rank 1.34, p=0.25). Vascular access thrombosis caused vascular access loss in 20/31 cases (64.5%) in patients with a PTFE graft and in 4/56 cases (7.1%) in patients with TCC (P <0.001). Vascular access loss was due to infection in 4/31 cases (12.9%) in the PTFE group and in 9/56 cases (16.1%) in the TCC group (p=NS). The mean time interval between vascular access placement and the onset of these major complications was 7.5±7.9 months in the PTFE group and 13.0±14.9 months in the TCC group (p=NS). Vascular access infection occurred after a mean time of 9.4±7.2 months after vascular access placement in the PTFE group and after 16.4±15.6 months in the TCC group (p=NS). The time between vascular access placement and the diagnosis of thrombosis was 7.1±8.1 months in the PTFE group and after 1.8 ± 1.2 months in the TCC group (p=NS). The overall infectious and thrombotic complications of vascular access during the follow-up (any complication) were more frequent in the PTFE graft group compared with the TCC group: 13/31 (41.9%) in the PTFE group versus 7/56 (12.5%) in the TCC group (p<0.001).

Timing of adverse effects: Patients were monitored 3 times a week for adverse events during their hemodialysis sessions. Final follow-up was at 24 months.

Factors that predict response: Cox regression analysis adjusted for age, gender, type of vascular access, number of previously created arterial venous fistulae, diabetes, atrial fibrillation, and cigarette smoking confirmed that the survival of the vascular assess was similar between the TCC and the PTFE group at 12 months follow-up. However, in this analysis, diabetes (p=0.02) and all thrombotic and infectious complications of vascular access (p=0.01) proved to be significant independent predictors of access survival. In particular after 12 months, nondiabetic patients experienced vascular access survival 2.2 times higher than diabetic patients. Vascular access survived in 62.1% of nondiabetic patients, whereas it survived in 44.4% of diabetic patients during a 12-month follow-up. Moreover, patients experiencing any infectious or thrombotic complications had a 2.7 times higher risk of vascular access failure than those not experiencing complications. At the 24-month follow-up, only diabetes remained as a risk factor for vascular access survival. The absence of diabetes was significantly associated with an improvement in vascular access survival (p=0.02). Patients without diabetes had a 1.9 times higher probability of vascular access survival than that of diabetic patients independent of the type of vascular access. Vascular access survival was 27.8% in diabetic patients and 43.1% in nondiabetic patients.

Source Citation: Shemesh et al. 2015[27]

Study Design: Single-arm study

Device or Material: Standard ePTFE graft or a heparin-bonded ePTFE (PROPATEN) graft for hemodialysis access

Contact Duration: NR

Dose: Tapered 4- to 7-mm stretch ePTFE (W. L. Gore & Associates)

Frequency/Duration: Single administration

Response: Assisted primary patency, Bleeding complications, Cannulation time, Occlusion, Primary patency, Secondary patency, Thrombosis, Thrombolytic treatment

Patient characteristics (gender, mean age): 77 men and 83 women; mean age PROPATEN 69.9±10.2, standard 67.8±12 years

Number per group: 80 patients per group

Observed adverse effects: Primary patency was 35% and 14% for heparin-bonded grafts and 29% and 12% for standard ePTFE grafts at 6 and 12 months, respectively (p=0.48). Assisted primary patency was 54%, 41%, and 27% for heparin-bonded grafts and 41%, 30%, and 23% for standard grafts at 12, 24, and 36 months, respectively (p=0.12) by log-rank, p=0.04 by Gehan-Breslow-Wilcoxon. Secondary patency was 83%, 83%, and 81% for heparin-bonded grafts and 81%, 73%, and 68% for standard grafts at 12, 24, and 36 months, respectively (p=0.33). All grafts were ready for cannulation between 2 and 4 weeks postoperatively with no difference between the groups. Of 80 standard grafts, 24 were eventually abandoned vs. 17 heparin-bonded grafts (p=0.188). Bleeding complications and intervention rates were similar in both groups. Mean time to first thrombosis was 9.7±10 months in the heparin-bonded group and 7.8±10.6 months in the standard group (p=0.17). An anatomic cause for occlusion in the first month could be found in 5 (83%) of the 6 heparin-bonded grafts compared with only 8 (50%) of the 16 standard grafts (p=0.18). There were no differences between upper and lower arm access and between the 2 graft types in the upper arm and the 2 graft types in the lower arm. Although the number of thrombolytic treatments was lower by 18% and the time to first thrombosis was longer by 24% in the heparin-bonded group, these differences did not reach statistical significance. 50/80 heparin-bonded grafts thrombosed during the follow-up period and required 119 thrombolytic treatments (range 0-8) compared with 57/80 standard grafts, which required 145 thrombolytic treatments (range 0-8) (p=0.16). 17 grafts were abandoned in the heparin-bonded group vs. 24 in the standard group (p=0.188).

Timing of adverse effects: Through median study follow-up period 23.5 months

Factors that predict response: There were significantly fewer thromboses in heparin-bonded grafts during the first month (8% vs. 20%, p=0.025) and first 5 months (p=0.02).

Source Citation: Attia et al. 2014[22]

Study Design: Non-randomized comparative study

Device or Material: Femoropopiteal bypass surgery for lower limb ischemia with PTFE vs. saphenous vein graft

Contact Duration: Mean and median follow-up period was 12 and 18 months, respectively

Dose: NR

Frequency/Duration: Single administration

Response: Patency

Patient characteristics (gender, mean age): 35 males and 15 females; median age 62 years (range 44 to 70)

Number per group: PTFE 18 patients and saphenous vein graft 32 patients

Observed adverse effects: Use of a prosthetic graft and construction of an intragenicular anastomosis (12 cases) was associated with lower graft patency rates, but statistical significance was not reached. According to study authors "The reversed saphenous vein is the preferred conduit in the present study. However when the

different surgical subgroup are examined separated femoro-distal bypass with vein graft is associated with increased patency rate than femoro distal bypass with synthetic graft."

Timing of adverse effects: Patients were assessed 6 weeks postoperation and at 3, 6, 9, 12, and 18 months.

Factors that predict response: NR for the PTFE patients. The authors looked at risk factors across all 50 patients combined, regardless of graft material.

Source Citation: Rychlik et al. 2014[10]

Study Design: Systematic review

Device or Material: Dacron versus PTFE grafts for above-knee femoropopliteal artery bypass

Contact Duration: ≤10 years

Dose: 5 to 8 mm grafts

Frequency/Duration: Single administration

Response: Antiplatelet/anticoagulation use, Primary patency, Secondary patency

Patient characteristics (gender, mean age): Mean age 66 years, gender NR

Number per group: 8 publications reporting on 6 RCTs with 601 Dacron and 591 PTFE

Observed adverse effects: Although primary and secondary patency rates at 12 months were not significantly different (RR 0.78; p=.08, and RR 0.84; p=0.52), 24-, 36-, and 60-month primary patency rates were significantly better with Dacron compared with PTFE grafts (RR 0.79; p=0.003; RR 0.80; p=0.03; RR 0.85; p=0.02). Statistical analysis also supported higher secondary patency rates for Dacron at 24 months (RR 0.75; p=0.02) and 60 months (RR 0.76-0.77; p=0.03-0.27). Although primary patency was similar between grafts (28% vs. 28%; p=0.12), secondary patencies were better with Dacron at 10 years (49% vs. 35%; p=0.01).

Timing of adverse effects: ≤10 years

Factors that predict response: There was no meta-analysis of this although individual RCTs identified some factors. One study that favored Dracon found that "in patients with only 1 patent crural vessel, the authors noticed decreased patency of both grafts and favored the use of PTFE graft". A second study that favored Dracon found "that the number of outflow vessels had a significant impact on the graft patency; 67% of patients with more than one crural vessel had patent graft (p=0.01). Another study that found no difference between PTFE and Dracon reported "a small graft size (5-6 mm) was a significant predictor of graft failure (p=0.0006). In another study that did not find a difference between Dracon and PTFE authors reported that "multivariate analysis revealed that below-knee anastomosis was the independent predicting factor of primary graft failure (RR 1.7; CI 1.05–2.8). Impaired secondary patency was associated with a below-knee bypass RR of 3.3 (CI 1.8–6.3) and distal gangrene RR of 2.0 (CI 1.01–3.8; p=0.048). Major amputation was predicted by infragenicular bypass, tissue necrosis, and poor runoff."

Source Citation: Van der Slegt 2014[23]

Study Design: Non-randomized comparative study

Device or Material: Precuffed ePTFE grafts compared with autologous saphenous vein (ASV) grafts used in patients with peripheral arterial disease

Contact Duration: ≤5 years

Dose: NR

Frequency/Duration: Single administration

Response: Bladder retention, Compartment syndrome, Decubitus ulcer, Hemorrhage, Primary patency, Primary assisted patency, Secondary patency, Seroma, Wound necrosis

Patient characteristics (gender, mean age): Mean age (range) PTFE 73.0 (41.0-92.7) and ASV 70.1 (36.8-96.5) years; 150 female and 317 male

Number per group: 169 precuffed ePTFE grafts and 298 ASV grafts

Observed adverse effects: **Primary patency rates** at 1, 2, and 5 years were supragenicular ePTFE 56%, 42%, 25% and for ASV 68%, 60%, and 60%, respectively ($p<0.05$); infragenicular PTFE 34%, 18% and 8% vs. ASV 65%, 60%, and 54%, respectively ($p<0.05$); femoro-crural PTFE 24%, 24%, 9% vs. ASV 39%, 39%, and 18%, respectively ($p\geq0.05$).

Primary assisted patency rates at 1, 2, and 5 years were supragenicular ePTFE 59%, 45%, 27% and for ASV 87%, 82%, and 82%, respectively ($p<0.05$); infragenicular PTFE 36%, 22%, and 11% vs. ASV 79%, 77%, and 74%, respectively ($p<0.05$); femoro-crural PTFE 24%, 24%, 9% vs. ASV 45%, 43%, and 30%, respectively ($p<0.05$).

Secondary patency rates of ePTFE vs. ASV at 1 and 5 years, respectively, were as follows: for 134 supragenicular femoropopliteal bypasses, 60% and 27% vs 89% and 85% ($p<.05$); for 190 infragenicular femoropopliteal bypasses, 40% and 25% vs. 86% and 79% ($p<.05$); and for 84 femoro-crural bypasses, 30% and 14% vs. 50% and 50% ($p<.05$).

Minor events PTFE vs. ASV: bladder retention 2 (1%) vs. 2 (1%) p=.62, decubitus 0 vs. 4 (1%) (p=0.30) Surgical events PTFE vs. ASV: wound necrosis 3 (2%) vs. 2 (1%) (p=0.36), seroma 4 (2%) vs. 3 (1%) (p=0.26); hemorrhage 11 (7%) vs. 15 (5%) (p=0.53), compartment syndrome 2 (1%) vs. 0 (p=0.13)

Timing of adverse effects: Mean follow-up PTFE 28.8 months and ASV 36.1 months; adverse events per procedure were recorded until 1 month after discharge of the primary procedure. Follow-up after ASV bypass surgery included routine duplex ultrasound and ABI at 3 months, 6 months, 1 year, and 2 years after the initial procedure, followed by ABI every subsequent 2 years. Follow-up after ePTFE bypass surgery was restricted to duplex ultrasound and ABI examination at 3 months, 1 year, and 2 years after the initial procedure. ABI was measured every subsequent 2 years. All other interim duplex ultrasound examinations were performed after suspicion of graft-related problems.

Factors that predict response: NR

Source Citation: Moulakakis et al. 2013[24]

Study Design: Non-randomized comparative study

Device or Material: Anaconda (Sulzer Vascutek, Bad Soden, Germany); Zenith (Cook Inc, Bloomington, Ind); Excluder (W. L. Gore and Assoc, Flagstaff, Ariz); and Endurant (Medtronic, Minneapolis, Minn)

Contact Duration: ≤30 day follow-up

Dose: NR

Frequency/Duration: Single administration

Response: Endoleaks, Hematoma

Patient characteristics (gender, mean age): Mean (SE) age years: Anaconda 73.11 (0.86), Zenith 73.08 (1.06), Excluder 70.87 (1.34), Endurant 74.17 (1.55); 81 males and 6 females

Number per group: Anaconda 28 patients, Zenith 26 patients, Excluder 23 patients, and Endurant 10 patients

Observed adverse effects: Endografts were successfully implanted in all patients. There were no open conversions, no deaths, and no major perioperative complications. There was no postoperative increase in troponin

levels. Minor complications included local hematomas in femoral incisions in 3 patients (1 each in Anaconda, Zenith, and Excluder), who were treated conservatively. At 1-month follow-up, endoleaks were recorded in 12 (13.8%) patients (Anaconda n=5, 17.9%; Zenith n=3, 11.5%; Excluder n=3 patients, 13.0%; Enduran, 1 patient, 10%). No statistically significant differences were recorded for the presence of endoleak with regard to the endograft type.

IL-10: the Anaconda group showed the highest mean value at 24 hours and differed significantly from the Excluder (p<.001) and Endurant (p=0.04) groups. The Zenith group also showed higher mean values than the Excluder (p=0.01). Comparisons among the groups of endograft types at 48 hours showed that mean values in patients treated with Anaconda endografts were higher compared with Endurant (p<0.001) and Excluder (p<0.001) endografts, whereas mean values in patients treated with Zenith endografts were significantly higher compared with Endurant (p<0.001) and Excluder (p<0.001) endografts. Patients treated with Anaconda endografts showed the highest IL-6 mean values at 24 hours postoperatively. Statistically significant differences were observed among patients treated with the Anaconda vs. the Excluder (p<0.001), Anaconda vs. Endurant (p=0.04), and Zenith vs. Excluder (p=0.01). Comparisons at 48 hours showed significant differences for Anaconda vs. Excluder (p<0.001), Anaconda vs. Endurant (p<0.001), Zenith vs. Excluder (p<0.001), and Zenith vs. Endurant (p<0.001). With regard to IL-8, although patients treated with Anaconda endografts showed the highest mean values at 24 hours and 48 hours postoperatively, no statistical differences were observed among the patients treated with different types of endografts. Patients in the Excluder group showed statistically lower mean values at 24 hours and 48 hours postoperatively.

For white blood cells (WBC), higher mean values were recorded after 24 hours in patients treated with the Anaconda endograft compared with the Excluder (p<0.001) and Zenith (p<0.001) endografts and the Endurant endograft compared with the Excluder (p=0.001) and Zenith (p=0.01) endografts. After 48 hours, statistically significant differences were observed among Anaconda vs. Excluder (p<0.001), Anaconda vs. Zenith (p<0.001), Anaconda vs. Endurant (p<.001), Endurant vs. Excluder (p=0.004), and Zenith vs.Excluder (p=0.02) groups.

Timing of adverse effects: Operative outcomes were recorded. Temperature, WBC count, platelet count, and serum concentrations of cytokines (IL-6, IL-8, and IL-10) were measured preoperatively, 24 hours postoperatively, and 48 hours postoperatively. Final follow-up was 30 days.

Factors that predict response: NR

Source Citation: Dorigo et al. 2012[25]

Study Design: Registry data

Device or Material: Heparin-bonded ePTFE graft (PROPATEN Gore-Tex, W.L. Gore & Associates Inc, Flagstaff, AZ, USA) and autologous saphenous vein in below-knee femoropopliteal bypasses

Contact Duration: 28.5±22.1 months

Dose: NR

Frequency/Duration: Single administration

Response: Adjunctive procedures, Antiplatelet/anticoagulation therapy, Primary patency, Secondary patency, Thrombosis

Patient characteristics (gender, mean age): 224 women and 726 male; median age PROPATEN 72.7 years and ASV 72.4 years

Number per group: PROPATEN 556 patients, and ASV group 394 patients

Observed adverse effects: Patients in HePTFE group more frequently had adjunctive procedures performed at distal anastomotic sites in order to improve run-off status. Postoperative and long-term medical treatment consisted of single antiplatelet therapy in 40% of HePTFE group and in 39% (p=NS) in ASV group, double

antiplatelet therapy in 17% of HePTFE group and 21% (p=NS) in ASV group and of oral anticoagulants in 43% of the HePTFE group and 40% (p=NS) in ASV group, the regimen for anti-coagulation or anti-platelet being determined on the basis of surgeon's preference. Primary patency rate at 48 months was significantly better in ASV group (61%) than in HePTFE group (44.5%; p=0.004).

In below-knee bypasses, the corresponding figures were 45.2% in HePTFE group (SE 0.03) and 69% in ASV group (SE 0.04; p<0.001); in tibial bypasses, they were 39% (SE 0.07) and 53% (SE 0.04; p=0.04).

The rates of secondary patency at 48 months were 57% in HePTFE group (SE 0.03) and 67.5% in ASV group (SE 0.03), without significant differences between the two groups (p=0.1).

Early postoperative results: early graft thrombosis occurred in 55 patients (35 in HePTFE group and 20 in ASV group), with cumulative 30-day graft patency rates of 94 % and 95%, respectively (p=0.3).

Long-term follow-up: during follow-up, 263 new graft thromboses (173 in HePTFE group and 90 in ASV group) occurred. In 33 cases (8 in HePTFE group and 25 in ASV group) significant stenoses at anastomotic sites or at saphenous valves without graft thrombosis were detected; in 16 cases percutaneous transluminal angioplasty of the distal anastomosis or of the residual valves was performed, while in 13 patients endarterectomy of the common femoral artery with patching of the proximal anastomosis was required. Four patients were medically managed without developing graft occlusion.

Timing of adverse effects: Mean duration of follow-up was 28.5±22.1 months, Follow-up was performed within the third postoperative month, at 12 months and then yearly.

Factors that predict response: At univariate analysis, female gender, secondary intervention, distal tibial anastomosis, adjunctive distal procedures, poor run-off score, and kind of graft were found to significantly affect long-term primary patency; at multivariate analysis female gender, secondary intervention and kind of graft maintained their significance. For secondary patency, female gender, secondary intervention, distal tibial anastomosis, critical limb ischemia, adjunctive distal procedures, and poor run-off score were found to significantly affect it at univariate analysis, while at multivariate analysis only secondary interventions-maintained significance.

AAA = abdominal aortic aneurysm; ABI = ankle-brachial index; AE = adverse event; AS = anterior sector; ASV = autologous saphenous vein; CI = confidence interval; ECFP = Extra-cardiac Fontan procedure; HR = hazard ratio; IL = interleukin; IRHV to IVC = inferior right hepatic vein to inferior vena cava; LOS = length of stay; MAE = major adverse events; MHV = middle hepatic vein; NR = not reported; NS = not significant; OR = odds ratio; p = p value; PTFE = polytetrafluoroethylene; $PY^{-}1$ = incidence rate per patient year; RL = right lobe; RR = relative risk; SD = standard deviation; SE = standard error; TCC = tunneled cuffed catheter

Table 12: Stents - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Zhou et al. 2020[32]

Study Design: Non-randomized controlled study

Device or Material: PTFE-covered stent (Viatorr Endoprosthesis, GORE and Assoc., AZ, USA vs. ET with NSBB drugs

Contact Duration: Median 20 months

Dose: NR

Frequency/Duration: Single administration

Response: Variceal rebleeding, Hepatic encephalopathy, overall adverse events (includes local and systemic)

Patient characteristics (gender, mean age): Patients with liver cirrhosis and endoscopically confirmed gastroesophageal variceal bleeding; 56.4% male; 59.1 and 53.9 years, by group

Number per group: 179 total; 77 TIPS with PTFE-covered stents; 102 ET with NSBB

Observed adverse effects: **Variceal rebleeding** significantly less for PTFE-stent group (7.8% vs. 39.2% for ET group; p<0.001); **Hepatic encephalopathy** not significantly different between TIPS and ET groups (15.6% vs. 12.7%; p=0.73); **Overall adverse events** not significantly different between groups (56% for PTFE vs. 56% for ET; p=0.53). Shunt dysfunction (on placement) 7.8% for PTFE stent group.

Timing of adverse effects: Rebleeding rate over 2 years. Median follow-up time was 20 months.

Factors that predict response: Subgroup multivariate analysis showed patients with **HVPG, gastro-renal shunts, and ep-GVs** showed significantly different **2-year rebleeding free rate** when compared between treatment groups. Values higher for PTFE stent group than ET group for subjects with **HVPG ≥ 20 mmHg** (91% vs. 67%; p=0.02); for PTFE stent group with **gastro-renal shunts** (94% vs. 59%; p=0.03); and for PTFE-stent subjects with **ep-GVs** (90% vs. 58%; p=0.016). Variceal rebleeding influenced by treatment and etiology.

Source Citation: Hernandez-Enriquez et al. 2018[37]

Study Design: Non-randomized controlled study

Device or Material: **PTFE-covered** (Jostent-Graftmaster stent; Abbott Vascular, Santa Clara, CA) vs. **PUR-covered** stent (PK Papyrus stent; BIOTRONIK, Berlin)

Contact Duration: 1 year

Dose: NR

Frequency/Duration: Single administration

Response: In-stent restenosis, Thrombosis, Pericardial effusion

Patient characteristics (gender, mean age): Patients with coronary artery perforation (CAP); 75% male; mean 77 years

Number per group: 39 (65%) PTFE; 22 (36%) PUR

Observed adverse effects: **Stent thrombosis** not significantly different between groups (n=1/group; 3% PTFE vs. 6% PUR); **restenosis** not significantly different between groups (n=1, 3% PTFE vs. n=2, 12% PUR); **pericardial effusion** higher for PTFE group (72% vs. 41%; p=0.028)

Timing of adverse effects: Up to 1 year

Factors that predict response: NR

Source Citation: Kim et al. 2017[34]

Study Design: Non-randomized controlled study

Device or Material: PTFE (ext/int)- vs. PUR-covered REMs; Niti-S Urethral Stent, Taewoong, S. Korea

Contact Duration: Long-term follow-up of 18 years

Dose: NR

Frequency/Duration: Frequency/duration variable depending on results; 39.5% removed electively after mean 95 days; 60.5% removed at mean 48.6 days due to complications

Response: Overall complications, Tissue ingrowth, Granulation tissue, Patency, Stent migration

Patient characteristics (gender, mean age): Patients with recurrent benign urethral strictures; 100% male; 51 years (range 16 to 77)

Number per group: 54 patients: 21 (38.9%) internal PTFE; 20 (37%) external PTFE; 13 (24.1%) PUR; 114 REMs placed: 47 int-PTFE, 41 ext-PTFE, and 26 PUR REMs

Observed adverse effects: **Overall complications** significantly higher for ext-PTFE (78.7%) than other 2 groups (46.3% and 50% for ext-PTFE and PUR, respectively); **Tissue ingrowth/membrane separation** significantly higher for int-PTFE (17.0%) and PUR (23.1%) groups vs. ext-PTFE (0%); **Granulation tissue** formation not significantly different between groups (8.5% int-PTFE; 14.6% ext-PTFE; 11.5% PUR); **Stent migration** significantly higher for int-PTFE group (51.1%) vs. ext-PTFE (26.8%) and PUR (15.4%) groups; **patency** (up to 6 months) longer for ext-PTFE (significantly better than int-PTFE; not significantly different than PUR); **maintained patency** not significantly better for any group beyond 6 months and up to 18 years

Timing of adverse effects: Overall complications: mean 67.3 months; migration 29.7 months; tissue ingrowth 58 months; granulation tissue 89.9 months

Factors that predict response: **Stent indwelling time** only significant factor associated with maintained patency after temporary placement (OR 5.4; p=0.02)

Source Citation: Piazza et al. 2017[35]

Study Design: Non-randomized controlled study

Device or Material: PTFE-covered self-expanding stents vs. BMS (specific devices not reported)

Contact Duration: Mean 23±17 months; up to 36 months

Dose: N/A

Frequency/Duration: Single Administration

Response: Patency

Patient characteristics (gender, mean age): Patients with IAOs; 79% male; mean 68 years

Number per group: 128 patients total; 78 PTFE-covered; 50 BMS (n=47 per group for propensity matched cohort)

Observed adverse effects: **Overall primary patency** not significantly different (but borderline significant) but worse for BMS group (68.3 vs. 88.3 for unmatched cohort; p=0.07, and 66.1 vs. 87.1 for matched cohort; p=0.06). **Patency** for TASC II D-classified lesions significantly worse for BMS group (56.8 vs. 89.7 for unmatched cohort; p=0.01 and 54.3 vs. 88.6 for matched cohort; p=0.03). No significant difference found for TASC B and C classifications.

Timing of adverse effects: Mean 23±17 months; up to 36 months

Factors that predict response: Patency favored PTFE-covered stents for **IAO size** > 3.5 cm in length (p=0.04), **total lesion length** > 6 cm (p=0.04), and **IAO with calcification** > 75% of the arterial wall circumference (p=0.01).

Source Citation: Perarnau et al. 2014[29]

Study Design: RCT

Device or Material: PTFE-covered stent vs. BMS

Contact Duration: 2 years

Dose: NR

Frequency/Duration: Single administration

Response: Shunt dysfunction, Early complications, Hepatic encephalopathy

Patient characteristics (gender, mean age): 75% male, 58 years

Number per group: 137 (66 covered, 71 bare) patients undergoing TIPS

Observed adverse effects: The risk of shunt dysfunction was significantly reduced in the covered stent group compared to the bare stent group (HR 0.60, 95% CI 0.38–0.96; p=0.032). Early complications of the procedure (including death, thrombosis, and fever up to the first month of follow-up) were not significantly different between the groups (covered: 22.4%, bare: 34.9%; p=0.13). The risk of hepatic encephalopathy was not significantly different between the groups (HR 0.84, 95% CI 0.46–1.55; p=0.58).

Timing of adverse effects: 1 month to 2 years

Factors that predict response: NR

Source Citation: Sohrabi et al. 2014[30]

Study Design: RC

Device or Material: PTFE-covered stent vs. BMS (NuMed, Hopkinton, New York)

Contact Duration: Up to 60 months (Mean 31.1 months)

Dose: NR

Frequency/Duration: Single administration

Response: Recoarctation, Pseudoaneurysm, Left subclavian artery obstruction, Aortic dissection, Postcoarctation of aorta syndrome

Patient characteristics (gender, mean age): 67% male, 23.6 years

Number per group: 120 (60 per group) coarctation of aorta patients

Observed adverse effects: Recoarctation was not significantly different between groups (covered: 0%, bare: 6.7%). Pseudoaneurysm was not significantly different between groups (covered 3.3%, bare: 0%). There were no occurrences of obstruction, dissection, or postcoarctation of aorta syndrome.

Timing of adverse effects: 1 month to 60 months

Factors that predict response: NR

Source Citation: Grimme et al. 2012[28]

Study Design: Systematic review (including RCTs and cohort studies/case series)

Device or Material: PTFE-covered stent vs. BMS

Contact Duration: Range of mean of 8 to 21 months across included studies

Dose: NR

Frequency/Duration: Single administration

Response: Recurrent stenosis, Patency, Complications

Patient characteristics (gender, mean age): Range of 24% to 100% male, 46 to 71 years

Number per group: 4,188 (262 covered, 3,926 bare) with focal infrarenal aortic occlusive disease, aortoiliac complex occlusive disease, or iliac artery occlusive disease across 49 studies

Observed adverse effects: Recurrent stenosis rate ranged from 0% to 8% in studies with patients receiving covered stents and 0% to 75% in studies with patients receiving bare stents. 1-year primary patency rates ranged from 70% to 100% in studies of patients with either covered or bare stents. 1-year secondary patency rates ranged from 88% to 100% in studies of patients with covered stents and from 84% to 100% in those of patients with bare stents. No studies of patients with covered stents reported on 4-year primary or secondary patency. Complication rates ranged from 0% to 17% in studies of patients with covered stents and 0% to 29% in those of patients with bare stents.

Timing of adverse effects: 1 to 4 years

Factors that predict response: NR

Source Citation: Clark et al. 2011[36]

Study Design: Non-randomized controlled study

Device or Material: PTFE-covered stent vs. BMS

Contact Duration: Median of 19 months

Dose: NR

Frequency/Duration: Single administration

Response: Shunt dysfunction, Reinterventions for stenosis, Hepatic function deterioration

Patient characteristics (gender, mean age): 61% male, median 56 years

Number per group: 246 (176 covered, 70 bare) patients undergoing TIPS

Observed adverse effects: Shunt dysfunction occurred in 22% of patients with covered stents and 57% of patients with bare stents (p=0.05). Reinterventions for stenosis occurred in 19% of patients with covered stents and 33% of patients with bare stents (p=0.01). Hepatic function deterioration occurred in 30% of patients with covered stents and 31% of patients with bare stents (p=0.32).

Timing of adverse effects: Up to 167 months

Factors that predict response: NR

Systemic Response/Toxicity

Source Citation: Zhou et al. 2020[32]

Study Design: Non-randomized controlled study

Device or Material: PTFE-covered stent (Viatorr Endoprosthesis, GORE and Assoc., AZ, USA vs. ET with NSBB drugs

Contact Duration: Median 20 months

Dose: NR

Frequency/Duration: Single administration

Response: Survival, overall adverse events (includes local and systemic)

Patient characteristics (gender, mean age): Patients with liver cirrhosis and endoscopically confirmed GEVB; 56.4% male; 59.1 and 53.9 years, by group

Number per group: 179 total; 77 TIPS with PTFE-covered stents; 102 ET with NSBB

Observed adverse effects: **Survival** not significantly different between groups (6.5% and 8.8% died in stent and ET groups after 36 months; p=0.53) **Overall adverse events** not significantly different between groups (56% for PTFE vs. 56% for ET; p=0.53).

Timing of adverse effects: Median follow-up time was 20 months. Median times of individual adverse events NR.

Factors that predict response: Hepatic encephalopathy influenced by **albumin**; survival influenced by **total bilirubin**, **albumin**, and **model for end-stage liver disease score**.

Source Citation: Hernandez-Enriquez et al. 2018[37]

Study Design: Non-randomized controlled study

Device or Material: PTFE-covered stent vs. PUR-covered stent

Contact Duration: 1 year

Dose: NR

Frequency/Duration: Single administration

Response: All-cause mortality, MACE, Cardiac death, MI

Patient characteristics (gender, mean age): Patients with CAP; 75% male, 77 years

Number per group: 39 (65%) PTFE; 22 (36%) PUR

Observed adverse effects: **All-cause mortality** not significantly different between groups (n=16, 41% PTFE vs. n=5, 26% PUR); **MACE** not significantly different (n=22, 56% PTFE vs. n=11, 58% PUR); **Cardiac death** not significantly different (n=14, 36% PTFE vs. n=5, 26% PUR); **MI** not significantly different (n=3, 8% PTFE vs. n=2, 11% PUR)

Timing of adverse effects: Up to 1 year

Factors that predict response: NR

Source Citation: Piazza et al. 2017[35]

Study Design: Non-randomized controlled study

Device or Material: PTFE-covered self-expanding stents vs. BMS (specific devices not reported)

Contact Duration: Mean 23±17 months; up to 36 months

Dose: N/A

Frequency/Duration: Single Administration

Response: Overall medical complications, Intra- or perioperative major cardiac events requiring intervention, Respiratory failure (embolism or respiratory distress), Dialysis, Death

Patient characteristics (gender, mean age): Patients with IAOs; 79% male; mean 68 years

Number per group: 128 patients total; 78 PTFE-covered; 50 BMS (n=47 per group for propensity matched cohort)

Observed adverse effects: No significant differences between groups: overall complications (p=0.45), major cardiac events (p=1.0), respiratory failure (p=0.53), dialysis (p=1.0), and death (p=1.0); propensity matched group also not significant.

Timing of adverse effects: Medical complications <30 days from treatment

Factors that predict response: NR

Source Citation: Perarnau et al. 2014[29]

Study Design: RCT

Device or Material: PTFE-covered stent vs. BMS

Contact Duration: 2 years

Dose: NR

Frequency/Duration: Single administration

Response: Mortality, Hospitalization

Patient characteristics (gender, mean age): 75% male, 58 years

Number per group: 137 (66 covered, 71 bare) patients undergoing TIPS

Observed adverse effects: Mortality was not significantly different between the groups. The average number of hospitalizations in the covered group was 6.4 vs. 7.9 in the bare group. The average number of hospital days was 32 in the covered group vs. 37.5 in the bare group.

Timing of adverse effects: 1 month to 2 years

Factors that predict response: NR

Source Citation: Sohrabi et al. 2014[30]

Study Design: RCT

Device or Material: PTFE-covered stent vs. BMS (NuMed, Hopkinton, New York)

Contact Duration: Up to 60 months (Mean 31.1 months)

Dose: NR

Frequency/Duration: Single administration

Response: Mortality, Hospitalization, Hypertension

Patient characteristics (gender, mean age): 67% male, 23.6 years

Number per group: 120 (60 per group) coarctation of aorta patients

Observed adverse effects: Mortality was not significantly different between the groups (covered: 0, bare: 1). Duration of hospitalization was not significantly different between groups (covered: 3.05 days, bare: 3.44

days). The numbers of normotensive patients after the procedure were not significantly different between the groups (covered: 78.3%, bare: 73.3%).

Timing of adverse effects: 1 month to up to 60 months

Factors that predict response: NR

Source Citation: Bennett et al. 2013[31]

Study Design: RCT

Device or Material: Symbiot covered stent (Boston Scientific, Natick, MA) vs. BMS + FilterWire EX (Boston Scientific, Natick, MA) vs. BMS alone

Contact Duration: 7.3 to 7.6 years by group

Dose: NR

Frequency/Duration: Single administration

Response: All-cause mortality, MI, Target vessel failure (composite for MACE: all-cause death, MI, and target lesion revasularization)

Patient characteristics (gender, mean age): Patients with degenerative SVG lesions; 88% male; mean 70 years

Number per group: 90 patients; 30 patients per device

Observed adverse effects: **All-cause mortality** not significantly different between groups at 6 months (10%, 7%, and 3% for Symbiot, FilterWire, and BMS groups) or long-term (20%, 43%, and 37%); **MI** not significantly different between groups at 6 months (7%, for all groups) or long-term (23%, 17%, and 23%, respectively, for Symbiot, FilterWire, and BMS groups); **target vessel failure** (composite end point of all-cause death, Q-wave or non-Q-wave MI, or target lesion revascularization) not significantly different between groups at 6 months (20%, 13%, and 10% for Symbiot, FilterWire, and BMS groups) or long-term (57%, 57%, and 60%)

Timing of adverse effects: Reported at 6 months and long-term

Factors that predict response: NR

Source Citation: Grimme et al. 2012[28]

Study Design: Systematic review (including RCTs and cohort studies/case series)

Device or Material: PTFE-covered stent vs. BMS

Contact Duration: Range of mean of 8 to 21 months across included studies

Dose: NR

Frequency/Duration: Single administration

Response: Distal embolization

Patient characteristics (gender, mean age): Range of 24% to 100% male, Range of 46 to 71 years

Number per group: 4188 (262 covered, 3926 bare) with focal infrarenal aortic occlusive disease, aortoiliac complex occlusive disease, or iliac artery occlusive disease across 49 studies

Observed adverse effects: Distal embolization rates were all 0% in studies reporting this outcome for patients with covered stents and ranged from 0% to 89% in studies on patients with bare stents.

Timing of adverse effects: 1 to 4 years

Factors that predict response: NR

Source Citation: Clark et al. 2011[36]

Study Design: Non-randomized controlled study

Device or Material: PTFE-covered stent vs. BMS

Contact Duration: Median of 19 months

Dose: NR

Frequency/Duration: Single administration

Response: Mortality

Patient characteristics (gender, mean age): 61% male, Median 56 years

Number per group: 246 (176 covered, 70 bare) patients undergoing TIPS

Observed adverse effects: Median survival time was 33 months for patients receiving covered stents and 31 months for those receiving bare stents (p = 0.5).

Timing of adverse effects: Up to 167 months

Factors that predict response: NR

BMS= bare metal stent; CAP= coronary artery perforation; CI= confidence interval; Ep-GV= extraluminal para-gastric vein; ET= endoscopic therapy; GEVB= gastroesophageal variceal bleeding; HR= hazard ratio; HVPG= hepatic vein pressure gradient; IAO= iliac artery occlusion; MACE= major adverse cardiac event; MI= myocardial infarction; NR= not reported; NSBB= non-selective β-blockers; OR= odds ratio; PTFE= polytetrafluoroethylene; PUR= polyurethane; REMS= retrievable self-expandable metallic stent; SVG= saphenous vein graft; TASC II= Trans-Atlantic InterSociety Consensus; TIPS= transjugular intrahepatic portosystemic shunt

Table 13: Stent-Grafts - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Bosiers et al 2020[44]

Study Design: RCT RELINE trial (NCT01108861)

Device or Material: Stent-graft (Viabahn with PROPATEN Bioactive Surface [W.L. Gore]) vs. PTA to treat restenotic or reoccluded lesions in the femoropopliteal arteries

Contact Duration: Follow-up 24 months

Dose: Lesion length 30 to 330 mm

Frequency/Duration: Single administration

Response: Primary Patency

Patient characteristics (gender, mean age): 74.4% male. 67.7 years

Number per group: 83 (39 stent-graft, 44 PTA)

Observed adverse effects: No patients were reported to have device-related serious adverse events within 30 days postprocedure. At 12 months, the primary patency rates were 74.8% for the stent-graft group and 28.0% for the PTA group ($p<0.001$), and at 24 months were 58.4% and 11.6%, respectively ($p<0.001$). No stent fractures were observed through 12 months.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Martinelli et al 2020[47]

Study Design: Non-randomized comparative cohort

Device or Material: Stent-graft (Excluder & C3 [W.L. Gore]) vs. chromium-cobalt endoskeleton (AFX Endologix) for EVAR

Contact Duration: Mean follow-up 24 months

Dose: NR

Frequency/Duration: Single administration

Response: New-onset thrombus

Patient characteristics (gender, mean age): 84.1% male, 74±10 years

Number per group: 110 (43 PTFE stent-graft, 56 AFX device)

Observed adverse effects: New-onset thrombus occurred in 21% of ePTFE stent-grafts.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Kavan et al 2019[45]

Study Design: RCT

Device or Material: Stent-graft [Fluency Plus [Bard Peripheral Vascular]) vs. self-expanding BMS (E-Luminexx [Bard Peripheral Vascular]) vs. PTA to treat failing hemodialysis access

Contact Duration: Median follow-up 22.4 months

Dose: Reference diameter 6.3 mm

Frequency/Duration: Single administration

Response: Occlusion, Restenosis, Thrombosis

Patient characteristics (gender, mean age): 71% female, 64 years

Number per group: 50 (20 stent-graft, 19 BMS, 20 PTA)

Observed adverse effects: Stent-graft required significantly fewer secondary interventions at 1 year (mean 1.7±2.1; p=0.015), and 2 years (mean 2.2±5.1, p=.037) compared to both PTA and BMS. Thrombosis occurred in 1 case. Patency was 65% at 12 months and 37% at 24 months, significantly better than for PTA or stent (p<0.0001). Secondary patency rates were 89% at 12 months and 79% at 24 months, and did not significantly differ.

Timing of adverse effects: NR

Factors that predict response: Greater residual stenosis after initial PTA (HR=1.048; p=0.007) is a risk factor for loss of patency. Smaller diameter of the reference segment adjacent to the stenosis (HR=0.498, p=0.005) and the use of a deep vein as the outflow (HR=0.457, p=0.022) are predictors of primary patency.

Source Citation: Venturini et al 2017[51]

Study Design: Non-randomized comparative cohort

Device or Material: Stent-graft (Viabahn [W.L. Gore]) vs. transcatheter embolization (TE) to treat VAAs and VAPAs

Contact Duration: Median follow-up 32.8 months

Dose: Diameter 5 to 9 mm, length 2.5 to 5 cm

Frequency/Duration: Single administration of 1 to 3 stent-grafts

Response: Hemorrhage, Occlusion, Patency

Patient characteristics (gender, mean age): 58% men, 59±14 years

Number per group: 100 (30 covered-stent, 70 TE)

Observed adverse effects: Complications included hemorrhage requiring stent removal (n=1) and occlusion (n=2). Two deaths occurred within 30 days in patients who were treated emergently and had septic complications; therefore, not device related. In covered-stent patients, aneurysm exclusion and stent patency were observed in 20/22 patients at 3 to 6 months and aneurysm exclusion in 19/19 patients and stent patency in 17/19 after >6 months.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Haskal et al 2016[42]

Study Design: RCT RENOVA trial (NCT00677235)

Device or Material: Stent-graft (FLAIR [BARD Peripheral Vascular]) vs. PTA to treat failing hemodialysis access

Contact Duration: Follow-up 24 months

Dose: Mean length 44.6 mm ±4.9

Frequency/Duration: Single administration of 1-2 stent-grafts

Response: Embolism, Hematoma, Hemorrhage, Occlusion, Patency, Pseudoaneurysm, Restenosis, Vessel rupture

Patient characteristics (gender, mean age): 64.1% female, 63.1 years

Number per group: 270 (142 stent-grafts in 128 patients [21 straight, 121 flared]; 132 PTA)

Observed adverse effects: The overall rate of stenosis requiring reintervention was significantly lower in the stent-graft group (63.0%) compared with the PTA group (82.6%; p<0.001). The 12-month device-related/procedure-related AE rate was 2.3% for the stent graft, compared to 8.7 for PTA (p=0.001). Adverse events included thrombotic occlusion (n=60), hemorrhage (n=10), pseudoaneurysm (n=9), hematoma (n=5), vessel rupture (n=2), embolism (n=1). There were no instances of device migration or kinking. Death was comparable in the stent-graft group (n=38) and PTA group (n=36); no deaths were reported as device-related. ACPP was significantly higher for the stent-graft group at 12 (24%; p=0.007) and 24 months (9.5%; p=0.011) compared to PTA. TAPP at 12 months was significantly better for the stent graft group (47.6%) compared with PTA group (24.8%; p<0.001), and remained significant at 24 months, 26.9% versus 13.5% (p<0.001).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Falk et al 2016[40]

Study Design: RCT RESCUE trial (NCT01257438)

Device or Material: Stent-graft (Fluency Plus [Bard Peripheral Vascular]) vs. PTA to treat failing hemodialysis access

Contact Duration: Follow-up 24 months

Dose: Median diameter 8 and 9 mm, median length 40 and 60 mm

Frequency/Duration: Single administration

Response: Binary restenosis, Patency

Patient characteristics (gender, mean age): 51.3% male, 61.9 years

Number per group: 275 (132 stent-graft, 143 PTA)

Observed adverse effects: Binary restenosis occurred in 19.7% of patients in the stent-graft group compared to 73.4% in the PTA group. ACPP was significantly higher in the stent-graft group (18.6%) than in the PTA group (4.5%; p<0.001) at 6 months. TAPP was higher for the stent-graft group (15.6%) compared to PTA (2.2%) at 24 months. Major complications that resulted in death occurred in 4 stent-graft recipients (3%) but they were not classified as device-related.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Lauermann et al 2015[46]

Study Design: Non-randomized comparative cohort

Device or Material: Stent-graft (Viatorr [W.L. Gore]) vs. BMS (Wallstent [Boston Scientific]) for TIPS

Contact Duration: NR

Dose: Mean length 92.29 mm, mean diameter 9. 71 mm

Frequency/Duration: Single administration

Response: Occlusion, Patency, Restenosis

Patient characteristics (gender, mean age): 67.1% male, 56±12 years. Portal hypertension, primarily due to liver cirrhosis.

Number per group: 163 (83 stent graft, 80 BMS)

Observed adverse effects: The stent-graft showed significantly better primary patency after 14 days (100%; p=0.004), 6 months (95%; p=0.047) and 2 years (82.9%; p=0.037) compared to BMS. Revisions were required in 13.4% of cases, primarily due to stenosis, occlusion, and HE.

Timing of adverse effects: NR

Factors that predict response: Portal venous thrombosis was identified as a major risk factor for technical failure. Liver capsule perforation was associated with significantly lower probability of 1-year survival (38.1% vs. 86.4%; p<0.001).

Source Citation: Grimme et al 2014[49]

Study Design: Non-randomized comparative cohort

Device or Material: Stent-graft [Josent [Abbott Laboratories]; Advanta V12 [Atrium Medical]) vs. BMS (Genesis [Cordis Corporation]) for F-EVAR

Contact Duration: Follow-up 4 years, median follow-up 13 months

Dose: NR

Frequency/Duration: NR

Response: Occlusion, Patency, Restenosis, Stent fracture

Patient characteristics (gender, mean age): 89.1% male. 73 years.

Number per group: 138

Observed adverse effects: Renal artery patency was 97.3% at one year and 92.4% at 4 years for stents-grafts, not significantly higher than bare-metal stents. Freedom from stenosis in renal artery stents (occluded stents excluded) was 92.9% at 1 year and 86.7% at 4 years for stent-grafts, significantly higher than bare-metal stents (84.5% and 58.9%, respectively; p=0.04). Freedom from occlusion and stenosis was 91.4% at 1 year and 80.9% at 4 years for covered stents. Stent fractures were seen in 2 covered stents (1.2%).

Timing of adverse effects: NR

Factors that predict response: Material fracture significantly reduced stent patency. Stent-grafts fractured significantly less than uncovered stents (p=0.01). PTFE-covered stent-grafts may less prone to fracture due to greater flexibility provided by a strong fixation of the PTFE layers to the arteries. Renal dysfunction was significantly associated with renal stent occlusion or stenosis.

Source Citation: Geraghty et al 2013[43]

Study Design: RCT VIBRANT trial (NCT00228384)

Device or Material: Stent-graft (Viabahn [W.L. Gore]) vs. BMS for symptomatic superficial femoral artery disease

Contact Duration: Follow-up 36 months

Dose: Diameter 6 to 8 mm

Frequency/Duration: Single administration of a median of two stent-grafts

Response: Occlusion, Patency, Restenosis, Stent fracture

Patient characteristics (gender, mean age): 62.5% male, 69 years (patients receiving the Viabahn device were significantly older than those receiving bare nitinol stents.)

Number per group: 148 (72 Viabahn stent-graft, 76 bare nitinol stent)

Observed adverse effects: Stent fractures (2.6%) were significantly less common with the stent-graft, compared to bare nitinol stent (50%; $p<0.001$). At 3 years, primary patency rates did not significantly differ between the stent-graft group and the bare nitinol stent group (24.2% vs. 25.9%; $p=0.392$). Primary-assisted patency rate was significantly lower for stent-grafts (69.8%) compared to bare nitinol stents (88.8%; $p=0.04$). Secondary patency rates did not differ. There was no significant difference in overall re-intervention rates between the stent-graft (34.7%) and bare nitinol stent (34.2%). Death occurred in 9 patients (12%), compared to 3 (3.9%) in the bare stent group, none were determined to be device-related.

Timing of adverse effects: Patency rates diminish most rapidly in the first year after device implantation.

Factors that predict response: NR

Source Citation: Ikoma et al 2013[52]

Study Design: Non-randomized comparative cohort

Device or Material: ePTFE-covered stent-graft (Excluder [W.L. Gore]) vs. polyester stent-graft (Zenith [Cook Inc.]) for EVAR

Contact Duration: 10 days

Dose: NR

Frequency/Duration: Single administration

Response: Endoleak

Patient characteristics (gender, mean age): 76.4 years.

Number per group: 88 (37 PTFE, 51 polyester)

Observed adverse effects: Postoperative endoleak occurred in 13 cases (35.1%).

Timing of adverse effects: NR

Factors that predict response: A change in FDP of ≤3.1 μg/mL at day 7 was predictive of an endoleak after EVAR. The lack of pores in PTFE may improve tissue repair by preventing platelets and inflammatory cells from crossing the graft, preventing the formation of a thrombus.

Source Citation: Möllenhoff et al 2013[39]

Study Design: Systematic Review

Device or Material: Viabahn [W.L. Gore] and Hemobahn [W.L. Gore] stent-grafts to treat popliteal aneurysms

Contact Duration: Mean follow-up 36.9 months

Dose: Mean PPA diameter 29 mm

Frequency/Duration: Single administration of 1 to 4 stent-grafts

Response: Access site hematoma, Acute thrombosis, Endoleak, Stent fracture, Migration, Occlusion, Restenosis, Patency

Patient characteristics (gender, mean age): 92.3% male, 72.4 years.

Number per group: 8 studies included; 251 PPA in 222 patients

Observed adverse effects: Perioperative complications (1.6%) included access site hematomas (n=3) and acute endograft thrombosis (n=1). Postoperative complications included endoleak (6%, n=15) and endograft migration (5.2%; n=13). Endograft fracture (5.6%; n=14) resulted in occlusion (n=6) and type III and IV endoleaks (n=2). Endograft failure (n=46) was due to occlusion (n=42) and stenosis (n=4). Amputation was required in 2 patients due to endograft occlusion, one of these patients died within 30 days from acute endograft thrombosis leading to acute MI. Primary patency rate at 1 year was 85.6%, and 78.5% at 2 years. Secondary patency rate at 1 year was 93.5% and 90.4% at 2 years.

Timing of adverse effects: NR

Factors that predict response: Repetitive motility of the knee joint may predispose the endograft to kinking, fracture, and occlusion.

Source Citation: Doomernik et al 2012[38]

Study Design: Systematic review

Device or Material: Stent-grafts (Viabahn [W.L. Gore] and Hemobahn [W.L. Gore]) to treat long de novo lesions of the SFA

Contact Duration: Follow-up ranging 2 to 5 years

Dose: Mean length 2.5 to 47 cm; diameter 5 to 8 mm

Frequency/Duration: Single administration

Response: Hematoma, Acute thromboembolism, Edge-stenosis, Patency, Restenosis

Patient characteristics (gender, mean age): Gender NR. 58 to 73 years.

Number per group: 14 studies included; 789 stent-grafts in 747 patients

Observed adverse effects: Treatment-related complications seen in 17.9% (99/554), including groin hematoma, acute thromboembolism, and edge dissection. Distal embolism rate was low (3%). Graft failure was related to acute thrombosis due to disease progression, causing edge-stenosis and stent kinking. In-stent restenosis reported in 5 cases. One-year primary patency rate varied between 44 and 86%, and secondary patency rates between 58 to 93%.

Timing of adverse effects: NR

Factors that predict response: Significantly better patency with devices with a diameter of 6 mm or larger. No statistically significant difference in patency rates was observed with regard to age, smoking, comorbidities (hypertension, diabetes, CAD).

Source Citation: Stone et al 2011[41]

Study Design: RCT

Device or Material: PTFE-covered stent (JOSTENT/GraftMaster [Abbott]) vs. BMS for PCI post-CABG

Contact Duration: Follow-up 5 years; mean age of graft

Dose: Mean length 20.7 mm

Frequency/Duration: Single administration of 1-2 stent-grafts

Response: Binary restenosis, Occlusion, Thrombosis, TVF

Patient characteristics (gender, mean age): 81.5% male; 67.9 years.

Number per group: 243 (115 stent-graft; 128 BMS)

Observed adverse effects: There were no significant differences in adverse events at 30 days or 9 months. Occurring significantly more often in the stent-graft group than in the BMS group after 2 years and annually up to 5 years, were target vessel failure (68.3%; p=0.0007), target vessel revascularization (48.2%; p=0.04), and target lesion revascularization (43.9%; p=0.04). Stent thrombosis (10.9%) and target vessel occlusion (14%) were comparable to BMS at 5 years.

Timing of adverse effects: TVF and TVR occurred more frequently after 2 years

Factors that predict response: NR

Systemic Response/Toxicity

Source Citation: Martinelli et al 2020[47]

Study Design: Non-randomized comparative cohort

Device or Material: PTFE stent-graft (Excluder & C3 [W.L. Gore]) vs. chromium-cobalt endoskeleton (AFX Endologix) for EVAR

Contact Duration: Mean follow-up 24 months

Dose: NR

Frequency/Duration: Single administration

Response: PIS (fever coinciding with elevated serum CRP level)

Patient characteristics (gender, mean age): 84.1% male, 74±10 years

Number per group: 110 (43 PTFE stent-graft, 56 AFX device)

Observed adverse effects: PIS incidence between the ePTFE stent-graft group (46.6%) and the chromium-cobalt endoskeleton group (33.29%) was not significantly different (p=0.333) at 72 hours postprocedure.

Timing of adverse effects: NR

Factors that predict response: New-onset mural thrombus may release pro-inflammatory cytokines.

Source Citation: Lauermann et al 2015[46]

Study Design: Non-randomized comparative cohort

Device or Material: Stent-graft (Viatorr [W.L. Gore]) vs. BMS (Wallstent [Boston Scientific]) for TIPS

Contact Duration: NR

Dose: Mean length 92.29 mm, mean diameter 9.71 mm

Frequency/Duration: Single administration

Response: Hepatic encephalopathy, Death

Patient characteristics (gender, mean age): 67.1% male, 56±12 years; Portal hypertension, primarily due to liver cirrhosis

Number per group: 163 (83 stent graft, 80 BMS)

Observed adverse effects: Hepatic encephalopathy occurred in 19.3% of cases (n=16), requiring at least one revision in 4.8% of cases (n=4). Death during the first year was 8.4% (n=7), not significantly different than BMS.

Timing of adverse effects: NR

Factors that predict response: Revisions due to hepatic encephalopathy were within 1 year of initial implantation.

Source Citation: Kadoglou et al 2014[50]

Study Design: Non-randomized comparative cohort

Device or Material: PTFE-covered stent-graft (Excluder [W.L. Gore]) vs. polyester-covered stent-graft (Anaconda [Vascutek], Talent, Endurant [Medtronic], Zenith FB [Cook Inc.]) for EVAR

Contact Duration: Follow-up 12 months

Dose: Mean diameter 2.65±.24, mean length 12.75±1.63

Frequency/Duration: Single administration

Response: Increased PWV, an and index of arterial stiffening, Increased serum IL-8 and IL-10, Decreased WBC, Decreased hsCRP

Patient characteristics (gender, mean age): 100% male. 71±8 years.

Number per group: 118 (46 PTFE-covered stent-grafts, 72 polyester-covered stent-grafts)

Observed adverse effects: At 12 months, PWV (mean change +2.82±.25 m/s; p=0.003), and serum levels of IL-8 (17.97±8.1 pg/mL; p<0.05) and IL-10 (8.39±2.22 pg/mL; p<0.05) significantly increased from baseline in both groups. However, the effect on PWV and ILs was significantly less pronounced for PTFE compared to polyester. WBC (mean change -878±152; p<0.05), hsCRP (mean change -4.8±1.01; p<0.05), and OPG (10.51±4.46 pmol/L; p<0.05), and decreased significantly from baseline for the PTFE group.

Timing of adverse effects: NR

Factors that predict response: Mean blood pressure, OPG, and AAA diameter were independently associated with PWV (R^2=0.729, p=0.036).

Source Citation: Ikoma et al 2013[52]

Study Design: Non-randomized comparative cohort

Device or Material: ePTFE-covered stent-graft (Excluder [W.L. Gore]) vs. polyester stent-graft (Zenith [Cook Inc.]) for EVAR

Contact Duration: 10 days

Dose: NR

Frequency/Duration: Single administration

Response: Elevated WBC, Elevated CR

Patient characteristics (gender, mean age): 76.4 years.

Number per group: 88 (37 PTFE, 51 polyester)

Observed adverse effects: WBC count and CRP increased on day 1 after EVAR, peaked at day 3, and returned to pretreatment level by day 7 in both groups, but the magnitude of change was significantly less in the ePTFE group.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Voute et al 2012[48]

Study Design: Non-randomized comparative cohort

Device or Material: ePTFE stent-graft (Excluder [W.L. Gore]) vs. polyester stent-graft (Talent & Endurant [Medtronic]) for EVAR

Contact Duration: 4 days

Dose: Mean in-graft volume 37.7± 10.6 mL

Frequency/Duration: Single administration

Response: PIS (fever coinciding with elevated serum CRP level)

Patient characteristics (gender, mean age): 87.9% male. 72.6±7.5 years.

Number per group: 149 (67 ePTFE stent graft, 82 woven polyester stent-graft)

Observed adverse effects: Incid ence of PIS was 17.9%, significantly lower than the polyester stent-graft group (56.1%; $p<0.001$).

Timing of adverse effects: PIS occurred almost exclusively in the first 2 days after ePTFE implantation.

Factors that predict response: The amount of graft material implanted, and new-onset thrombus were not associated with PIS.

Source Citation: Stone et al 2011[41]

Study Design: RCT

Device or Material: PTFE-covered stent (JOSTENT/GraftMaster [Abbott]) vs. BMS for PCI post-CABG

Contact Duration: Follow-up 5 years; mean age of graft

Dose: Mean length 20.7 mm

Frequency/Duration: Single administration of 1 to 2 stent-grafts

Response: Death, MI

Patient characteristics (gender, mean age): 81.5% male, 67.9 years.

Number per group: 243 (115 stent-graft; 128 BMS)

Observed adverse effects: All-cause death (29.8%) and MI (26.2%) were comparable to BMS at 5 years.

Timing of adverse effects: NR

Factors that predict response: NR

AAA = abdominal aortic aneurysm; ACPP = access circuit primary patency; AE = adverse event; BMS = bare-metal stent; CABG = coronary artery bypass graft; CRP = C-reactive protein; EVAR = endovascular abdominal aortic aneurysm repair; F-EVAR = fenestrated endovascular abdominal aortic aneurysm repair; FDP = fibrinogen degradation product; HE = hepatic Encephalopathy; HR = hazard ratio; hsCRP = high sensitivity C-reactive protein; IL = interleukin; MI = myocardial infarction; NR = not reported; OPG = osteoprotegerin; PCI = percutaneous coronary intervention; PIS = post-implantation syndrome; PPA = popliteal artery aneurysm; PTA = percutaneous transluminal angioplasty; PWV = pulse wave velocity; RCT = randomized controlled study; SFA = superficial femoral artery; TAPP = treatment area primary patency; TIPS = transjugular intrahepatic portosystemic shunt; TVF = target vessel failure; TVR = target vessel revascularization; WBC = white blood cell

Table 14: Sutures - Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Pacella 2016[53]

Study Design: Systematic review

Device or Material: Suture for frontalis suspension surgery

Contact Duration: NR

Dose: NR

Frequency/Duration: Single Administration

Response: Infection, Granuloma, Preseptal cellulitis, Abscess

Patient characteristics (gender, mean age): NR, NR.

Number per group: PTFE: 5 studies including 216 patients, total: 53 studies including 1,921 patients using fascia lata, Mersilene, PTFE, and silicone.

Observed adverse effects: PTFE has a significant lower overall incidence of complications (5%, 95% CI 0.6–13%) compared to fascia lata (25%, CI 14–39%). However, PTFE had a higher rate of infections (1.9%, CI 0.2–5.4% vs. 1%, CI 0.5–1.6%).

Timing of adverse effects: NR

Factors that predict response: NR

CI= confidence interval; NR= not reported; PTFE= polytetrafluoroethylene

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Appendix F. Surveillance Event Reports - PSO and Accident Investigation

Provided with this report as separate Excel spreadsheet.

Appendix G. Regulatory and Manufacturer Safety Alerts

Specific search terms are provided here. The associated alerts are provided with this report as a separate PDF.

PFAS in Medical Devices: What You Need to Know

Update: September 1, 2026

The FDA has updated this page with a new Frequently Asked Questions (FAQs) section. Scroll down for answers to common questions about PFAS in medical devices.

The FDA reviews and monitors the safety and effectiveness of medical devices, including devices that contain materials from the PFAS (per- and polyfluoroalkyl substances) chemical family. The PFAS materials used in devices are often plastics known as fluoropolymers. This page explains what fluoropolymers are, why they are used in medical devices, and how the FDA has determined their safety.

Feedback

Key Takeaways

- Fluoropolymers used in medical devices are not the same as the PFAS linked to environmental contamination or health concerns. They differ in chemical structure, molecular size, and how the body reacts to them.
- Certain materials, like large-molecule PFAS (fluoropolymers), are critical components of life-saving medical devices, including catheters, cardiovascular implants, tubing and wound dressings, because of their unique properties including biocompatibility, durability, electrical resistance and lubricity.
- The FDA's determination based on available scientific studies is that there is no reason to restrict the continued use of fluoropolymers in medical devices.

What are PFAS?

PFAS are a large group of more than 15,000 chemicals that are used in a variety of products. They are not all the same. Some PFAS, typically those chemicals comprised of small molecules, have been linked to health concerns and have been detected in drinking water and other parts of our environment.

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The PFAS used as components in medical devices are different. Many medical devices rely on plastic materials comprised of large molecules (fluoropolymers), which are part of the PFAS family and have been safely used for decades.

Why Are Fluoropolymers Used in Medical Devices?

Medical devices are critical components of health care delivery. Fluoropolymers have unique properties that are essential for devices to function. Currently no other materials exist that can perform the same critical roles in medical devices.

They provide:

- Lubricity (slipperiness) for devices such as the stents used to treat heart and blood vessel problems, and delivery systems used in minimally invasive surgical procedures.
- Electrical insulation, for example, in the wires that lead from a pacemaker to a person's heart.
- Biostability, allowing medical devices to remain in the body for long periods of time without the likelihood of breaking down. Degradation of medical devices in the body could lead to pieces of the devices breaking off and potentially causing life-threatening medical issues for patients.

What Types of Devices Use Fluoropolymers?

Fluoropolymers are found in a wide range of medical devices, including:

- Cardiovascular implants such as stents and vascular grafts
- Catheters and guidewires used in minimally invasive procedures
- Tubing and wound dressings
- Other devices that require durable or low-friction surfaces

The role that fluoropolymers play, and their level of patient contact, varies significantly across these device types. An implanted cardiovascular device, a temporary catheter, and an external wound dressing involve very different patterns of use and exposure. The FDA considers those differences when evaluating device safety.

The fluoropolymers used in medical devices are typically comprised of molecules that are too large to cross through cell membranes and, as a result, are very unlikely to cause toxicity to patients.

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How Does the FDA Evaluate These Devices Before and After Market?

The FDA conducts premarket review and post-market monitoring of medical devices. For devices that do not require premarket review, the FDA oversees them through safety monitoring and adverse event reporting systems. The FDA considers:

- How the device is used and how it contacts the body
- How long the device is in contact with the body
- Whether materials could migrate or be released from the device
- Whether the overall benefits outweigh the risks for patients

The FDA monitors the safety of fluoropolymers in medical devices based on available scientific information. We will update this page as appropriate to keep the public informed as additional information becomes available.

Frequently Asked Questions

Find answers to common questions about PFAS in medical devices below:

1. Are all PFAS the same?

No. The term PFAS is used to describe a very broad class of chemicals that are characterized by having at least one carbon-fluorine bond. In the same way that the term carbohydrate (or “carbs”) can be used to classify everything from table sugar to cellulose (the main component of wood), the properties of PFAS chemicals are just as wide-ranging.

2. What does the evidence say about the safety of PFAS in medical devices?

PFAS in the form of fluoropolymers have been used as materials of construction in medical devices since the 1950s. They are now used in many thousands of devices from catheters to pacemakers, and no toxicity issues have been connected to the use of fluoropolymers in devices.

The FDA has investigated this area closely through the post-market monitoring program for all marketed medical devices. The FDA also commissioned an outside research organization, called ECRI, to independently study polytetrafluoroethylene (PTFE), the most widely used PFAS material in medical devices.

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ECRI collected data from over 1,800 health care provider organizations around the country and over 1,750 published and peer-reviewed scientific articles relevant to the safety profile of PTFE in medical applications. The ECRI review in 2021 found no conclusive evidence of patient health issues associated with PTFE as a material.

The FDA is not aware of any evidence that suggests the fluoropolymer PFAS materials in medical devices have harmful public health effects, and the FDA has determined there is no reason to restrict their use in devices.

3. How does the FDA evaluate and regulate PFAS in medical devices?

The FDA regulates medical devices as finished products, not the individual materials used to make them. Whether a material is safe depends on how it is used in a device.

4. How does the FDA continue monitoring devices after they are on the market?

There are several regulations and requirements that manufacturers of medical devices must follow, including the reporting of certain malfunctions or adverse events to the FDA. In some cases, devices may be temporarily or permanently removed from the market if the risk of using the device outweighs the benefit for the patient. Other products may require specific post-marketing clinical studies to be conducted.

5. Are PFAS-free alternative devices available?

PFAS in the form of fluoropolymers remain essential materials for many devices. There is considerable research being conducted to find alternatives, but in most cases, no other materials have been shown to possess the combination of unique properties that are necessary for their essential function in medical devices.

Imagine a patient who has a very sick heart: she may have a stent in an artery. Her metal stent is likely coated in a fluoropolymer (for example, PTFE) to ensure it does not cause blood clotting. A guidewire coated in PTFE to make it slippery enough to safely move through the vessels would have been used to place the stent during her original surgical procedure.

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PFAS fluoropolymers have been used in medical devices for roughly 75 years, and their use has grown as devices have improved over time. The FDA is not aware of any evidence that fluoropolymer PFAS materials in medical devices are harmful and has determined there is no reason to restrict their use in devices.

6. Where can I learn more, and what should I do if I have a concern?

Several resources are available if you have further questions. You may also contact the Center for Devices and Radiological Health's Division of Industry and Consumer Education (DICE) (/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice). If you have a problem with a medical device, please report the problem to the FDA through MedWatch (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program).

RESOURCES

- Per- and Polyfluoroalkyl Substances (PFAS) (/food/environmental-contaminants-food/and-polyfluoroalkyl-substances-pfas)
- Medical Device Material Performance Study: PTFE Safety Profile (/media/158495/download?attachment)
- EPA: Our Current Understanding of Human Health and Environment Risks of PFAS (https://www.epa.gov/pfas/our-current-understanding-human-health-and-environmental-risks-pfas)

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Report on the Use of PFAS in Cosmetic Products and Associated Risks

Prepared by:
U.S. Food and Drug Administration
Office of the Chief Scientist
Office of Cosmetics and Colors

December 2025

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i. Glossary/List of Abbreviations

ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	Area under the concentration curve
BfR	German Federal Institute for Risk Assessment
CAS	Chemical Abstracts Service
CCL2	C-C motif chemokine ligand 2
CID	Compound ID
CIR	Cosmetic Ingredient Review Panel
CN	Cosmetics Notification
CosIng	EU Inventory of Cosmetic Ingredients
CPSC	Consumer Product Safety Commission
CRDE	Calculated Relative Daily Exposure
CYP450	Cytochrome P450
DAF	Dermal Absorption Factor
DART	Developmental and Reproductive Toxicity
DMSO	Dimethyl sulfoxide
DNEL	Derived No Effect Level
DRG	Dorsal root ganglion
DTH	Delayed-type hypersensitivity
EAE	Experimental Allergic Encephalomyelitis
EC	European Commission
ECHA	European Chemicals Agency
EEA	European Economic Area
EEC	European Economic Community
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
EU	European Union
FDA	U.S. Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GABA	Gamma-Aminobutyric Acid
GHS	Globally Harmonized System of Classification and Labelling of Chemicals

GLP	Good Laboratory Practice
GNPD	Mintel's Global New Products Database
HPFO-DA	Hexafluoropropylene oxide dimer acid
IARC	International Agency for Research on Cancer
ICCR	The International Cooperation on Cosmetics Regulation
IFNγ	Interferon-gamma
IL-4	Interleukin-4
IMAP	Inventory Multi-tiered Assessment and Prioritisation
INCI	International Nomenclature of Cosmetic Ingredients
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KEMI	Swedish Chemicals Agency
LC_{50}	Lethal Concentration, 50%
LD_0	The Lowest Lethal Dose
LD_{50}	Lethal Dose, 50%
LLNA	Local Lymph Node Assay
LOAEL	The lowest observed adverse effect level
LPS	Lipopolysaccharide
MCP-1	Monocyte chemoattractant protein-1
MDA	Malonaldehyde
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MOE	Margin of Exposure
MSDS	Material Safety Data Sheet
NESIL	No Expected Sensitization Induction Level
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NNG	Net nuclear grains
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
NPDWR	National Primary Drinking Water Regulation
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development

OSHA	Occupational Safety and Health Administration
PBPK	Physiologically based pharmacokinetic modelling
PC	Protein carbonyls
PFAAs	Perfluoroalkyl acids
PFAS	Per- and polyfluoroalkyl substances
PFBS	Perfluorobutanesulfonic acid
PFCAs	Perfluorocarboxylates or perfluorocraboxylic acids
PFHxA	Perfluorohexanoic acid or undecafluorohexanoic acid
PFHxS	Perfluorohexane sulfonic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFPrA	Perfluoropropanoic acid
PFSAs	Perfluorosulfonates or Perfluorosulfonic acids
PMMA	Polymethylmethacrylate
PBPK	Physiologically based pharmacokinetic modelling
POD	Point of Departure
PTFE	Polytetrafluoroethylene
QSR	Quantitative structure-activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RF	Retention Factor
ROS	Reactive Oxygen Species
SAF	Safety Assessment Factor
SCCNFP	The Scientific Committee on Cosmetic Products and Non-food products intended for Consumers
SCCP	The Scientific Committee of Consumer Products
SCCS	The Scientific Committee of Consumer Safety
SDS	Safety Data Sheet
SED	Systemic Exposure Dose
SID	Substance ID
SVHC	Substances of very high concern
TFE	Tetrafluoroethylene
TNF-α	Tumor necrosis factor-alpha
TTC	Threshold of Toxicological Concern

UF	Uncertainty Factor
VCRP	Voluntary Cosmetic Registration Program
WHO	World Health Organization

ii. Executive Summary

The Modernization of Cosmetics Regulation Act (MoCRA), signed into law on December 29, 2022, is the most significant expansion of the U.S. Food and Drug Administration's (FDA) authority to regulate cosmetics since the Federal Food, Drug, and Cosmetic Act (FD&C Act) was passed in 1938. The FD&C Act [sec.201(i)] defines the term "cosmetic" as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance," and "articles intended for use as a component of any such articles; except that such term shall not include soap." MoCRA amended the FD&C Act to include the term "cosmetic product," which is defined as "a preparation of cosmetic ingredients with a qualitatively and quantitatively set composition for use in a finished product" [FD&C Act, sec.604(2)]. This new law will help ensure the safety of cosmetic products many consumers use daily. Section 3506(a) of MoCRA requires an assessment of the use of perfluoroalkyl and polyfluoroalkyl substances (PFAS) in cosmetic products and the scientific evidence regarding the safety of such use in cosmetic products, including any associated risks with such use. This report summarizes the results of FDA's assessment and fulfills the mandate to publish such a report, as required by section 3506(b). The scope of this report is limited to PFAS that are intentionally added to cosmetic products as an ingredient and does not include PFAS that may be present in the final product as contaminants.

PFAS, a group of synthetic chemicals, have been widely used in industrial and consumer products, including cosmetic products because they are water- and oil-resistant, and are long-lasting. However, their use has raised significant health and environmental concerns due to their persistence and potential toxicity, leading to tightened global regulatory oversight including bans and restrictions by a growing number of states in the United States (U.S.).[1] Certain PFAS are intentionally added as ingredients to some cosmetic products, such as lipsticks, eyeshadows, moisturizers, nail polish and enamel, blushers and rouges, and cleansers. These PFAS are used in cosmetic products to condition and smoothen skin and hair, making them appear shiny, or to modify product consistency and texture.

Under the FD&C Act, cosmetic ingredients or products do not require FDA approval before they go on the market, with the exception of color additives which are subject to FDA approval before use. Otherwise, manufacturers are generally allowed to use any ingredient in the formulation of a cosmetic product, as long as the ingredient and the finished product are safe, the product is appropriately labeled, and the use of the ingredient does not render the cosmetic product adulterated or misbranded under FDA's laws. There are currently no federal regulations that specifically address the use of PFAS in cosmetic products in the U.S. PFAS that are intentionally added to cosmetic products as an ingredient are not currently prohibited and do not, based on presence alone, render the cosmetic product adulterated or misbranded.[2]

[1] Eleven states (California, Colorado, Connecticut, Maine, Minnesota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, and Washington) passed legislation to prohibit the use of intentionally added PFAS substances in cosmetics which takes effect between 2025 and 2028 (as of May 15, 2025).

[2] Please note that this position may be subject to change as new scientific evidence emerges.

Our analysis of cosmetic product listing data,[3] submitted to the FDA as required by MoCRA, revealed that 51 PFAS are intentionally added as ingredients in a total of 1,744 cosmetic product formulations sold in the U.S. (as of August 30, 2024) (see **Table 2.1**). These PFAS-containing cosmetic products represent 0.41% of the total products registered as of August 2024. Eye shadows, face and neck products (leave-on), eyeliners, face powders, and foundations were the top five product categories and constitute approximately 56% of PFAS-containing cosmetic products.

While information from FDA's now-sunset Voluntary Cosmetic Registration Program (VCRP)[4] and Mintel's Global New Products Database (GNPD)[5] indicated an overall declining trend in the use of PFAS in cosmetic products in recent years, the lack of historical data due to the recent implementation of cosmetic product listing requirements per MoCRA prevented further analysis.

Based on the FDA's cosmetic product listing data, polytetrafluoroethylene (PTFE) is the most frequently used PFAS in cosmetic products in the U.S., appearing in 490 products and accounting for 28.1% of all PFAS-containing cosmetic products. This is followed by perfluorononyl dimethicone, trifluoroacetyl tripeptide-2, tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate, perfluorohexylethyl triethoxysilane, methyl perfluorobutyl ether, and methyl perfluoroisobutyl ether, used in 232 (13.3%), 164 (9.4%), 156 (8.9%), 124 (7.1%), 114 (6.5%) and 108 (6.2%) cosmetic products, respectively (see **Table 2.1**).

Based on cosmetic product listing data, the top 25 PFAS used in 10 or more products (see **Table 2.1**), account for over 96% of PFAS used in cosmetic products marketed in the U.S. Therefore, these 25 PFAS were prioritized for a safety review in this report, allowing for a focused assessment of those most prevalent, and potentially impactful, PFAS ingredients.

To gather existing safety data to assess human health risk of exposure to these PFAS, we conducted a comprehensive search of PubMed and Web of Science, consulted existing official safety assessments from government agencies and scientific advisory groups, such as the Cosmetic Ingredient Review Panel (CIR) and the Scientific Committee on Consumer Safety (SCCS), and explored the European Chemicals Agency (ECHA) chemicals database.

Our safety assessment considered the potential exposure pathways based on the product types and ingredient toxicokinetics, i.e., absorption, distribution, metabolism and excretion (ADME) processes, specific to exposure from cosmetic products use. Dermal contact is expected to be the primary route of exposure since most cosmetic products are applied to the skin. Other routes of exposure may include inhalation through aerosolized sprays like hairspray or face powder, and oral ingestion from lipstick or mouthwash use. For each of the 25 PFAS, we evaluated toxicological data encompassing both systemic effects (acute toxicity, genotoxicity, carcinogenicity, repeated dose toxicity, developmental and

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[3] Cosmetic product listing information, as required by MoCRA, can be submitted through one of the following options: Cosmetics Direct, Electronic Submission Gateway (ESG), SPL Xforms, and paper forms. For more details, refer to: Registration & Listing of Cosmetic Product Facilities and Products | FDA.

[4] Voluntary Cosmetic Registration Program (VCRP): https://www.fda.gov/cosmetics/voluntary-cosmetic-registration-program. The FDA stopped accepting submissions to the VCRP on March 27, 2023 due to a MoCRA mandate regarding mandatory facility registrations and product listings. FDA began enforcing the requirements regarding mandatory cosmetic product facility registration and cosmetic product listing data on July 1, 2024.

[5] Mintel's Global New Products Database (GNPD) provides comprehensive tracking of new product launches across various markets, including cosmetics. It offers insights into market trends, product innovations, and consumer preferences.

reproductive toxicity, and neurotoxicity) as well as port-of-entry effects (via the skin, eyes, and respiratory tract). Based on data availability, the potential health risks associated with the use of PFAS-containing cosmetic products were assessed following standard risk assessment procedures, which include hazard identification, dose-response assessment, exposure assessment and risk characterization to derive Margin of Exposure (MOE) values, where appropriate. MOE is the ratio used in risk assessment to evaluate the safety of a substance by comparing the level of toxicological threshold or reference dose to the estimated level of human exposure.

Table ES.1 presents a high-level summary of the safety conclusion of our assessment. The safety of most (N=19 or 76%) of the reviewed PFAS could not be definitively determined due to the lack of critical toxicological data. Five PFAS (PTFE, perfluorodecalin, HC Yellow No. 13, perfluorohexane, and tetrafluoropropene) were considered to pose low safety concerns in cosmetic products under intended use conditions. One PFAS, namely perfluorohexylethyl triethoxysilane, was identified as having a potential safety concern when used in body lotion at the highest use level (i.e., the concentration of an ingredient in a final product).

Table ES.1. Summary of Review Conclusions for Individual PFAS

Insufficient data for safety conclusion
Perfluorononyl Dimethicone
Trifluoroacetyl Tripeptide-2
Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate
Methyl Perfluorobutyl Ether
Methyl Perfluoroisobutyl Ether
Polyperfluoromethylisopropyl Ether
Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer
Pentapeptide-34 Trifluoroacetate
Trifluoropropyldimethyl/trimethylsiloxysilicate
Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate
Perfluoroperhydrophenanthrene
Dimethiconol Fluoroalcohol Dilinoleic Acid
Ethyl Perfluorobutyl Ether
Trifluoromethyl C1-4 Alkyl Dimethicone
Perfluorononylethyl Stearyl Dimethicone
Acetyl Trifluoromethylphenyl Valylglycine
Perfluorodimethylcyclohexane
Trifluoropropyl Cyclopentasiloxane
Perfluoromethylcyclopentane
Low safety concern based on available data for the intended conditions of use
PTFE
Perfluorodecalin
HC Yellow No. 13*
Perfluorohexane
Tetrafluoropropene
A potential safety concern based on available data at highest concentration of use in body lotion

	Perfluorohexylethyl Triethoxysilane

* HC Yellow No. 13 is a synthetic coal tar dye which does not require FDA approval or batch certification when used in hair dyes. In 2010, SCCS concluded that HC Yellow No. 13 is safe for use up to 2.5% in hair dye as specified in the Opinion document (SCCS 2011).

This assessment is subject to significant uncertainties, including limited data on use level, lack of dermal and oral absorption data, and mechanistic information, as well as the absence of dermal toxicity data. As further data becomes available for these PFAS ingredients, these assessments could be refined to provide a more accurate evaluation of the safety and potential risks associated with their use in cosmetic products. Our assessment underscores significant data gaps for PFAS used in cosmetic products. The FDA will continue to monitor emerging data on PFAS to ensure the continued safety of cosmetic products.

1 Introduction

Overview of PFAS

PFAS are a diverse group of synthetic chemicals used in a wide range of consumer and industrial products for their water- and oil-repellent properties, as well as their resistance to heat and chemical degradation (Gluge, Scheringer et al. 2020).

There is currently neither a consensus definition of PFAS internationally nor a federal definition in the U.S. (Hammel, Webster et al. 2022, Gaines, Sinclair et al. 2023, NSTC 2023). The U.S. Congress did not define the term "PFAS" in Sec. 3506 of the MoCRA requirement for a PFAS report either. Regulators from various jurisdictions such as the European Union (EU) and the U.S. have proposed different definitions based on chemical structures. While the exact PFAS definition is still under discussion and evolving, this report uses a definition proposed by the Organization for Economic Co-operation and Development (OECD) in 2021 (OECD 2021) that is currently accepted widely. OECD defines PFAS as "*fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), i.e., with a few noted exceptions, any chemical with at least a perfluorinated methyl group (−CF3) or a perfluorinated methylene group (−CF2−) is a PFAS.*" The "noted exceptions" refer to a carbon atom with a H/Cl/Br/I atom attached to it (Wang, Buser et al. 2021). This OECD definition broadens the scope of PFAS initially introduced by Buck et al. (2011) who defined PFAS as highly fluorinated aliphatic substances that contain the perfluoroalkyl moiety C_nF_{2n+1-}. As scientific understanding and regulations regarding PFAS evolve, PFAS definitions may continue to change according to specific needs in the future regulatory landscape.

Chemically, the PFAS family encompasses a wide range of chemical compounds characterized by a very strong fluorine-carbon bond, with variations in chain length, functional groups, molecular structural features, and thus properties. Therefore, individual PFAS can be very different in their physicochemical and toxicological properties, and the safety of PFAS should be assessed taking these differences into consideration. In general, PFAS are classified into two primary categories: nonpolymers and polymers. Further, nonpolymer PFAS encompass two major subclasses including perfluoroalkyl substances and polyfluoroalkyl substances, each further divided into many groups and subgroups. Polymer PFAS include fluoropolymers, polymeric perfluoropolyethers, and side-chain fluorinated polymers (Buck, Franklin et al. 2011). Polymeric PFAS usually have distinct physicochemical and toxicological profiles compared with nonpolymer PFAS due to their large molecular weight and complex molecular structures.

In addition, PFAS, especially perfluoroalkyl acids (PFAAs) and their associated anions are classified according to their chain length based on the number of carbons present in the C-F chain as either long-chain, short-chain or ultrashort-chain PFAS. Long-chain PFAS have 7 or more perfluorocarbons for perfluorocarboxylates (PFCAs), and 6 or more perfluorocarbons for perfluorosulfonates (PFSAs). Short-chain PFAS have 3 to 6 perfluorocarbons for PFCAs, and 4 to 5 perfluorocarbons for PFSAs. Ultrashort-chain PFAS have 2 or fewer perfluorocarbons for PFCAs, and 3 or fewer perfluorocarbons for PFSAs. Ultrashort-chain PFAS also includes trifluoroacetic acid (TFA) and perfluoropropanoic acid (PFPrA) (Buck, Franklin et al. 2011, Neuwald, Hubner et al. 2022, Pizzorno 2023).

The exact number of PFAS in global commerce is unclear due to varying definitions and methodologies. In 2018, OECD identified over 4,700 PFAS by CAS numbers (OECD 2018). The number was estimated to

be 38,382 by Williams et al. (Williams, Gaines et al. 2022). According to U.S. EPA's CompTox chemicals dashboard, there are over 16,000 PFAS substances[6] and in 2023, EPA identified at least 770 PFAS currently in use in the U.S. based on EPA's own working definition of PFAS.[7]

It is important to note that except for a very small number, most of these PFAS have limited or no safety data that is publicly available. Some PFAS, such as legacy PFAS perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), have been associated with adverse health effects, including liver toxicity, increased cholesterol levels, lower antibody response to some vaccines, developmental and reproductive toxicity, and increased risk of some cancers (ATSDR 2021).[8] However, we note that neither PFOA or PFOS are intentionally added to cosmetic products as ingredients (see discussion below). It is noteworthy to mention that some PFAS, such as PFOS and 6:2-fluorotelomersulfonic acid, may be present in cosmetic products unintentionally for various reasons, for example due to their presence in raw material impurities or due to the breakdown of intentionally added PFAS that form other types of PFAS. These contaminant PFAS are not within the scope of this report.

Overview of Regulatory Landscape of PFAS Use in Cosmetic Products

The regulatory landscape for PFAS in cosmetics is complex, varying both internationally and domestically, and continues to evolve as PFAS definitions change and additional studies on their impacts are conducted.

International Landscape

In early 2024, New Zealand announced regulations on PFAS, which appear to phase out the use of all PFAS (>10,000 chemicals) in cosmetic products starting January 1, 2027, when the import or manufacturing of cosmetics containing intentionally added PFAS will be prohibited. In New Zealand, selling cosmetics containing PFAS will be banned starting January 1, 2028, while all PFAS-containing cosmetic products must be disposed of before July 1, 2028.[9] Our understanding is that a similar measure has been under review in the EU since 2023, as Germany, Denmark, the Netherlands, Norway, and Sweden submitted a dossier that proposes to ban the manufacture and use of approximately 10,000 PFAS, targeting a number of uses, including the use of PFAS in cosmetics.[10] This restriction is currently under evaluation by the ECHA. France passed legislation that reportedly mandates a gradual ban on PFAS, starting with their use in cosmetics, ski waxes and textiles by January 2026, and extending to all non-essential uses by 2030.[11]

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[6] EPA PFAS chemical lists: 1) PFAS with explicit structures https://comptox.epa.gov/dashboard/chemical-lists/PFASSTRUCT, and 2) PFAS without explicit structures https://comptox.epa.gov/dashboard/chemical-lists/PFASDEV3 (accessed 5/1/2024).

[7] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-section-8a7-reporting-and-recordkeeping (accessed 5/1/2024).

[8] How PFAS Impacts Your Health. https://www.atsdr.cdc.gov/pfas/about/health-effects.html (accessed 5/1/2024).

[9] Updated rules for cosmetics. https://www.epa.govt.nz/hazardous-substances/rules-notices-and-how-to-comply/specific-substance-guidance/cosmetics/updated-rules-for-cosmetics/ (accessed 1/24/2025).

[10] https://echa.europa.eu/-/echa-and-five-european-countries-issue-progress-update-on-pfas-restriction (accessed 1/24/2025).

[11] https://www.sgs.com/en-rs/news/2025/03/safeguards-04025-france-bans-pfas-on-consumer-products (accessed 3/31/2025).

Canada also appears to prohibit the manufacture, use, sale, offer for sale or import of cosmetics that contain long chain-PFCAs, with a limited number of exemptions.[12] Canada published a Notice of Intent[13] to address the broad class of PFAS in 2021 and issued a final report on the state of PFAS that provides a qualitative assessment of the fate, sources, occurrence, and potential impacts of PFAS on the environment and human health in 2025 (Health Canada 2025).

The Ministry of Food and Drug Safety in the Republic of Korea appears to prohibit the intentional use of approximately 190 PFAS as ingredients in cosmetic products. If PFAS substances are detected in cosmetics due to unintentional contamination, our understanding is that providing objective evidence confirming the unintentional origin is required. The determination of the potential harm is concluded after a risk assessment (ICCR 2023).

National Landscape

At least 11 states in the U. S. have banned the use of PFAS substances in cosmetics and other products, while at least 8 other states have proposed legislation to ban or limit the use of these ingredients in cosmetics. California,[14] Colorado,[15] Connecticut,[16] Maine,[17] Minnesota,[18] New Hampshire,[19] New Mexico,[20] Oregon,[21] Rhode Island,[22] Vermont,[23] and Washington[24] recently passed legislation to prohibit the use of all intentionally added PFAS substances[25] in cosmetics which takes effect between 2025 and 2028.[26] The following states have proposed, but not yet enacted state laws to ban or limit the use of

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[12] https://www.canada.ca/en/environment-climate-change/services/management-toxic-substances/prohibition-regulations.html (accessed 1/24/2025).

[13] https://www.canada.ca/en/health-canada/services/chemical-substances/other-chemical-substances-interest/per-polyfluoroalkyl-substances.html (accessed 1/24/2025).

[14] California Assembly Bill 2771. AB-2771. Cosmetic products: safety. Chapter 804. October 2022. https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=202120220AB2771 (accessed 1/28/2025).

[15] https://leg.colorado.gov/sites/default/files/2022a_1345_signed.pdf (accessed 1/28/2025).

[16] https://www.cga.ct.gov/2024/ACT/PA/PDF/2024PA-00059-R00SB-00292-PA.PDF (accessed 1/28/2025).

[17] https://www.maine.gov/dep/spills/topics/pfas/PFAS-products/ (accessed 1/28/2025).

[18] Sec. 116.943 MN Statutes. https://www.revisor.mn.gov/statutes/cite/116.943 (accessed 1/28/2025).

[19] https://legiscan.com/NH/text/HB1649/id/3003140 (accessed 1/28/2025).

[20] https://legiscan.com/NM/text/HB212/2025 (accessed 8/7/2025).

[21] Oregon Senate Bill 546-A, relating to chemicals used in cosmetic products. June 2023. https://olis.oregonlegislature.gov/liz/2023R1/Downloads/MeasureDocument/SB546/Enrolled (accessed 1/28/2025).

[22] https://legiscan.com/RI/text/H7356/id/3008263 (accessed 1/28/2025).

[23] https://legislature.vermont.gov/Documents/2024/Docs/ACTS/ACT131/ACT131%20As%20Enacted.pdf (accessed 1/28/2025).

[24] Washington House Bill 1047. Concerning the use of toxic chemicals in cosmetic products. May 2023 Link: Bill Text: WA HB1047 | 2023-2024 | Regular Session | Chaptered | LegiScan (accessed 1/28/2025).

[25] PFAS substances means a class of fluorinated organic chemicals containing at least one fully fluorinated carbon atom.

[26] January 1, 2025 in California, Colorado, Minnesota and Washington, January 1, 2026 in Maine and Vermont, January 1, 2027 in New Hampshire, Oregon and Rhode Island, and January 1, 2028 in New Mexico and Connecticut. Connecticut's law also contains a provision to prohibit the uses earlier, by January 1, 2026 unless the manufacturer of the product provides prior notification in writing to the State, additional required information outlined in the legislation, and/or the products are clearly labeled as containing PFAS.

PFAS ingredients in cosmetic products: Georgia,[27] Hawaii,[28] Illinois,[29] Massachusetts,[30] New Jersey,[31] New York,[32] North Carolina,[33] Ohio,[34] Pennsylvania,[35] and Tennessee.[36]

2 PFAS Use in Cosmetic Products

To assess PFAS use in cosmetic products and evaluate scientific data regarding safety (including any associated risks) of such use, the FDA collected, reviewed and summarized information on this topic.

Overview of PFAS Use in Cosmetic Products

PFAS have been used as intentionally added ingredients in a diverse range of cosmetic product types and for various technical functions. The Swedish Chemicals Agency (KEMI) conducted a study examining PFAS usage in cosmetics and market share[37] of PFAS-containing cosmetic products within the European Union/European Economic Area (EU/EEA) as well non-EU/EEA countries (KEMI 2021). This report identified 169 PFAS with INCI (International Nomenclature of Cosmetic Ingredients) names based on the CosIng database[38] (as of May 2020) and estimated the market share of PFAS-containing cosmetic products in the EEA market to be between 0.33% and 1.4% depending on the database utilized. The CosmEthics database, deemed to be the most representative of the EU market, indicated that 1.4% of all registered products contained PFAS as ingredients (KEMI 2021). Further analysis of the CosmEthics data revealed that makeup contained the highest percentage of products with PFAS (4.1%), followed by facial care products and male grooming products (1.2% each). Baby and children's products accounted for 0.03% of PFAS-containing cosmetic products. No fragrances were found to contain PFAS. In addition, PTFE, perfluorooctyl triethoxysilane, C9-15 fluoroalcohol phosphate, perfluorononyl dimethicone and perfluorodecalin were found to be the top five most frequently listed ingredients in these products (KEMI 2021).

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[27] Georgia General Assembly - HB 390: https://www.legis.ga.gov/legislation/64348 (accessed 1/28/2025).

[28] Hawaii Senate Bill 2427: https://www.capitol.hawaii.gov/sessions/session2024/bills/SB2427_.HTM (accessed 1/28/2025).

[29] Illinois bill 5024: https://ilga.gov/legislation/fulltext.asp?DocName=&SessionId=112&GA=103&DocTypeId=HB&DocNum=5042&GAID=17&LegID=153031&SpecSess=&Session=.

[30] Bill S.1504: https://malegislature.gov/Bills/194/S1504 (accessed 1/28/2025).

[31] NJ Legislature: https://www.njleg.state.nj.us/bill-search/2024/S1042/bill-text?f=S1500&n=1042_I1 (accessed 1/28/2024).

[32] New York State Assembly Bill 2025 A1635: https://www.nysenate.gov/legislation/bills/2025/A1635 (accessed 1/28/2024).

[33] NC House Bills 686 and 881: https://legiscan.com/NC/bill/H686/2025 and https://legiscan.com/NC/bill/H881/2025 (accessed 8/7/2025).

[34] OH House Bill 272: https://legiscan.com/OH/text/HB272/2025 (accessed 8/7/2025).

[35] PA house bill 2238: House Bill 2238 Information; 2023-2024 Regular Session - The Official Website of the Pennsylvania General Assembly (accessed 1/28/2025).

[36] TN SB 1786: https://wapp.capitol.tn.gov/apps/BillInfo/default.aspx?BillNumber=SB1786&GA=113 (accessed 1/28/2025)..

[37] In this report, market share is defined as the percentage of the total cosmetic products that contain PFAS in a database such as CosmEthics and Mintel's GNPD.

[38] CosIng is the European Commission database for information on cosmetic substances and ingredients. It can be accessed via: https://ec.europa.eu/growth/tools-databases/cosing.

In contrast, the market share of PFAS-containing cosmetic products in the U.S. market has not been previously studied or reported. To better understand the extent of PFAS usage in cosmetic products, we first created an inventory of PFAS that could potentially be used in cosmetic products. A search of the term "fluoro" was conducted in February 2024 in wINCI, the online version of the *International Cosmetic Ingredient Dictionary & Handbook*. The resulting list of cosmetic ingredients were then reviewed against the current OECD PFAS definition to ensure that the inventory included only qualified PFAS, i.e., substances containing at least one $-CF_2-$ or $-CF_3$, were included. This process yielded a list of 176 PFAS.

The 2021 KEMI report revealed that polyvinylidene fluoride was not retrieved from our search but was confirmed to be a PFAS in the wINCI database. Therefore, it has been added to our inventory, bringing the total to 177 PFAS (**Table S1**). The CAS Registry Number (CAS RN) for each ingredient, along with their reported functions and associated product categories obtained from the wINCI database, are also summarized in **Table S1**.

Functions of PFAS in Cosmetic Products

PFAS are commonly used as emulsion stabilizers, bulking agents, and for their ability to repel oil and water as well as enhancing product durability (Gluge, Scheringer et al. 2020, Wahlström, Pohjalainen et al. 2021, Gaines, Sinclair et al. 2023). PFAS in cosmetic products serve various functions, including as skin and hair conditioners, cleansers, emulsifiers, antistatics, stabilizers, surfactants, film formers, viscosity regulators, binding agents, solvents, and accelerants for hair dyeing (KEMI 2021, ECHA 2023, OECD 2024).

Market Share of PFAS-Containing Cosmetic Products in the U.S.

MoCRA established a requirement for registration of cosmetic product facilities and listing of cosmetic products.[39] Although certain small businesses, as defined in Section 612 of the FD&C Act, are exempt from this requirement, this new authority significantly improves the FDA's knowledge about cosmetic product facilities and products sold in the U.S. and allows the FDA to gather more comprehensive information about cosmetic ingredients, as compared to the now-sunset VCRP. Cosmetic product listing information is currently submitted to the FDA through various avenues including the Cosmetics Direct portal,[40] the Electronic Submission Gateway (ESG) or any Structured Product Labeling (SPL)[41] authoring software, including SPL Xforms, and paper forms.

To identify PFAS-containing cosmetic products sold in the U.S. market, the 177 PFAS were cross-referenced against the cosmetic product listing data submitted to the FDA, the VCRP and Mintel's GNPD.

A search of the FDA's cosmetic product listing data revealed that, as of August 30, 2024, 51 (out of 177) types of PFAS are used in 1,744 cosmetic product formulations (**Table 2.1**). These PFAS-containing cosmetic products account for 0.41% of the total number of cosmetic products registered (N=430,134).

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[39] Refer to the following FDA webpage for more information regarding this topic: https://www.fda.gov/cosmetics/registration-listing-cosmetic-product-facilities-and-products.

[40] Cosmetics Direct: https://www.fda.gov/cosmetics/registration-listing-cosmetic-product-facilities-and-products/cosmetics-direct.

[41] Structured Product Labeling (SPL): https://www.fda.gov/industry/fda-data-standards-advisory-board/structured-product-labeling-resources.

It should be noted that some products contain more than one type of PFAS. As a result, the total count (i.e., frequency of use) of individual PFAS in **Table 2.1** exceeds 1,744 cosmetic product formulations.

Table 2.1. PFAS Reported in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024).

No.	CAS Number from wINCI	PFAS Name	Frequency of Use*	Percentage of Total (%)#
1	9002-84-0	PTFE	490	28.1
2	259725-95-6	Perfluorononyl Dimethicone	232	13.3
3	64577-63-5	Trifluoroacetyl Tripeptide-2	164	9.4
4	934368-60-2	Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate	156	8.9
5	51851-37-7	Perfluorohexylethyl Triethoxysilane	124	7.1
6	163702-07-6	Methyl Perfluorobutyl Ether	114	6.5
7	163702-08-7	Methyl Perfluoroisobutyl Ether	108	6.2
8	306-94-5	Perfluorodecalin	71	4.1
9	69991-67-9	Polyperfluoromethylisopropyl Ether	54	3.1
10	10442-83-8	HC Yellow No. 13	40	2.3
11	355-42-0	Perfluorohexane	40	2.3
12	NA	Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer	35	2.0
13	NA	Pentapeptide-34 Trifluoroacetate	33	1.9
14	NA	Trifluoropropyldimethyl/trimethylsiloxysilicate	28	1.6
15	NA	Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate	27	1.5
16	306-91-2	Perfluoroperhydrophenanthrene	25	1.4
17	NA	Dimethiconol Fluoroalcohol Dilinoleic Acid	24	1.4
18	29118-24-9	Tetrafluoropropene	23	1.3
19	163702-05-4	Ethyl Perfluorobutyl Ether	22	1.3
20	NA	Trifluoromethyl C1-4 Alkyl Dimethicone	21	1.2
21	NA	Perfluorononylethyl Stearyl Dimethicone	18	1.0
22	379685-96-8	Acetyl Trifluoromethylphenyl Valylglycine	17	1.0
23	26637-68-3 335-27-3	Perfluorodimethylcyclohexane	17	1.0

No.	CAS Number from wINCI	PFAS Name	Frequency of Use*	Percentage of Total (%)#
24	NA	Trifluoropropyl Cyclopentasiloxane	11	0.6
25	1805-22-7	Perfluoromethylcyclopentane	10	0.6
26	163702-06-5	Ethyl Perfluoroisobutyl Ether	8	0.5
27	NA	Biotinyl Histidyl D-Tryptophanyl Dipeptide-29 Lysinamide Trifluoroacetate	8	0.5
28	429-67-4	Trifluoropropyl Cyclotetrasiloxane	7	0.4
29	NA	Perfluorononylethyl Carboxydecyl PEG-10 Dimethicone	6	0.3
30	NA	Trifluoromethylphenethyl Mesalazine	6	0.3
31	NA	Trifluoropropyl Dimethicone/Trifluoropropyl Divinyldimethicone Crosspolymer	6	0.3
32	115361-68-7	Trifluoropropyl Dimethicone	5	0.3
33	1185851-52-8	Ethyl tafluprostamide	4	0.2
34	460-73-1	Pentafluoropropane	4	0.2
35	2374-14-3	Trifluoropropyl Cyclotrisiloxane	4	0.2
36	355-04-4	Perfluoroisohexane	3	0.2
37	NA	Adamantanylcarboxamido Trifluoromethylbenzonitrile	2	0.1
38	355-02-2	Perfluoromethylcyclohexane	2	0.1
39	88645-29-8	Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether	2	0.1
40	NA	C12-16 Alkyl PEG-7 Methacrylate/Perfluorohexylethyl Methacrylate Copolymer	1	0.1
41	138495-42-8	Decafluoropentane	1	0.1
42	2001566-55-6	Difluorocyclohexyloxyphenol	1	0.1
43	NA	Fluoro C2-8 Alkyldimethicone	1	0.1
44	NA	Heptapeptide-50 Trifluoroacetate	1	0.1
45	NA	Isopropyl Titanium Triisostearate/Perfluorooctyl Triethoxysilane Crosspolymer	1	0.1
46	NA	PEG-10 Acrylate/Perfluorohexylethyl Acrylate Copolymer	1	0.1

No.	CAS Number from wINCI	PFAS Name	Frequency of Use*	Percentage of Total (%)#
47	NA	PEG-8 Trifluoropropyl Dimethicone Copolymer	1	0.1
48	NA	Perfluoroalkylsilyl Mica	1	0.1
49	NA	Perfluorononylethyl Carboxydecyl Lauryl Dimethicone	1	0.1
50	NA	Polyperfluoroisopropyl Ether	1	0.1
51	NA	Trifluoropropyl Dimethiconol	1	0.1

NA: not available.

* Frequency of use refers to the total number of cosmetic products that contain a particular ingredient.

The percentage of total is calculated by dividing the frequency of use number with the total number of PFAS-containing cosmetic products (N=1744) * 100.

The cosmetic product listing data following the MoCRA mandate is considered more complete and more reliable than that in the VCRP, although there may still be underreporting of certain products. Among 17 cosmetic product categories from the cosmetic product listing data (**Table S2**), 12 contain products with PFAS. **Table S3** provides the number of PFAS-containing cosmetic products in each category. Products in the top five categories add up to 56% of all PFAS-containing cosmetic products: eye shadows (20.5%), face and neck care products (leave-on) (15.9%), eyeliners (8.4%), face powders (6.6%), and foundations (traditional applications) (4.5%). The rest of the product categories each represents 0.1-4.0% of all products (**Table S3**).

It is worth noting that the PFAS frequency of use from the cosmetic product listing data is based on input we received solely from the responsible person,[42] and doesn't reflect the whole market, due to certain exemptions outlined in MoCRA (such as small businesses). Please also note that the cosmetic product listing data is subject to change over time as new data is collected. As such, this report only represents the data collected as of August 30, 2024. In addition, as the wINCI database is updated, the total number of PFAS identified may increase, and the number of PFAS currently found in cosmetic products may also change.

The VCRP, the FDA's former voluntary reporting system, contains data on cosmetic products in commercial distribution until March 2023. As of July 1, 2024, it was replaced by a mandatory data submission program for cosmetic product facility registrations and product listings as required by MoCRA. The VCRP remains a valuable resource for examining the prevalence of PFAS-containing products in the U.S. before its March 2023 sunset. A search of the VCRP using the INCI names of the 177

[42] MoCRA defines "responsible person" as the manufacturer, packer, or distributor of a cosmetic product whose name appears on the label of such cosmetic product in accordance with section 609(a) of the FD&C Act or section 4(a) of the Fair Packaging and Labeling Act.

PFAS revealed that 32 of these PFAS were reported to be used in a total of 570 products, which represents 1.71% of all products voluntarily registered in the VCRP database (**Table 2.2**).

Table 2.2. List of PFAS Used in Products Reported in the VCRP (as of March 27, 2023)

No.	CAS No.	PFAS Name	Frequency of Use
1	51851-37-7	Perfluorohexylethyl Triethoxysilane	172
2	9002-84-0	Polytetrafluoroethylene (PTFE)	79
3	934368-60-2	Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate	39
4	429-67-4	Trifluoropropyl Cyclotetrasiloxane	31
5	999004-82-1*	Trifluoropropyl Cyclopentasiloxane	31
6	259725-95-6	Perfluorononyl Dimethicone	29
7	306-94-5	Perfluorodecalin	28
8	163702-07-6	Methyl Perfluorobutyl Ether	23
9	163702-08-7	Methyl Perfluoroisobutyl Ether	22
10	64577-63-5	Trifluoroacetyl Tripeptide-2	21
11	355-42-0	Perfluorohexane	18
12	69991-67-9	Polyperfluoromethylisopropyl Ether	12
13	460-73-1	Pentafluoropropane	8
14	306-91-2	Perfluoroperhydrophenanthrene	7
15	10442-83-8	HC Yellow No. 13	6
16	163702-05-4	Ethyl Perfluorobutyl Ether	5
17	335-27-3	Perfluorodimethylcyclohexane	5
18	999004-53-1*	Trifluoropropyldimethyl/trimethylsiloxysilicate	4
19	999004-94-9*	Trifluoropropyl Dimethicone/Trifluoropropyl Divinyldimethicone Crosspolymer	4
20	163702-06-5	Ethyl Perfluoroisobutyl Ether	3
21	1805-22-7	Perfluoromethylcyclopentane	3
22	999001-10-7*	C9-15 Fluoroalcohol Phosphate	3
23	80977400-67-1*	Perfluorononyl Dimethicone/Methicone/Amodimethicone Crosspolymer	3
24	1557087-30-5	Acrylates/Perfluorohexylethyl Methacrylate Copolymer	3
25	999001-44-7	Trifluoromethyl C1-4 Alkyl Dimethicone	2

No.	CAS No.	PFAS Name	Frequency of Use
26	115361-68-7	Trifluoropropyl Dimethicone	2
27	50285-18-2	Perfluoro Dimethylethylpentane	2
28	999002-90-5	Trifluoropropyl Dimethiconol	1
29	999003-11-0*	Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate	1
30	88645-29-8	Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether	1
31	2001566-55-6	Difluorocyclohexyloxyphenol	1
32	29118-24-9	Tetrafluoropropene	1

* These are VCRP Code Numbers. In the VCRP database, ingredients were assigned VCRP Code Numbers when they lacked a valid CAS Number.

The Mintel's GNPD is a comprehensive online resource that tracks and analyzes new product launches across various industries, including beauty and personal care products.[43] It provides detailed information on product formulations, packaging, claims, and marketing trends from around the world. Mintel's GNPD was chosen as a data source due to its comprehensive coverage of the beauty and personal care market, including a wide range of product categories that align closely with the definition of cosmetic products. Using the same approach used in the VCRP search, a search of the 177 PFAS in Mintel's GNPD (conducted in July 2024) identified 79 PFAS used in 13,093 products globally, representing 0.51% of the total 2,544,109 products launched globally. Mintel's GNPD also provides the number of products launched into the market over a 5-year period (August 2019 to July 2024) and in the last year of that period (August 2023 to July 2024). According to the data, 3,476 PFAS-containing cosmetic products were launched globally from 2019 to 2024 (August 2019 to July 2024), among which only about 10% (442) were launched between August 2023 to July 2024. Focusing on products launched over the last 5 years and 1 year, the prevalence of PFAS-containing cosmetic products decreased to 0.45% (53 PFAS in 3,476 products launched out of 777,648 total cosmetic products launched from 2019-2014) and 0.28% (30 PFAS in 442 products launched out of 155,526 cosmetic products launched from 2023-2024), respectively. In the U.S. there have been 57 PFAS used in 2,858 products, accounting for 0.75% of the total 382,917 products launched into the market. There has been a decline in the number of products launched in the U.S. that contain PFAS in the past 5 years (719 products launched between 2019-2024 compared to 74 that were launched from August 2023 to July 2024). In 2024, 0.37% of the newly launched products in the U.S. contain PFAS, compared to 0.28% in the global market and 0.15% in the EU market. For a more detailed data summary, please see **Table 2.3**.

Table 2.3. Total Number of Launched Cosmetic Products and Market Share of PFAS-Containing Cosmetic Products Based on Mintel's GNPD (As of July 27, 2024)

[43] Mintel uses the term "beauty & personal care" for its industry category which is a broader category than "cosmetic products." However, we used Mintel data on beauty & personal care products as a proxy of cosmetic products in this report based on our assumption that cosmetic products, as defined in the FD&C Act, represent a significant portion (or the majority) of the beauty and personal care market.

Regions	Time period	Total number of cosmetic products	Cosmetic products containing PFAS	Proportion of cosmetic products containing PFAS (%)
Global	All time	2,544,109	13,093	0.51
	5 year	777,648	3,476	0.45
	1 year	155,526	442	0.28
U.S.	All time	382,917	2,858	0.75
	5 year	98,463	719	0.73
	1 year	20,032	74	0.37
Europe	All time	939,671	3,338	0.36
	5 year	257,152	711	0.28
	1 year	47,963	70	0.15
Asia Pacific	All time	692,196	4,743	0.69
	5 year	229,069	1,404	0.61
	1 year	47,190	183	0.39
Latin America	All time	297,247	1,282	0.43
	5 year	107,995	448	0.41
	1 year	20,692	96	0.46
Middle East & Africa	All time	139,261	340	0.24
	5 year	67,153	129	0.19
	1 year	13,915	19	0.14

Overall, the data in Mintel's GNPD indicate a gradual decline in PFAS usage within the cosmetics industry across the U.S., the EU, and globally over time. This trend aligns with the growing public awareness of potential environmental and health risks associated with PFAS chemicals and the subsequent surge in demand for safer alternatives.

Trends in PFAS Use in the U.S. Cosmetics Industry

Recent data on the most frequently used PFAS in cosmetic products indicate a declining trend in the usage of some PFAS. For example, PTFE usage has significantly declined over recent years, dropping from 249 registered products in 2019 to just 79 products by early 2023, as shown by the FDA's VCRP (**Table S4**). This decline may reflect responses to state-level legislation banning or restricting PFAS in cosmetics. Mintel's GNPD data corroborates this trend, reporting only four PTFE-containing cosmetic products launched between August 2023 and July 2024, among 222 over a 5-year period (August 2019 to July 2024) in the U.S. (**Table S4**). Some other PFAS, such as perfluorodecalin and perfluorohexane,

have maintained relatively stable usage (**Table S4**). The use information of each individual PFAS is discussed in detail in **Appendix 1** of this report.

After the enactment of MoCRA, FDA collected information from the cosmetics industry on PFAS usage. The results, based on responses from a limited number of participants, indicate that cosmetic manufacturers in the U.S. have started reformulating their products to remove PFAS. FDA reached out to a total of nine firms, all of which have used PFAS in their products according to their submission to the VCRP. Of the five firms that provided responses, two have discontinued their PFAS-containing cosmetic products and reformulated them with non-PFAS alternative ingredients, such as cellulose-based raw material. Another firm responded that it had stopped using PFAS in its products to comply with California's bill AB2771 banning products (including cosmetics) that contain intentionally added PFAS substances effective on January 1, 2025. This firm stated that it started to require all of its suppliers to provide PFAS information; any suppliers that fail to provide PFAS statements are removed from the approved suppliers list and replaced with another supplier who does provide them with the PFAS statement. The two remaining firms responded that they were making efforts to discontinue and reformulate their PFAS-containing cosmetic products.

It should be noted that FDA's cosmetic product listing requirement, mandated by MoCRA and effective since December 18, 2023, with enforcement beginning July 1, 2024, is fairly recent. As a result, insufficient historical data is available at this time to allow for the extrapolation of trends in PFAS usage in cosmetic products.

Use Concentration of PFAS in Cosmetic Products

In contrast to regulations in some jurisdictions, such as Brazil,[44] Canada[45] and the EU,[46] where our understanding is that manufacturers are required to disclose the concentrations (or concentration ranges) and functions of intentionally added ingredients, such requirements do not apply in the U.S. MoCRA does not mandate companies to report ingredient concentrations when submitting product listing information. Because this information is often considered proprietary, it is generally not accessible in any publicly available, searchable databases.

In preparation for this report, the FDA searched for PFAS use concentration information from multiple publicly available sources, including but not limited to: CIR safety assessment reports, scientific publications, raw material suppliers' recommendations and product brochures. For example, the CIR safety assessment for PTFE (Johnson, Bergfeld et al. 2023) reported ingredient use levels in various cosmetic formulations based on the Personal Care Products Council's (PCPC's) industry survey data. The recent scientific publication by Balan et al. (2024) offers reported and recommended concentration ranges for different PFAS in skin care, hair care, and makeup products. Supplier data from some

[44] In Brazil, cosmetics are regulated by the National Health Surveillance Agency (ANVISA) under resolutions such as RDC No. 7/2015 and related guidelines. See https://www.adipec.com.br/assets/pdf/ANVISA-DIRECTIVE-RDC-No7-10-FEBRUARY-2015.pdf (accessed 8/8/2025).

[45] In Canada, cosmetics are regulated by Cosmetic Regulations under the Food and Drugs Act, administered by Health Canada. See https://gazette.gc.ca/rp-pr/p2/2024/2024-04-24/html/sor-dors63-eng.html (accessed 8/8/2025).

[46] EU regulates cosmetics under the Cosmetics Regulation (EC) No 1223/2009, enforced by European Commission and member state authorities. See https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:02009R1223-20250501 (accessed 8/8/2025).

cosmetic companies provide recommended use concentrations for raw materials, noting that the actual concentrations in finished products may vary. These sources collectively were used to inform estimated PFAS concentration ranges in cosmetic products. The five companies that responded to FDA's PFAS in Cosmetics assignment questionnaire provided specific use concentration levels of PFAS in their products.

In general, while the exact concentration data for most PFAS that are reported to be used in cosmetic products are not available to the FDA, the limited information available indicates that PFAS concentrations vary depending on the ingredient and product type among the most frequently used PFAS in the U.S. market. For example, PTFE is used up to 13% in mascara, 12% in eye shadow, and at lower concentrations in other products. Perfluorononyl dimethicone is used in skin care products from 0.006% to 1%, while perfluorohexylethyl triethoxysilane use concentrations range between 0.03% and 0.82%. Some PFAS, such as trifluoropropyldimethyl/trimethylsiloxysilicate, are used at higher levels (2% to 20%) in eyeliners. This is consistent with information provided in Cosmetic Notifications submitted to Health Canada that showed most PFAS-containing cosmetic products (87%) have concentrations at or below 3%, while about 4% contain PFAS above 10% (Health Canada 2025).

The lack of use concentration information presents challenges in estimating consumer exposure to PFAS from the use of cosmetic products and the downstream assessment of the potential health risks associated with their use.

3 Scope of the Report and Methods for Data Collection and Safety Assessment

Scope of the Report

This report provides context and a specific overview of current publicly available data pertaining to the safety of select PFAS used in cosmetic products. The scope of this report does not include PFAS present in the final product as contaminants, but rather focuses on intentionally added PFAS in cosmetic formulations in the U.S., specifically the top 25 PFAS based on their frequency of use. We determined the frequency of use from cosmetic product listing information submitted to the FDA as required by MoCRA. Since the mandatory cosmetic product listing data consists of a significantly larger number of products marketed in the U.S. compared with the VCRP or Mintel's GNPD, it is considered the most comprehensive list of cosmetic ingredients and products in the U.S. Therefore, we relied on the cosmetic product listing data as the basis for selecting and prioritizing the list of PFAS we reviewed for this report.

According to FDA's cosmetic product listing data, the top 25 (out of 51) PFAS all have a frequency of use of 10 products or greater (i.e. used in more than 10 products). Their uses, added together, contribute to 96.02% of all PFAS uses in cosmetic products (**Table 2.1**). The remaining 26 PFAS are each used in 1 to 8 products, making up the rest (~4%) of all PFAS uses. The FDA's current effort in assessing the safety of PFAS use in cosmetic products is limited to the top 25 PFAS identified as the most prevalent. Subsequent evaluation of the remaining PFAS will be conducted as resources permit. It is critical to point out that with increasing compliance with MoCRA regulations, the reported numbers are expected to change over time. The overall trend is anticipated to remain consistent or potentially decline, reflecting growing

global concerns about PFAS safety and tightened state regulations and restrictions on PFAS use in general.

We conducted a safety assessment for each of these 25 PFAS, considering factors including intended applications, toxicokinetics, as well as both systemic and site of contact toxicity. The findings of these reviews are presented in **Appendix 1** in descending order of their frequency of use. Based on the intended uses for each PFAS, consumer exposure pathways evaluated include dermal absorption, incidental ingestion (such as for lip products), incidental inhalation (such as for face powders), and ocular contact (especially with eye makeup), as appropriate.

Methodology on Toxicity Data Collection and Safety Assessment

Collection of Toxicity Data

To ensure that relevant and credible toxicological information was retrieved to the greatest extent, a tiered approach was implemented. Specifically, for each PFAS, we first searched for existing safety assessments performed by government agencies or scientific advisory groups, such as CIR, the Scientific Committee on Consumer Safety (SCCS), and the International Agency for Research on Cancer (IARC). A full list of sources for such assessments is provided in **Table S5**.

Then, we conducted searches of published literature in both PubMed and Web of Science. **Tables S6-S9** outline the literature syntax for obtaining toxicity data on these PFAS. Specifically, for data-rich PFAS such as PTFE, perfluorodecalin and perfluorohexane, the literature search was conducted with individual toxicity endpoints. For PFAS with limited toxicity data like perfluorononyl dimethicone, the literature search was conducted with the chemical name, CAS number and the technical names as key words. In addition, data on toxicokinetics or ADME which provides critical information for risk assessment was also gathered.

In addition, we consulted the ECHA Chemicals Database (ECHA CHEM)[47] if any REACH registration dossier(s) existed for the PFAS under evaluation. It should be noted that REACH dossiers provide only limited publicly available information and the original study reports were inaccessible for FDA's review. Thus, the quality of the data could not be independently and fully evaluated in the preparation of this report.

If no relevant toxicity data was found through any of the above sources, we referred to the Safety Data Sheet (SDS), or Material Safety Data Sheet (MSDS) provided by raw material suppliers (if publicly available) for safety information as a last resort. While these documents often contain information regarding the toxicological endpoints of a substance, it should also be noted that the SDS/MSDS provides only limited publicly available information, and the original study reports were inaccessible to FDA for review. Thus, the quality of the data could not be independently and fully evaluated in the preparation of this report.

Safety Assessment Approach

Based on data availability, we conducted the safety assessment for select PFAS following a tiered approach. Ideally, with sufficient data, we performed a quantitative assessment according to the principles of chemical risk assessment. Briefly, this process includes hazard identification and dose-response assessment (identifying the No Observed Adverse Effect Level, or NOAEL), exposure

[47] ECHA CHEM is a public chemicals database with information from all REACH registrations received by the ECHA. Chemicals can be searched through the link: https://chem.echa.europa.eu/.

assessment (estimating the systemic exposure dose, or SED), and the calculation for a margin of exposure (MOE) (SCCS 2023). This numerical value of MOE represents the ratio between the NOAEL and the SED, indicating whether there is a concern or not for systemic toxicity at the expected human exposure level of an ingredient. An MOE of 100 or greater is generally considered to indicate safe or low risk for cosmetic ingredients, particularly for threshold endpoints including cancer that may occur via a non-genotoxic mechanism of action.

This report evaluates all toxicity endpoints relevant to consumer exposure from the use of cosmetic products. The endpoints assessed include those from systemic effects, such as acute toxicity, repeated dose toxicity, genotoxicity, carcinogenicity, developmental and reproductive toxicity (DART), and other endpoints like neurotoxicity. It also examines local (or site of contact) effects including dermal irritation and sensitization, ocular irritation, respiratory irritation and photo-induced toxicity. In the assessment, we determine the potential exposure pathways based on the product types in which an individual PFAS is used. Dermal contact is expected to be the primary route of consumer exposure since most cosmetic products are applied to the skin. Other routes of exposure may include inhalation through aerosolized sprays like hairspray or face powder, and oral ingestion from lipstick or mouthwash use.

When data is insufficient for a quantitative assessment, we attempted a qualitative safety assessment. In such cases, we used a weight-of-evidence approach to gather available scientific information to categorize potential risks as low, moderate, or high concern.

Finally, if data on a particular PFAS was so limited that neither quantitative nor qualitative assessment was possible, we concluded that the safety of that PFAS use in cosmetic products and the risks associated with such use cannot be determined presently due to lack of data. Across all tiers, consideration of data quality and uncertainty is essential.

Assessments for Individual PFAS

The use and safety information about the 25 PFAS assessed in this report are provided in **Appendix 1**. Each assessment includes a general introduction of the chemical, data that describes its current uses in cosmetic products, and details of available relevant toxicological information. When adequate safety and exposure data were available, a quantitative risk assessment was conducted.

4 Overall Conclusions

Based on the mandatory cosmetic product listing data submitted to the FDA, 51 different PFAS are used in a total of 1,744 cosmetic formulations (as of August 30, 2024). These PFAS are used as ingredients in a variety of cosmetic products due to their unique properties, such as water repellency, smooth texture, and film formation. The primary route of exposure from the use of PFAS-containing cosmetic products is dermal, although inhalation (e.g., from powder or spray formulations), ocular (e.g., eye makeup), and incidental ingestion (e.g., lipsticks) are also possible. The VCRP and Mintel's GNPD suggest that the use of some PFAS in cosmetic products has declined in recent years. However, a definitive use trend cannot be demonstrated at present using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

In this report, we conducted safety evaluations for the top 25 PFAS (out of a total of 51 PFAS) based on their frequency of use in cosmetic products, identified using the mandatory cosmetic product listing information submitted to the FDA. In general, toxicological data for a majority of these PFAS are

incomplete or unavailable. Based on the available toxicological data, our evaluations reveal significant variability in risk profiles depending on the specific PFAS chemical. While 5 of the 25 PFAS evaluated appear to have low safety concerns under their intended conditions of use in cosmetic products, the majority of the PFAS (19/25 or 76%), safety cannot be assessed at present due to lack of critical toxicological data. One PFAS, specifically, perfluorohexylethyl triethoxysilane, was identified as having a potential safety concern, however, significant uncertainties remain due to limited toxicity data on which the conclusion has been based.

Overall, the safety of most of the PFAS reviewed could not be definitively established due to insufficient toxicological data available to the FDA. The FDA will continue to monitor emerging information on the cosmetic use and safety of PFAS.

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6 Appendices

Appendix 1. Safety Assessments for Individual PFAS

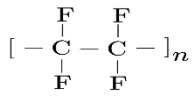
1. PTFE (Polytetrafluoroethylene)

Introduction

Polytetrafluoroethylene (CAS No. 9002-84-0; PubChem SID: 223914423), with an INCI name of PTFE, is a linear fluoropolymer. It is formed by the polymerization of tetrafluoroethylene (TFE). **Table A.1.1** describes the physical and chemical properties of PTFE. PTFE appears as a white translucent to opaque solid in its typical form and has a molecular weight of 400,000 to 10,000,000 Daltons (Da). PTFE is highly thermally stable. Its melting point ranges from 320-330 °C, decomposing only at high temperatures (315-375 °C). It is highly hydrophobic (or water repellant) and is practically insoluble in most known solvents or chemicals (Johnson, Bergfeld et al. 2023).

PTFE is commercially known as Teflon for its use as a non-stick coating for kitchen pots and pans due to its extraordinary performance in terms of heat, chemical and corrosion resistance. It is also widely used in numerous other commodities, including industrial applications, medical devices and consumer products, including cosmetic products, owing to its exceptional chemical resistance, low-friction, oil and water repellence, thermal stability, durability, and biocompatibility (Radulovic and Wojcinski 2024). PTFE has distinct properties from its monomer, tetrafluoroethene, which is a gas at room temperature and highly reactive and flammable.

Table A.1.1. Physical and Chemical Properties of PTFE

Element	Description
Name	Polytetrafluoroethylene
INCI name	PTFE
Synonyms	Politef; Teflon; Tetrafluoroethene Homopolymer; Fluoroflex; Fluoroplast; Ftoroplast; Halon; Polyfene; Tetron; etc.
CAS#	9002-84-0
Structure	
Molecular formula	$(C_2F_4)_n$
Molecular weight	400,000 to 10,000,000 Da
Particle size	100-500 µm (powders)
Physical form	White translucent to opaque solid. Three major forms of PTFE are granular, fine powder and aqueous dispersions (Ebnesajjad 2020)
Density	2.25 g/cm^3 (2.1 – 2.3 g/cm^3)[48]

[48] PTFE (Polytetrafluoroethylene) - Uses, Structure & Material Properties (specialchem.com) (accessed on July 23, 2024).

Solubility	Virtually insoluble in all common solvents including water
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	320-330 °C
Boiling point	NA
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	315 to 375 °C; up to 500 °C to a variety of oxidized product. Burning PTFE releases toxic fumes that may contain a variety of toxic chemicals that cause PTFE fume fever when inhaled by humans (Correia and Horowitz 2024)
Additional properties	Low friction coefficient (static 0.08 and dynamic 0.01)

NA: Not available. Sources: CIR (Johnson, Bergfeld et al. 2023); specified otherwise.

Use in Cosmetic Products

According to INCI, PTFE is used as a bulking agent and slip modifier in a variety of cosmetic products, including but not limited to eye shadows, blushers and rouges, lipsticks, face powders, eye lotions, eyeliners, makeup preparations (not eye), moisturizers, shaving preparations, body and hand preparations, eye makeup preparations, eyebrow pencils, face and neck preparations, foundations, makeup bases, mascara, night skin care preparations, and shaving cream (aerosol, brushless and lather).[49]

Based on mandatory cosmetic product listing data submitted to the FDA, PTFE is currently used as an ingredient in 490 cosmetic products (**Table A.1.2)**. The majority of these products (69%, n=338) are for eye makeup, with eye shadows being the most common (>65%). Please see **Table S2** for a full list of cosmetic product categories. Other eye makeup products include eyelash and eyebrow adhesives, glues, and sealants, mascaras, eyebrow pencils, eyeliners, and eye lotions. Makeup preparations (not eye) contribute to over 23% of products with blushers and rouges being the most prevalent, followed by lipsticks and lip glosses, face powders and foundations. Hair care preparations account for nearly 4% of these products with shampoo and rinses being the most common. Skin care products account for less than 3% of PTFE-containing products, primarily consisting of leave-on face and neck care products. The remaining 1% fall under the category of other preparations (**Table A.1.2**).

Table A.1.2. Frequency of Use of PTFE in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

[49] INCI ingredients. See https://incipedia.personalcarecouncil.org/.

Product Category	Number of Products	Percentage of Total (%)[50]
Eye makeup		
Eye shadows	322	65.7
Eyelash and eyebrow adhesives, glues, and sealants	6	1.2
Mascaras	5	1.0
Eyebrow pencils	3	0.6
Eyeliners	1	0.2
Eye lotions	1	0.2
Eye makeup total	**338**	**69.0**
Hair preparations		
Shampoo	7	1.4
Rinses	5	1.0
Hair conditioners	1	0.2
Other hair preparations, leave-on	5	1.0
Hair preparations total	**18**	**3.7**
Makeup preparations (not-eye) (other than makeup preparations for children)		
Blushers and rouges	48	9.8
Face powders	29	5.9
Foundations, traditional applications	8	1.6
Lipsticks and lip glosses	30	6.1
Makeup preparations (not-eye) total	**115**	**23.5**
Skin care		
Face and neck, leave-on	10	2.0
Moisturizing	2	0.4
Night	1	0.2
Other skin care preparation, leave-on	1	0.2
Skin care total	**14**	**2.9**
Other preparations	**5**	**1.0**

[50] The total numbers for each product may vary due to rounding.

Product Category	Number of Products	Percentage of Total (%)[50]
Grand total	**490**	**100**

Historical data available to the FDA suggests a decreasing trend in the use of PTFE in cosmetic products in recent years. According to the VCRP, PTFE was reported to be used in 249 cosmetic products in the U.S. in 2019, decreasing to 102 in 2021, and 79 in March 2023, prior to the sunsetting of the VCRP (**Table S4**). Information obtained from Mintel's GNPD corroborated this finding. In Mintel's GNPD, there were 222 PTFE-containing cosmetic products that entered the U.S. market over a 5-year period (August 2019 to July 2024), compared to only 4 between August 2023 and July 2024 (**Table S4**). The use trend of PTFE cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for PTFE is not available to the FDA. However, according to the CIR Assessment (Johnson, Bergfeld et al. 2023), PTFE is used at concentrations up to 13% in all leave-on products (mascara), up to 12% in leave-on dermal products (eye shadow), and up to 2.4% in rinse-off products (hair bleaches). In addition, PTFE was reported to be used at approximately 0.005% in a retinol moisturizer and eye cream, and 0.01% in a regenerating cream from one manufacturer, according to a recent FDA survey.

Based on the product types that contain PTFE as an ingredient, ocular exposure to PTFE may occur from its use in products used near the eye, e.g., eye shadow, mascara, eyelash and eyebrow, and other eye makeup preparations. Similarly, mucous membrane exposure and incidental ingestion may occur from PTFE use in lipsticks and lip glosses. In addition, incidental inhalation exposure to PTFE is also possible from its use in face powder formulation. As such, effects relevant to ocular, incidental ingestion, and inhalation exposure will be assessed. Exposure assessment will be performed based on the amount of use of the products containing PTFE, the frequency of use,[51] and the concentration use of PTFE as mentioned above.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

To evaluate the current state of knowledge regarding the safety of PTFE in cosmetic products, we conducted a comprehensive review of existing assessments published by domestic and international government agencies and assessments done by scientific advisory groups such as SCCS, CIR, and IARC as outlined in **Table S5.** We identified several relevant evaluations, including those by CIR and IARC.

The CIR reviewed the safety of 12 polyfluorinated polymers, including PTFE, in cosmetic products in 2018 and published their review report in 2023 (Johnson, Bergfeld et al. 2023). They concluded that PTFE is safe in cosmetics in the present practices of use and concentration. IARC, which is a part of the

[51] The product use amount and frequency of use information will be obtained from the SCCS Note of Guidance document: https://health.ec.europa.eu/document/download/32a999f7-d820-496a-b659-d8c296cc99c1_en?filename=sccs_o_273_final.pdf (see also the citation SCCS 2023).

World Health Organization (WHO), evaluated the available data relating to carcinogenicity of PTFE in 1979 and determined that the evidence was insufficient to assess the carcinogenic risk from exposure to PTFE in humans (IARC 1979).

In addition to published literature, we also independently reviewed and summarized studies cited in both the CIR Assessment and IARC Monograph, if deemed appropriate, for inclusion in the following sections.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S6** identified 1,934 publications (searched on 4/22/2024). After title and abstract screening, we identified 31 articles with relevant information on PTFE ADME. Following full text reviews, we deemed 25 publications to be relevant to the ADME of PTFE. Among these 25 publications, two were pharmacokinetic/toxicokinetic studies of PTFE in lab animals, and the rest were studies using radioactive labeled PTFE particles for tests of lung functions and particle deposition.

In one study (Miyakita and Puri 1994), 0.5 mL PTFE paste was administered to mini pigs and dogs through subureteral, intravenous (IV), or intra-arterial injection to investigate the migration of PTFE particles to the lungs and brain. The potential presence of PTFE in lung or brain tissues was determined by histological examination, polarized light microscopy, scanning electron microscopy, and x-ray microanalysis. From this study, PTFE was found only in lung tissues following IV administration, indicating that venous blood returns to lungs carrying PTFE. The presence of PTFE in brain tissues was only seen in animals with PTFE paste injected into the carotid artery which supplies blood to the brain. No PTFE was identified in tissues from animals that underwent subureteral injection. While these administration routes, i.e., IV and intra-arterial injection, are irrelevant to the exposure of cosmetic ingredients, the results provide useful information for PTFE distribution after entering the bloodstream and suggest that the distribution of PTFE to lungs and brain were through the direct blood supply.

Another study reported the pharmacokinetics of PTFE particles in female and male ICR mice (Lee, Kang et al. 2022). Two different sizes of PTFE particles, approximately 5 μm and 10-50 μm, were used for a single dose oral administration in mice. Blood samples were collected at 15, 30, 60, and 120 minutes and analyzed for the presence of PTFE particles. PTFE was not detected in any of the blood samples using Raman spectroscopy analysis, suggesting that the oral absorption of PTFE particles is very low. It is well known that the absorption and distribution of microplastics highly depends on particle size. According to the method of manufacture as summarized in the CIR Assessment (Johnson, Bergfeld et al. 2023), the average particle size of PTFE is 5.58 μm after micronized with jet mill (Oberdorster 2000, Prata 2023). The particle size of PTFE used in this study is close in size to that used in cosmetic products, and therefore, results indicate that the absorption of PTFE particles is low through oral exposure from cosmetic products.

In addition to pharmacokinetic studies, radioactive-labeled PTFE particles have been used to identify the deposition, lung retention and clearance of inhaled particles in animal studies as well as clinical applications. The regional deposition was estimated by measuring the gamma counts after exposure to radioactive-labeled PTFE particles. From these studies, experimental conditions, such as particle sizes (Svartengren, Linnman et al. 1987, Camner, Anderson et al. 1997, Philipson, Falk et al. 2000), the flow rate for inhalation exposure (Falk, Philipson et al. 1999, Svartengren, Sommerer et al. 2001), and physiological parameters such as the forced expiratory volume (Svartengren, Hassler et al. 1986) were

determined to have impacts on the disposition, retention, and clearance of PTFE particles. In contrast, some particle materials such as PTFE versus iron oxide (Stahlhofen, Gebhart et al. 1981), and some exposure devices including the elongated mouthpiece (Svartengren, Anderson et al. 1996) did not have impacts on particle disposition and clearance. Furthermore, people with some diseases and health conditions, including asthma (Svartengren, Lindestad et al. 1994, Svartengren, Lindestad et al. 1995, Svartengren, Philipson et al. 1996, Svartengren, Svartengren et al. 1999), bronchitis (Ericsson, Svartengren et al. 1995, Svartengren, Svartengren et al. 2004) and bronchoconstriction (Svartengren, Philipson et al. 1986, Svartengren, Philipson et al. 1989), have slower clearance and longer retention of PTFE particles. These studies may help to better understand the distribution of PTFE particles in lungs through inhalation exposure.

In summary, available studies showed limited absorption of PTFE through different exposure routes such as subureteral, IV and intra-arterial injection. The animal study with oral administration indicated low absorption of PTFE through oral exposure. In addition, we located no inhalation or dermal exposure PK studies from the literature search.

Hazard Assessment

We conducted a literature search on the acute and repeated dose toxicity of PTFE using the queries outlined in **Table S6**. The search yielded a total of 1,121 publications. After an initial title and abstract screening, 29 were considered relevant. Twenty-five of the 29 articles were confirmed to be relevant following full reviews of the texts. We reviewed and summarized these studies in the following sections. We did not identify a REACH dossier for PTFE in the ECHA database (searched on 4/22/2024).

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

We did not identify any published data regarding the acute toxicity of PTFE resulting from acute dermal exposure. However, according to an unpublished study cited in the CIR Assessment (Johnson, Bergfeld et al. 2023), PTFE powder (0.5 g) applied to abraded and intact skin of the trunk of 6 New Zealand White rabbits for 24 hours did not cause lethality of the animals or produce clinical signs or behavioral alteration during the course of the study.

Oral

The acute toxicity of PTFE microplastics was evaluated in ICR mice following OECD guideline 423[52] (Lee, Kang et al. 2022). Six-week-old specific-pathogen-free ICR mice (3/group/sex) were treated with a single oral dose of two sizes of PTFE microplastics, approximately 5 µm (6.03 ± 2.10 µm) and 10 – 50 µm (31.65 ±5.64 µm), prepared from PTFE raw materials (TF1641, Dyneon™). A total of four doses were given including control (corn oil), low-dose (500 mg/kg), mid-dose (1000 mg/kg), and high-dose (2000 mg/kg) of PTFE microplastics suspended in corn oil. After 2 weeks of observation following PTFE microplastics administration, no morbidity or death in mice was observed and no specific clinical symptoms were

[52] OECD Test No. 423: Acute Oral toxicity. https://www.oecd-ilibrary.org/environment/test-no-423-acute-oral-toxicity-acute-toxic-class-method_9789264071001-en.

recorded. In addition, no exposure-associated body weight changes or macroscopic changes were noted upon necropsy. Therefore, the study authors determined that the LD_{50} (median lethal dose) was 2000 mg/kg or greater.

In addition, according to the manufacturer's material SDS, the LD_{50} of PTFE fine powder is >11,280 mg/kg in rats (Chemours 2017). No details on how this LD_{50} was obtained are available.

Inhalation

No data.

In summary, acute toxicity studies of PTFE microplastics or fine powder have limited relevance to cosmetic products safety due to differing exposure routes (ingestion vs. skin contact), exposure duration (short vs. daily), and dosages (low vs. high). Nevertheless, these studies suggest low risk of acute toxicity from PTFE in cosmetic products, supported by the high LD_{50} values observed in animals.

Repeated Dose Systemic Toxicity

Dermal

No data.

Oral

The subacute toxicity of PTFE microplastics was evaluated in ICR mice in a 4-week repeated oral dose toxicity study, conducted with reference to OECD guideline 408 as noted by the study authors[53] (Lee, Kang et al. 2022). It should be noted that OECD 408 is designed for 90-day studies, while this study was conducted for 28 days. Six-week-old specific-pathogen-free ICR mice (5/group/sex) were orally dosed with PTFE microplastics of approximately 5 µm (6.03 ± 2.10 µm) and 10 – 50 µm (31.65 ± 5.64 µm), respectively. Each animal received either corn oil (vehicle control), low-dose (500 mg/kg), mid-dose (1000 mg/kg), or high-dose (2000 mg/kg) of PTFE microplastics suspended in corn oil once daily for 4 weeks. Upon conclusion of the study, no significant differences were observed in clinical signs, body weight, organ weight, water and food consumptions, macroscopic examination at necropsy, or clinical and histopathological changes upon examination. A no observed adverse effect level (NOAEL) for PTFE microplastics in ICR mice could not be established as no effects were seen even at the highest dose (2000 mg/kg). The actual NOAEL is expected to be higher than 2000 mg/kg which in general indicates low toxicity concern. Using this hypothetical mouse NOAEL, the authors estimated the human NOAEL to be 160 mg/kg (or 9.6 g per day) or higher for an adult with a body weight of 60 kg.[54]

In another subacute study, the potential for PTFE microplastics to cause immunotoxicity was evaluated in a subacute study on mice (Jo, Acharya et al. 2023). Six-week-old ICR mice, 4/group/sex, were treated via gastric intubation with two different sizes of PTFE microplastics (MPs) (6.0 ± 2.1 µm or 30.5 ± 10.5 µm) at 0 (corn oil vehicle control), 500, 1000, or 2000 mg/kg bw/day once daily for 4 weeks. Subacute oral

[53] Note: the author of the publication provided that the OECD Test No. 408 was followed: Repeated Dose 90-Day Oral Toxicity Study in Rodents. https://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents_9789264070707-en.

[54] Human equivalent dose calculation can be found in Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. https://www.fda.gov/media/72309/download (accessed 6/21/2024).

exposure to either sizes of the PTFE microplastics did not affect major thymic or splenic immune cell populations, including thymic $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ T lymphocytes, and splenic helper T cells, cytotoxic T cells, and B cells. The ratio of interferon-gamma (IFNγ) to interleukin-4 (IL-4) in culture supernatants from polyclonally activated splenic mononuclear cells ex vivo (48 hour) was dose-dependently decreased in female mice that received small- and large-size PTFE microplastics. The serum IgG2a/IgG1 ratio was dose-dependently increased in female animals dosed with large-size PTFE MPs, and in male animals dosed with small-size PTFE microplastics. These observations indicate PTFE microplastics could disturb immune homeostasis leading to imbalance between type I and type 2 immune responses. The consequence of such an imbalance was not stated. An *in vitro* study appears to provide supporting evidence that PTFE may affect immune response (Ding, Sun et al. 2009). In this study, PTFE treatment of lipopolysaccharide (LPS, a potent activator of monocytes and macrophages) stimulated macrophages isolated from young male SD rats resulted in increased production of tumor necrosis factor-alpha (TNF-α) and IL-1β compared with untreated control. In addition, PTFE treatment increased monocyte chemoattractant protein-1 (MCP-1), also known as C-C motif chemokine ligand 2 (CCL2) that regulates migration and infiltration of monocytes/macrophages, in human umbilical vein endothelial cells cultured in macrophage supernatant containing TNF-α and IL-1β.

In a subchronic dietary study, male and female rats (strain and number per group were not specified) were fed a diet containing 25% of three types of PTFE resin for up to 90 days (Clayton 1967). No toxicologically significant effects were observed on growth rate, behavior or microscopic evidence of tissue damage, other than a slight shift in the distribution and number of white blood cells. In addition, an increase in the relative size of the liver (relative to body weight) was seen in one group of rats fed with unsintered PTFE resin, without any histological abnormality. This study determined that the increase in liver weight was due to the presence of a dispersing agent in the test materials (Haskell Laboratories 1968).

In non-rodent species, a feeding study conducted on gastropods *Littorina brevicula* (a type of mollusk) aimed to study the effects of different-sized microparticles of plastic PTFE (0.1-10 µm) fed to mollusks for 7 days. The PTFE did not cause visible changes to their feeding behavior and activities (Chelomin, Slobodskova et al. 2023). While the experimental model is not directly relevant to the human body, the cellular-level findings from this study provided some mechanistic information for PTFE (discussed below under the "Genotoxicity" section).

Inhalation

Occupational exposure to PTFE has been reported to be linked with granulomatous lung disease due to inhalation of PTFE aerosols (Choi, Jung et al. 2014, Lee, Baek et al. 2018, Aoki, Saito et al. 2022).

In a spray inhalation study, rats (n=4) were exposed to 20% PTFE dispersion in $CCl_2F\text{-}CClF_2$ from a pressurized container. Exposure occurred 3 times/day for 9 days, with each session lasting 15 minutes in a sealed jar. A total of 26 exposures were administered. While rats exhibited symptoms of incoordination, labored breathing, and nose irritation during exposure, these effects were attributed to the propellants and dispersing agent (not specified), and they recovered immediately after exposure. No pathological changes linked to PTFE exposure were observed (Clayton 1967).

Of note, acute lung toxicity resulting from exposure to PTFE fumes has been documented. The conditions are commonly known as polymer fume fever or "Teflon flu" when PTFE is heated to higher temperatures causing it to release toxic fumes (Sajid and Ilyas 2017, Correia and Horowitz 2024). Almost all reports of

polymer fume fever were related to occupational exposure typically involving the heating of PTFE to high temperatures. Thus, it is extremely unlikely that this condition could occur from the typical use of PTFE-containing cosmetic products.

Other Routes of Exposure

Studies in animal models and clinical case reports associated with medical and surgical procedures involving PTFE injection or implantation have revealed that PTFE can incite persistent chronic inflammatory response in multiple organ systems, known as foreign-body granulomatous reaction, resulting in what is commonly referred to as a Teflon granuloma or "teflonoma." While Teflon granulomas are a concern in medical applications involving the injection or implantation of PTFE, they are deemed not relevant to the typical cosmetic use of PTFE by consumers. The risk of developing granulomas from using PTFE-containing cosmetic products is extremely low due to the differences in exposure routes and application methods.

Clinical cases of Teflon granulomas have been reported following endolaryngeal injection of Teflon paste for treating dysphonia, subureteral PTFE injection for vesicoureteral reflux treatment in children, and microvascular decompression using Teflon implants (Benjamin, Robb et al. 1991, Aragona, D'Urso et al. 1997, Deep, Graffeo et al. 2017, Rojas-Villabona, Magnaye et al. 2021). Relevant available studies in animal models are briefly summarized below.

An animal study was performed to evaluate the long-term histopathologic effects of injected PTFE particulates, specifically Polytef Paste brand PTFE, which has been used in patients suffering from recurrent urinary incontinence (Kossovsky, Millett et al. 1991). Four animal groups, each consisting of two mongrel dogs, five New Zealand White rabbits and 10 BALB/c mice, were injected with PTFE (1:1 ratio of Polytef and glycerine) and followed for 1 week, 3 months, 6 months, and 1 year periods. The injection sites (and injection volumes) of the mice, rabbits, and dogs were dorsal skin (0.05 ml), subareolar area (0.25 ml), subareolar area (0.5 ml) and/or periurethral tissue (0.1 ml), respectively. In all three animal species, histologic examination suggested initial acute inflammation consisting of necrosis and primarily neutrophil infiltration after 1 week, and persistent chronic inflammation with macrophages, giant cells and lymphocytes through 3 months to 1 year. Plasma cells were also noted in rabbits. The purity and particle size of PTFE are not provided in this article.

A study using C57BL/6 mice compared the induction of neutrophils, monocytes and macrophages recruitment (characteristics of acute inflammation) by six types of biomaterials, including PTFE, used in prosthetic implants (Busuttil, Drumm et al. 2005). In this study, these biomaterials, in the form of circular disks with a diameter of 12.7 mm and a thickness of 0.127 mm (5/1000 of an inch), were surgically implanted into the peritoneum. A non-surgical control and a sham control (mice underwent surgery without disk implantation) were also included. Mice were euthanized at 18 hours after surgery, and the recruitment of inflammatory cells was monitored. PTFE induced a substantial and similar inflammatory response as polyethylene terephthalate, titanium, and aluminum. In contrast, stainless steel induced a significantly less inflammatory response, while copper incited an overwhelming and fatal response.

Genotoxicity

Genotoxicity comprises all the potential mechanisms by which the DNA and its sequence can be damaged or altered. It is considered an important factor in evaluating the carcinogenicity potential of a

substance and its corresponding mode of action. We conducted a PubMed and Web of Science literature search of the genotoxicity potential of PTFE using the query syntax outlined in **Table S6**. The search yielded a total of 63 publications. After an initial title and abstract screening, we identified two publications, including one research article and one review article, as relevant to the current review. Most of the excluded articles were not studies on PTFE.

In one study (Chelomin, Slobodskova et al. 2023), the authors investigated the formation of oxidative stress and genotoxicity from exposure to microparticles of polymethylmethacrylate (PMMA) and PTFE. DNA damage was detected in the PMMA feeding group but not in the PTFE feeding group. There was also no accumulation of lipid peroxidation product malondialdehyde (MDA) or protein peroxidation product protein carbonyls (PC) in the PTFE-feeding group, indicating a lack of reactive oxygen species (ROS) generation and oxidative stress. These findings suggest that PTFE is devoid of genotoxicity in this experimental system. Although the dietary exposure model in this study is different than that of human exposure from cosmetics, the cellular response of the digestive tract to PTFE particle exposure may provide information for future studies in other biological systems. It should be noted that there was no positive control in any of the experiments in this study to demonstrate its reliability.

In another study, Henry et al. reviewed three standardized genotoxicity studies (an Ames bacterial mutagenesis assay, a mouse lymphoma assay, and an *in vivo* micronucleus study) that were performed with extracts of PTFE device (Henry, Carlin et al. 2018). In these studies, PTFE in three physical forms including ePTFE patch, fiber, and tube were extracted in polar and nonpolar solvents. None of the extracts showed genotoxic potential. Based on the negative response of PTFE in a series of toxicology studies and using PTFE as an example, the authors suggested that PTFE, among many other fluoropolymers, be considered as "polymers of low concern."

In a CIR Assessment (Johnson, Bergfeld et al. 2023), the genotoxic potential of anti-cohesive coating materials containing PTFE (60%-73%) was evaluated. The materials were considered negative in an Ames test and in an *in vivo* micronucleus test dosed by gavage. Details of the studies are not described in the CIR Assessment. The original study article is also not available for review.

In summary, a limited number of studies have examined the genotoxicity potential of PTFE, and the current evidence suggests that PTFE is not genotoxic.

Carcinogenicity

To identify relevant studies on the carcinogenic potential of PTFE use in cosmetic products, we conducted a literature search using the queries described in **Table S6**. This search yielded 518 articles. To select pertinent studies, we applied inclusion criteria such as PTFE as the testing substance, carcinogenicity endpoint, and relevant exposures (including dermal, oral, or inhalation), and excluded articles that used substances other than PTFE, investigated irrelevant endpoints, or involved irrelevant exposures.

After an initial review of articles by titles and abstracts, followed by a review of full texts, we identified four articles including two research publications, the 2023 CIR Assessment and the 1979 IARC Monograph as relevant to the current review.

Notably, both the CIR Assessment (Johnson, Bergfeld et al. 2023) and the IARC monograph (IARC 1979) have sections dedicated to PTFE carcinogenicity and cite nearly identical studies to evaluate the

carcinogenic potential of PTFE in mice and rats. Therefore, all the referenced studies cited by these two reports are included for review in this section. Studies focused on using PTFE implants for medical purposes to treat diseases, rather than investigating the carcinogenicity of PTFE, were excluded. We attempted to obtain and review the original reports. When these were unavailable, we relied on the summaries from the CIR Assessment and/or the IARC Monograph.

We reviewed those select studies in the CIR Assessment and IARC Monograph to evaluate the carcinogenicity potential of PTFE and categorized them by different exposure routes, including dermal, oral, subcutaneous, intraperitoneal, subcutaneous and submucosal injection, and inhalation.

Dermal

No data.

Oral

No data.

Subcutaneous

For the subcutaneous carcinogenicity of PTFE, multiple studies were conducted by testing various forms and sizes of PTFE subcutaneously implanted in mice and rats. Relevant information was also extracted and summarized in **Table A.1.3**.

The studies employed various strains of mice (including Swiss, C57BL, CTM albino, BALB/c, C3Hf/Dp and C57BL/He) and rats (Wistar, Evans and Sprague Dawley) and included either male, female, or both genders to assess carcinogenic potential of subcutaneously implanted PTFE.

Five studies in mice showed the development of either fibrosarcomas or sarcomas at or around the implant sites, ranging from 2% up to 98% of tumor incidence (Tomatis 1963, Tomatis and Shubik 1963) (Tomatis 1966, Tomatis and Parmi 1971, Menard and Porta 1976).

Four carcinogenicity studies of PTFE were conducted in different strains of rats, including Wistar, Evans, and Sprague Dawley implanted with PTFE subcutaneously. Three studies showed the occurrence of sarcomas, ranging from 3.6% to 26.7% of tumor incidence (Oppenheimer, Oppenheimer et al. 1953, Oppenheimer, Oppenheimer et al. 1955, Russell, Simmers et al. 1959). The fourth study did not show any tumors in PTFE implanted rats (Bryson and Bischoff 1969). Oppenheimer et al. suggested that the risk of carcinogenesis is reduced by perforated PTFE compared to non-perforated (smooth continuous surface) PTFE (Oppenheimer, Oppenheimer et al. 1955). However, the reasons were not specified (**Table A.1.3**).

Table A.1.3. Carcinogenesis of Subcutaneously Implanted PTFE in Animals.

Animals & Test Substances	Methods	Results	Citation(s)*
• 89 random-bred female Swiss mice • Square sheet of PTFE (12 x 12 x 1.2 mm)	PTFE was implanted subcutaneously in the left flank of 7–9-week-old mice. Survival rate was recorded every 10 weeks up to 100 weeks after implantation and any	Out of 89 mice, a total of 11 (12.5%) sarcomas at implant site was found after an average latent period of 54.5 weeks. The first local tumor developed 25 weeks after implantation.	(Tomatis and Shubik 1963)

Animals & Test Substances	Methods	Results	Citation(s)*
	formation of sarcomas at implant site was evaluated.		
• Random-bred Swiss mice • A variety of PTFE implants were used, including: 1) square sheets measuring 12 x 12 x 1.2 mm (89 females, 61 males); 2) 15 mm diameter discs (103 females); 3) fragments of discs (size unspecified) (53 females); 4) 20 mm diameter discs (54 females, 50 males); and 5) a combination of a 15 mm disc and a square PTFE implant (21 females)	7–9-week-old mice received subcutaneous PTFE implants.	Tumors (all fibrosarcomas) developed around the implant. Tumor incidences are 8/89 (10%) and 1/61 (2%); 23/103 (22.7%); 10/53 (21.2%); 7/54 (15.2%) and 4/50 (8%); and 3/21 (16.3%) in the groups described in the first column, respectively. No tumors were observed in 200 female and 100 male mice (untreated group).	(Tomatis 1963)
• Inbred C57BL mice (19 males and 27 females) • PTFE disc (15 x 1.2 mm)	7–9-week-old mice received subcutaneous PTFE disc implants and were observed for 90 weeks.	Local sarcomas developed in 4 out of 20 (20%) females that retained the implant and 4/15 (26%) males. Tumors were always found around the discs. No sarcomas were found in 30 male and 33 female non-implanted mice (control group) that were observed for 100 weeks.	(Tomatis 1966)
• Random-bred CTM albino mice (40 males and 40 females) • PTFE disc (15 x 1.2 mm)	8-week-old mice received subcutaneous PTFE disc implants into the right flank and were observed for lifespan.	Of the 80 mice, 27 mice (18 females and 9 males) developed sarcomas around the disc, corresponding to an incidence of 39% of the 69 survivors at the time of the appearance of the first tumor. No fibrosarcomas were found in 99 male and 98 female untreated mice (control group) that were observed for lifespan.	(Tomatis and Parmi 1971)
• BALB/c mice (38 females), C3Hf/Dp mice (38 females) and C57BL/He mice (39 females) • PTFE disc (15 x 1. 2 mm)	Three groups of 6–7-week-old mice received subcutaneous PTFE disc implants in the dorsal area. All mice were euthanized at 120 weeks of age.	Fibrosarcomas developed around the discs in 17/38 (44%) BALB/c, 36/38 (94%) C3Hf/Dp and 12/39 (30%) C57BL/He mice. The mean latent periods for tumor development were 78, 61, and 82 weeks, respectively.	(Menard and Porta 1976)
• Rats (strain and number not specified) • PTFE film (not specified)	Rats received subcutaneous PTFE film implants.	Malignant tumors (all sarcomas) were produced adjacent to or surrounding the PTFE film. Four sarcomas were produced, at which time 15 rats were still alive. It needs to be noted that the study was published with the results from experiments still in progress.	(Oppenheimer, Oppenheimer et al. 1953)

Animals & Test Substances	Methods	Results	Citation(s)*
• 65 Wistar rats (males and females) • PTFE implant (4 x 5 x 0.16 mm)	Rats received single subcutaneous PTFE implants in the abdominal wall. All rats were euthanized within 800 days after the operation.	Fifty-five rats were alive at the time of appearance of first tumor (i.e., 659 days). Two sarcomas were induced. No tumors were developed in control animals that received glass implants.	(Russell, Simmers et al. 1959)
• Wistar rats (2 groups) • PTFE disc (15 x 0.02 mm, 2 types; plain and perforated)	Rats received subcutaneous plain or perforated PTFE disc implants in the abdominal wall.	34 rats implanted with plain PTFE discs and 32 rats implanted with perforated discs survived the minimum latent period. The groups developed 8 sarcomas (23.5%) and 6 sarcomas (18.8%), respectively. Control groups were imbedded with various nonplastic materials. Among the completed controls (linters, surgical cotton, tin foil, glass coverslip and glass textile), only the glass coverslip control group developed one tumor in one rat out of fifty.	(Oppenheimer, Oppenheimer et al. 1955)
• Evans rats (males) • PTFE mesh surgical outflow patch (square, 20 x 20 mm) (39 rats) • PTFE shredded material (40 rats) • Control (41 rats)	Rats received subcutaneous PTFE patches or shredded PTFE implants. Experiment was terminated 19 months after implantation.	At 19 months after implantation, no local tumors were observed. 28 controls, and 24 and 23 PTFE implanted rats were still alive.	(Bryson and Bischoff 1969)

*All studies are cited in CIR 2023 and IARC 1979.

Intraperitoneal

In one study (Simmers, Agnew et al. 1963), weanling Wistar rats of approximately equal numbers of males and females were implanted intraperitoneally with either rectangular rods of PTFE measuring 10 x 2 x 2 mm (16 rats) or an equal amount of PTFE powder (17 rats). After 1 year, 10 out of 17 rats (treated with PTFE powder) and 13 out of 16 rats (implanted with PTFE rods) were still alive. Surviving rats were euthanized 27 months after operation. No tumors were observed in PTFE rod implanted rats whereas 2 intraperitoneal sarcomas (20%) were induced and became palpable in PTFE powder treated rats at 354- and 476-days post operation. Rats developed extraperitoneal tumors in 3 of 10 (30%) of the powder-treated, and 1 of 13 (7.7%) of the rod-treated groups. In the control group, 2 of 21 (9.5%) rats developed extraperitoneal tumors, while no intraperitoneal tumors were observed (Simmers, Agnew et al. 1963). While these findings suggest that the powder form of PTFE may increase the risk of carcinogenesis at the injection site, the cancer hazard of surgically implanted PTFE is minimal.

Subcutaneous and Submucosal Injection

In one study, Dewan et al. (1995) reported a long-term histological response to a single dose of subcutaneously injected Polytef (a commercial name of PTFE) in rats. Forty-eight infant Sprague Dawley rats (gender unspecified) were injected with 0.1 mL of Polytef, consisting of 50% PTFE particles of which 90% were less than 40 µm in diameter under the skin of the back. Rats were euthanized after 2 years of

injection. At least one tumor was found in 30 (63%) of the 48 Polytef-injected rats and 36 (75%) of the controls. Most of the tumors were breast and pituitary adenomas. The Polytef-injected group had 15 (31%) breast and 18 (38%) pituitary adenomas; the control group had 27 (56%) breast and 20 (42%) pituitary adenomas. No tumors were found at the injection site and no sarcomas were observed in either group. There was no significant difference in the tumor incidence between the PTFE-injected and control groups. The authors concluded that the carcinogenic risk from injected PTFE is low (Dewan, Owen et al. 1995).

A long-term animal study was conducted to histologically evaluate the potential for submucosal PTFE paste injection to induce bladder neoplasia in rats (Noe, Williams et al. 1994). Sixteen young adult female Sprague-Dawley rats were injected with 0.1 to 0.2 ml of PTFE paste into bladder submucosa. Four control rats were injected with equal amount of sterile saline. The animals were euthanized at various intervals: 3 at 3 months, 2 at 6 months, 3 at 9 months, 4 at 12 months, and 4 at 15 months. One control animal was euthanized at 6 months, and the remaining 3 were euthanized at 15 months post-surgery. Gross necropsy revealed no evidence of adenopathy or granuloma formation or tumor development. Histological examination showed chronic inflammation at 3 months and fibrous encapsulation with presence of chronic inflammatory cells at 6 months and later. There was no evidence of epithelial or sarcomatous tumors in any of the experimental or control animals.

Inhalation

No inhalation carcinogenicity studies of PTFE were found in the literature search. PTFE dust has been detected in workplace environments during the thermal processing of fluoroplastics (Okawa and Polakoff 1973, Okawa and Polakoff 1974). As described in the repeated dose toxicity section of this report, several studies reported that occupational exposure to PTFE aerosols by inhalation may have a link with granulomatous lung disease in humans (Choi, Jung et al. 2014, Lee, Baek et al. 2018, Aoki, Saito et al. 2022).

The National Toxicology Program (National Toxicology Program 1997) investigated the carcinogenicity of TFE, the monomer used to synthesize PTFE and found that inhalation exposure to TFE induced tumors in both mice and rats. However, according to the current production methods, trace levels of TFE in PTFE are not detected (detection limit: 75 ppb). Therefore, TFE is unlikely to pose a concern for consumers who use PTFE-containing cosmetic products.

In summary, available studies have not demonstrated a carcinogenic potential for PTFE when exposed through dermal, oral, or inhalation routes. While some studies found that subcutaneous PTFE device implants in mice or rats led to sarcomas at the implant site, some other studies suggested a low cancer risk from subcutaneous or submucosal injection exposure. It is important to note that most of the studies were published between the 1950s and 1970s, and no recent studies could be located. Additionally, the findings from these studies, while informative for surgically implanted PTFE devices, may not be directly applicable or relevant to the use of PTFE in cosmetic products, due to the differences in PTFE forms and exposure routes.

Developmental and Reproductive Toxicity (DART)

The PubMed and Web of Science literature search on DART using the queries outlined in **Table S6** yielded a total of 31 publications. After an initial abstract screening, we identified two publications (one technical report by CIR and one review article by Henry, Carlin et al. (2018)) as relevant to assessing the

DART endpoints of PTFE. Most of the excluded articles are not toxicity studies or on the subject of PTFE toxicity.

The CIR safety assessment of polyfluorinated polymers as used in cosmetics (Johnson, Bergfeld et al. 2023) cited an abstract that reported a toxicity study on PTFE containing anti-cohesive coating materials (containing 60% or 68-73% PTFE). The materials were administered by gavage once daily on gestation days 7–16 at a dose of 6.25 g/kg (60% PTFE) and at a dose of 1.25 g/kg (68 to 73% PTFE) in rats. The CIR concluded that this study indicated that both PTFE materials were found to be non-teratogenic. However, the original abstract was not accessible for review by the FDA. The review article (Henry, Carlin et al. 2018) stated that patients receiving permanently implanted PTFE cardiovascular medical devices demonstrate no reproductive, developmental, or endocrine toxicity. However, no clinical or experimental data were provided in this article to support the author's statement.

In summary, based on very limited information summarized in review articles, there is no evidence of reproductive or developmental toxicity of PTFE in experimental animals or in humans.

Neurotoxicity

A PubMed and Web of Science literature search for neurotoxicity using the queries outlined in **Table S6** yielded a total of 444 publications. After title and abstract review, we did not find any studies to be directly relevant to assessing the neurotoxicity of PTFE. Most PTFE-related studies on neurological systems focus on the efficacy of PTFE coated medical devices or ePTFE material used in neurosurgery, which are not applicable to PTFE use in cosmetic products. Below, we reviewed and summarized two studies that reported the neural responses in animals exposed to these materials .

Cunningham, Hallab et al. (2013) investigated the neural responses to epidural application of PTFE particulate wear debris (0.1–50 μm in diameter) produced from spinal instrumentation. In this study, New Zealand White rabbits were exposed to PTFE particles implanted directly onto the dura, creating interlaminar exposure of the dural sac. After 3 or 6 months, the animals were evaluated for neural and systemic histopathological responses. A chronic histiocytic reaction localized primarily within the epidural fibrous layers was observed. However, no evidence of polymorphonuclear giant cell reaction or other significant pathological changes was noted. Particulate debris remained localized to the epidural application site without intrathecal dissemination. Histopathologically, PTFE particles exhibited pronounced agglomeration. The authors concluded that there was no evidence of an acute neural or systemic histopathological response following exposure (Cunningham, Hallab et al. 2013).

Kim et al. (2011) conducted an *in vivo* study to evaluate the biocompatibility and degradation profile of a biomaterial in the rat spinal cord. ePTFE was used as a control material due to its non-degradable nature. Both materials were implanted in the intrathecal space, between the spinal cord and dura mater, and monitored for 6 months. Results showed no degradation of ePTFE, a minor foreign body response, and no chronic inflammatory response in the central nervous system tissue (Kim, Tator et al. 2011).

In summary, a comprehensive literature search did not identify evidence of neurotoxicity associated with PTFE. Given its widespread use as an implant device in neurosurgery and its inert nature, PTFE's neurotoxicity potential from cosmetic application is expected to be minimal.

Site of Contact Effects:

Dermal Irritation and Sensitization[55]

A PubMed and Web of Science literature search on dermal irritation and sensitization using the queries outlined in **Table S6** yielded a total of 274 publications. After title and abstract review, we did not find any studies to be directly related to assessing the skin irritation and skin sensitization of PTFE. Many articles focus on the use of PTFE material in healthcare products such implants and grafts, or the use of PTFE material in non-healthcare related products such as filters and ear-piercing tubes. These studies are not relevant to skin sensitization and are not applicable to PTFE use in cosmetics. We deemed a few articles relevant to skin sensitization and skin irritation from the use of PTFE as a device or instrument material. Since the articles mentioned dermatitis or hypersensitivity, this can be considered as indirect evidence supporting that PTFE is unlikely to be a skin irritant or skin sensitizer, even though the exposure scenarios are not directly related to cosmetic use and no specific tests for sensitization or irritation were performed.

In these publications, PTFE was widely used for different purposes in the medical field, including as a coating material on medical devices (Ishii, Kodani et al. 2006, Tamenishi, Usui et al. 2008, Taguchi, Maeba et al. 2014, Vodiskar, Schnoring et al. 2014), a liner (Hamilton and Adkinson 1997), or an implanting or grafting material (Trumpy, Roald et al. 1997, Iqbal, Bhandare et al. 2019), due to very low risk of contact dermatitis and to prevent contact dermatitis caused by components of the devices. It was also used as negative controls in studies on subcutaneous tissue or bone tissue, which did not cause hypersensitization or other tissue responses (Gjerdet, Kallus et al. 1987, Moura, Ferreira et al. 2014). While PTFE is generally well-tolerated, a rare case of hypersensitivity to PTFE graft in a patient for hemodialysis access was reported (Iqbal, Bhandare et al. 2019). Overall, PTFE grafts are extensively used in medical applications and show minimal risk of adverse events due to exceptional biocompatibility and chemical inertness. Several studies cited in the CIR Assessment (Johnson, Bergfeld et al. 2023) of polyfluorinated polymers as used in cosmetics demonstrated no evidence of dermal irritation or sensitization. In one study, the skin irritation was observed for a formula containing 7.6% PTFE in a 48-hour semi-occlusive patch test with 26 subjects. In another study, the skin sensitization potential of a formula containing 2.89% PTFE was evaluated in a human repeated insult patch test (HRIPT) using occlusive patches on 107 subjects. The dose per cm^2 of patch application was not specified in either of the studies. There was no evidence of dermal irritation or sensitization. In the third study, a cosmetic product containing 9% PTFE was applied to 206 subjects using occlusive patches and HRIPT and there was no evidence of skin sensitization. In addition, the skin irritation potential of PTFE (powder) was evaluated using six New Zealand White rabbits, where PTFE was classified as a non-irritant. The studies mentioned above were either unpublished or from anonymous sources as cited in the CIR Assessment (Johnson, Bergfeld et al. 2023).

[55] While dermal irritation and sensitization are pathologically distinct, their physical and histological differences can be difficult to distinguish. Tan, C. H., S. Rasool and G. A. Johnston (2014). "Contact dermatitis: allergic and irritant." Clin Dermatol **32**(1): 116-124. Both irritation and allergic contact dermatitis are common adverse reactions to cosmetic ingredients. A chemical can cause irritation, sensitization, or both simultaneously. Despite the availability of specific assays, many confounding factors, unexpected reactions, and variations in methods and interpretations in both animals and humans can make clear differentiation between an irritant and a sensitizer challenging. Therefore, this section discusses the combined irritation and sensitization effects, as well as other relevant data.

In a 2017 study by Harrison Research Laboratories, also cited in the CIR Assessment, there was no skin sensitization of an eye shadow product containing 6% PTFE in 111 subjects (Johnson, Bergfeld et al. 2023). Clayton (1967) reported a study which assessed the sensitization of PTFE (a 20% dispersion in CCl_2F-$CClF_2$) using the skin of 10 guinea pigs. As stated in this publication, when the CCl_2F-$CClF_2$ evaporated, the material hardened and produced moderate mechanical irritation. There was no evidence of skin sensitization. The details of the substance application were not reported.

In summary, information on dermal irritation and sensitization potential of PTFE is limited, overall. The available evidence suggests that PTFE is unlikely to be a skin irritant or sensitizer.

Ocular Irritation

A PubMed and Web of Science literature search on ocular irritation using the queries in **Table S6** yielded a total of 12 publications. After title and abstract screening, we considered none of these publications relevant to the current review, mostly due to irrelevant exposure scenarios where PTFE was used as an implanting or grafting material. Unpublished data cited in the CIR Assessment (Johnson, Bergfeld et al. 2023) indicated that a formula containing PTFE (2.89%) and a PTFE powder (0.1 g) had no potential for ocular irritation, based on an *in vitro* EpiOcular eye irritation test, and an *in vivo* study in New Zealand White rabbits, respectively. Similar to the dermal irritation study, Clayton (1967) reported mild conjunctival irritation in the eyes of rabbits, a symptom that disappeared in less than 72 hours, following exposure to PTFE as a 20% dispersion in CCl_2F-$CClF_2$. A mild corneal injury was also observed at 24 hours but disappeared at 48 hours. The study authors noted that these transient reactions were no greater than those produced by the CCl_2F-$CClF_2$ alone, suggesting PTFE itself is not irritating to the eyes. Details regarding the number and strain of animals were not provided.

Together, the available information suggests that PTFE is unlikely to be an ocular irritation hazard, particularly when the ingredient is used in cosmetic products that are not intended for use in direct contact with the eyes.

Respiratory Irritation

A PubMed and Web of Science literature search on the respiratory irritation potential of PTFE using the queries outlined in **Table S6** yielded 77 publications. After an initial title and abstract screening, we identified 24 as relevant after title and abstract screening. However, after full text review, we identified no articles that contained information relevant to the current review.

Most of the literature focused on acute lung toxicity from exposure to PTFE fumes that are produced when PTFE is heated to temperatures above 260^{o}C. This condition is highly unlikely to occur under the intended use conditions of PTFE-containing cosmetic products as they do not involve exposure to high temperatures. Nevertheless, PTFE particles have frequently been used as negative controls or to estimate the distribution of inhaled particles with various sizes in the human body. These studies can serve as indirect evidence that PTFE-containing cosmetic products are unlikely to cause respiratory irritation.

Photo-induced Toxicity

A PubMed and Web of Science literature search for photo-induced toxicity using the queries outlined in **Table S6** yielded 22 publications. None were considered relevant to the current review after title and

abstract screening. These studies were excluded for reasons such as irrelevant exposure or experimental species, a focus on the defluorination of PTFE, or the discussion of PTFE as materials for devices or instruments.

Review Summary

Uses: PTFE is used in a variety of cosmetic products as bulking agents and slip modifiers. According to the mandatory cosmetic product listing data submitted to the FDA (accessed on August 30, 2024), PTFE is used in 490 product formulations, of which 322 are eye shadows, accounting for 65.7% of the total. This is followed by blushers and rouges (all types), lipsticks and lip glosses, face powders and face and neck products with 48, 30, 29 and 10 products, respectively. The remaining products belong to a total of 15 categories and account for approximately 10% of all PTFE-containing products.

While data obtained from the VCRP and Mintel's GNPD suggested a decline in PTFE use in cosmetic products in recent years, it is currently not possible to determine a definitive trend using the cosmetic product listing data submitted to the FDA due to the lack of baseline or historical data. Moreover, comparing the frequency of use data of PTFE between the VCRP and the mandatory cosmetic product listing data submitted to the FDA is challenging due to the voluntary nature of the VCRP and the significantly higher number of the mandatory cosmetic product listing data submitted to the FDA compared with the VCRP.

Consumers are primarily exposed to PTFE in cosmetic products through dermal contact under the intended use conditions. However, incidental PTFE exposure via ingestion may occur with products such as lipsticks. Similarly, eye exposure may occur with eye cosmetic products, and incidental inhalation exposure may occur with products such as face powders. Other PTFE exposure pathways such as subcutaneous, submucosal, surgery implantation, intraperitoneal, and intravenous administration are not considered relevant to cosmetic product use.

Safety: PTFE is considered among the most chemically inert and nontoxic materials tested under normal use conditions (Henry, Carlin et al. 2018). While no studies have specifically examined the dermal pharmacokinetics of PTFE, it is not expected to be absorbed through the dermis due to its high molecular weight. PTFE is also not absorbed if ingested given the particle size of the ingredient used in cosmetic products, and PTFE is not metabolized, owing to its strong carbon-fluorine bond which is extremely difficult to break down. PTFE remains stable at temperatures below 260^{o}C.

Based on available published hazard information, PTFE does not appear to be acutely toxic by the oral route and does not show subacute or subchronic toxicity following repeated oral exposure in rodents. In mice, a single oral dose of 2000 mg/kg PTFE microplastics (approximately 5 µm in size) did not reveal any signs of clinical and pathological changes for 4 weeks (Lee, Kang et al. 2022). Rats administered with 25% PTFE in their diet for 90 days also did not show toxicologically significant effects (Clayton 1967).

Limited available information suggests that PTFE is not genotoxic. There is also no evidence demonstrating carcinogenicity following dermal, oral or inhalation exposure to PTFE. Some animal studies on PTFE implants reported the formation of localized sarcomas around the implant sites following procedures such as subcutaneous implantation, intraperitoneal injection or submucosal injection, but the results were not consistent. The FDA does not consider these effects to be relevant to PTFE use in cosmetic products.

There is no evidence indicating that PTFE induces developmental and reproductive toxicity, neurotoxicity, or immunotoxicity. While chronic inflammation and granuloma formation have been reported in some animal studies and clinical cases following PTFE injection or implantation, these adverse effects are not considered relevant to cosmetic products uses.

Available data also suggest that PTFE is not a skin irritant or a skin sensitizer in animals or humans. PTFE, as a device material, has a long history of widespread use in medical applications and shows minimal risk of adverse events due to its exceptional biocompatibility and chemical inertness. While ocular exposure to PTFE may occur from products used near the eyes, available information suggests that PTFE is not an ocular irritant, therefore, it is unlikely to pose a health risk to consumers. PFTE is not expected to be phototoxic based on its molecular structure which lacks chromophores. Furthermore, no published scientific literature has identified phototoxicity as a concern for PTFE.

Incidental inhalation exposure to PTFE is possible when using products like face powder. However, current evidence does not suggest that PTFE is an inhalation hazard to the lungs or acts as a respiratory irritant. Workplace exposure to PTFE has been associated with granulomatous lung diseases, typically due to heating PTFE to high temperatures, resulting in the release of toxic pyrolysis products. This scenario, however, is highly unlikely to occur with consumer use of cosmetic products. Conclusion

Based on the review of available data, there is a low concern for safety associated with PTFE when used as an ingredient in cosmetic products under intended conditions of use.

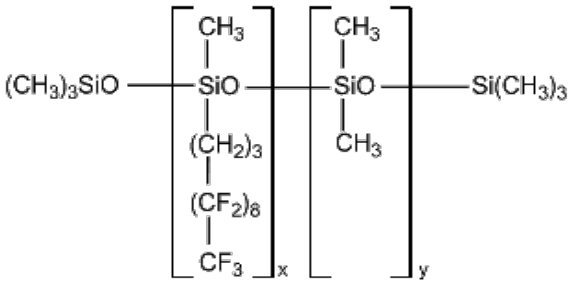
2. Perfluorononyl Dimethicone

Introduction

Perfluorononyl dimethicone (CAS No. 259725-95-6; PubChem SID: 472205417) is a fluorinated siloxane polymer composed of a silicone backbone and perfluorononyl side chains. **Table A.2.1** shows the chemical structure and physicochemical properties. Perfluorononyl dimethicone is a clear to pale yellow liquid that is insoluble in water. It may be odorless or have mild odor. The density and viscosity of perfluorononyl dimethicone can vary depending on the specific molecular weight and degree of polymerization and the manufacturing process. It is generally stable under normal storage and handling conditions, but decomposition may occur at very high temperatures, forming products such as carbon oxides, silicon dioxide, formaldehyde, and traces of incompletely burned carbon compounds.[56]

Table A.2.1. Physical and Chemical Properties of Perfluorononyl Dimethicone

[56] Safety Data Sheet for Fluorosil D2. https://www.siltech.com/wp-content/uploads/2017/11/MP5460.pdf (accessed 2/19/2025).

Element	Description
Name	Perfluorononyl Dimethicone
INCI name	Perfluorononyl Dimethicone
Synonyms	Siloxanes and Silicones, di-Me, Me 3,3,4,4,5,5,6,6,6-nonafluorohexyl Fluoropolymers, di-Me, Me 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-nonadecafluorododecyl polysiloxane- Fluorosil LF Fluorosil D2 Fluorosil 14 Fluorosil J15
CAS#	259725-95-6
Structure	
Molecular formula	NA
Molecular weight	NA
Particle size	Not applicable
Physical form	Clear to light yellow Liquid[56]
Density	Varies.[56]
Solubility	Insoluble in water[56]
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	NA
Boiling point	>100 ^{o}C@ 760 mmHg[56]
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	Stable under normal conditions but decomposition may occur during fire or at very high temperatures and form products such as carbon oxides, silicon dioxide, formaldehyde, and trace of incompletely burned carbon compounds.[56]
Additional properties	Viscosity: 10-40 cps at 25 ^{o}C[56]

Notes: NA, not available. Source: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, perfluorononyl dimethicone is a skin-conditioning agent (miscellaneous or occlusive)[57] and slip modifier commonly used in cosmetic products such as eye shadows, lipsticks, eyeliners, and miscellaneous non-eye makeup preparations. The ingredient is used in cosmetic products to improve skin appearance, reduce flaking and enhance hydration.

Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorononyl dimethicone is currently used as an ingredient in 231 cosmetic products; 64.5% (n=149) of them are listed in the eye makeup category; 57.6%, (n=133) are eyeliners, followed by other non-eye makeup preparations at 22.9%, (n=53). Other common eye makeup product categories containing this polymer include eye shadows (4.8%), mascaras (0.9%), and other eye makeup preparations (0.9%). The remaining cosmetic products that contain perfluorononyl dimethicone are lipsticks and lip glosses (6.1%), and hair care products (5.2%) (**Table A.2.2**). Please see **Table S2** for a full list of cosmetic product categories.

Table A.2.2. Frequency of Use of Perfluorononyl Dimethicone in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Eye makeup		
Eyeliners	133	57.6
Eye shadows	11	4.8
Mascaras	2	0.9
Eyelash and eyebrow	1	0.4
Other eye makeup preparations	2	0.9
Eye makeup total	**149**	**64.5**
Hair care		
Hair conditioners	2	0.9
Tonics, dressings, and other hair grooming aids	9	3.9
Other hair preparations, leave-on	1	0.4
Hair care total	**12**	**5.2**
Makeup preparations (non-eye) (other than makeup preparations for children)		
Foundations	1	0.4
Lipsticks and lip glosses	14	6.1

[57] The functions for cosmetic ingredients are defined in INCI dictionary and provided in the specific cross-reference section, Reported Functions. More details can be found in the following INCI link: https://incipedia.personalcarecouncil.org/sub-lists/sub-list-details/?id=157a4551-9c82-ec11-8d21-000d3a98a506&reportedfunctioninitvalue=69072ffb-35bf-48b6-a736-21f87b3bc453. Note: Membership/login is required to view the content.

Product Category	Number of Products	Percentage of Total (%)
Other makeup preparations (lip liners/pencils)	53	22.9
Makeup (non-eye) total	**68**	**29.4**
Shaving creams	**1**	**0.4**
Skin care, rinse-off	**1**	**0.4**
Grand total	**231**	**100.0**

Historical data available to the FDA suggests a decreasing trend in the use of perfluorononyl dimethicone in cosmetic products. For example, the VCRP data indicated a steady decrease in the use of perfluorononyl dimethicone from 65 products in 2019, to 33 products in 2021, and 29 products in 2023 (**Table S4**). Similarly, the Mintel's GNPD shows a decline in use from 61 perfluorononyl dimethicone-containing cosmetic products launched in the U.S. market over a 5-year period (August 2019 to July 2024), starting with an average of 12 products launched per year in 2019, to 6 products launched between August 2023 and July 2024 (**Table S4**). The use trend of perfluorononyl dimethicone cannot be currently determined using the cosmetic product listing data submitted to the FDA, due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for perfluorononyl dimethicone is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported the use of this ingredient at a concentration range of 0.006% to 1% in skin care products. Additionally, one supplier recommends use at a concentration range of 0.25% to 2% in hair care, skin care, color cosmetics, sun care, and baby products.[58] It is important to note that different suppliers of raw material may recommend varying concentrations of use, and that manufacturers or formulators ultimately determine the final concentration in their cosmetic products, which may be outside the range of suppliers' recommendations.

Given that over 60% of the products that contain perfluorononyl dimethicone are eye makeup products, such as eyeliners, eye shadows, and mascaras, intended for use near the eye area, there is potential for ocular exposure. Additionally, the presence of perfluorononyl dimethicone in lipsticks and lip glosses indicates a potential for incidental ingestion.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

[58] Based on the data sheet of Fluorosil LF by Biosil Technologies, Inc. Available at: https://www.knowde.com/stores/biosil-technologies-inc/documents/15553 (accessed 2/29/2025. Login is required for access).

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of perfluorononyl dimethicone by government agencies and other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S9** did not identify any published data on the toxicokinetics of perfluorononyl dimethicone. We also did not identify a REACH dossier for perfluorononyl dimethicone in the ECHA database (searched on 09/16/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of perfluorononyl dimethicone. The SDS from the supplier, Siltech Corp.,[56] indicates that perfluorononyl dimethicone does not pose a known risk of acute toxicity. While direct eye contact may cause temporary redness and discomfort, hazard from ingestion is low under normal or customary conditions of use. In addition, short-term exposure is not expected to cause significant skin or respiratory irritation. However, repeated ingestion or swallowing large amounts could potentially lead to internal injury. Importantly, we note that the specific data regarding these health effects are unavailable for our independent evaluation.

Review Summary/Conclusion

Uses: Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorononyl dimethicone, a fluorinated siloxane polymer, is currently used as an ingredient in 231 cosmetic products, primarily in eye makeup products, and in particular, in eyeliners. Additional data available to the agency, including information from Mintel's GNPD and the VCRP suggests a decline in the use of perfluorononyl dimethicone in cosmetic products. However, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, this trend cannot be demonstrated at this time.

Safety: Based on the product types containing perfluorononyl dimethicone, this ingredient may have multiple routes of exposure from its use in certain cosmetic products. In addition to dermal exposure, the use of perfluorononyl dimethicone in eye makeup products may have potential ocular exposure. Use of perfluorononyl dimethicone in other cosmetic products, such as in lipsticks and lip glosses, may also lead to incidental oral exposure. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of perfluorononyl dimethicone. The FDA does not have enough information to assess the potential for eye irritation, skin irritation or sensitization, and whether it could be absorbed and lead to systemic exposure and toxicity. Given the limited data and information available, the FDA cannot determine the safety of perfluorononyl dimethicone from its use in cosmetic products or risks associated with such use.

While the potential risks associated with the use of perfluorononyl dimethicone in cosmetic products remain to be determined, it is important to note that non-fluorinated alternatives, such as non-fluorinated silicones and fats, have been identified as viable replacements for this PFAS (OECD 2024). These alternatives have demonstrated a comparable level of performance to perfluorononyl dimethicone in lip pencils and are already in commerce for cosmetic product use (RISE 2022). As a result, the FDA expects the use of perfluorononyl dimethicone in cosmetic products to decline in the future.

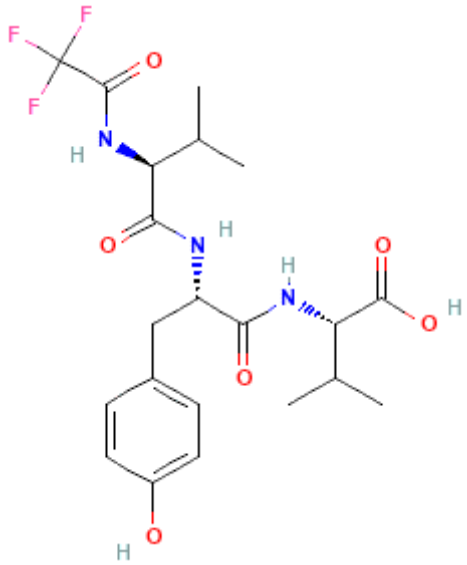
3. Trifluoroacetyl Tripeptide-2

Introduction

Trifluoroacetyl tripeptide-2 (CAS No. 64577-63-5; PubChem CID: 40785040) is the synthetic product of trifluoroacetic acid and tripeptide-2, a three amino acid biomimetic peptide with a sequence of Tfa-VAL-TYR-VAL-OH. **Table A.3.1** shows the chemical structure and physicochemical properties. It is a white to off-white powder, generally soluble in water and various solvents such as dimethyl sulfoxide (DMSO). Trifluoroacetyl tripeptide-2 is used in the commercial formulation WKPep®Antiprogerin by Winkey Technology[59] claimed to improve skin firmness and elasticity by a modulating progerin synthesis. Specifically, it decreases progerin synthesis and accumulation, and inhibits metalloproteinases (Schagen 2017, Naughton, Jiang et al. 2023).

Table A.3.1. Physical and Chemical Properties of Trifluoroacetyl Tripeptide-2

[59] https://www.winkey-china.com/products/Anti-aging-and-Repairing/WKPep%C2%AEAntiprogerin (accessed 8/13/2025).

Element	Description
Name	Trifluoroacetyl Tripeptide-2
INCI name	Trifluoroacetyl Tripeptide-2
Synonyms	Tfa-VAL-TYR-VAL-OH N-(trifluoroacetyl)-L-valyl-L-tyrosyl-L-valine (2*S*)-2-[[(2*S*)-3-(4-hydroxyphenyl)-2-[[(2*S*)-3-methyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]amino]propanoyl]amino]-3-methylbutanoic acid Progeline ECM-protect
CAS#	64577-63-5
Structure	
Molecular formula	$C_{21}H_{28}F_3N_3O_6$
Molecular weight	475.5 g/mol
Particle size	NA
Physical form	White to off-white powder
Density	1.299 g/ml[60]
Solubility	Generally soluble in water and various solvents[61]
Partition coefficient (Log K_{ow})	3.0 (predicted)
Vapor pressure	NA
Melting point	NA
Boiling point	695.4 - 815.4 °C[60]
Topological polar surface area	145 Å²
UV light absorption spectrum	NA

Decomposes	NA
Additional properties	Acid dissociation constant: 3.22 - 3.42 pKa[60]

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, trifluoroacetyl tripeptide-2 is used as both a skin protectant and skin-conditioning agent in facial and neck products. Based on the FDA's cosmetic product listing data, trifluoroacetyl tripeptide-2 is currently used as an ingredient in 164 cosmetic products (**Table A.3.2)**. It is most predominantly used for skin care (86.6%, n=142), in particular, face and neck care (59.1%, n=97). Other significant use categories under skin care include leave-on products for other areas (9.8%), moisturizing (7.3%), cleansing (3.0%), and night products (2.4%). In addition, foundations and other cosmetic preparations contribute to 6.1% and 3.0% of the ingredient's total usage. Other categories such as eye makeup, hair care, and shaving creams represent less than 3% of the total products (**Table A.3.2**). Please see **Table S2** for a full list of cosmetic product categories.

Table A.3.2. Frequency of Use of Trifluoroacetyl Tripeptide-2 in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

[60] https://www.specialchem.com/cosmetics/product/alfa-chemistry-trifluoroacetyl-tripeptide-2 (accessed 08/13/2025. Login is required for access).

[61] Safety Data Sheet for trifluoroacetyl tripeptide-2 (acetate): https://cdn.caymanchem.com/cdn/msds/35389m.pdf (accessed 9/6/2024).

Product Category	Number of Products	Percentage of Total (%)
Eye makeup	**4**	**2.4**
Hair care, leave on	**2**	**1.2**
Makeup preparations (not eye) (other than makeup preparations for children)		
Foundations	**10**	**6.1**
Shaving creams	**1**	**0.6**
Skin care		
Cleansing	5	3.0
Face and neck, leave-on	83	50.6
Face and neck, leave-on, moisturizing	14	8.5
Face and neck, rinse-off, moisturizing	1	0.6
Body and hand, leave-on	3	1.8
Moisturizing	12	7.3
Night	4	2.4
Paste masks (mud packs)	2	1.2
Others, leave-on	16	9.8
Others, rinse-off	2	1.2
Skin care total	**142**	**86.6**
Other preparations	**5**	**3.0**
Grand total	**164**	**100.0**

Data from the VCRP and Mintel's GNPD do not indicate a clear trend of the usage change for trifluoroacetyl tripeptide-2 in cosmetic products. There was no reported use of trifluoroacetyl tripeptide-2 in the VCRP in 2019 and 2021, but 21 uses were reported in 2023 (**Table S4**). Mintel's GNPD data revealed that the ingredient was used in 66 products launched in the U.S. market over a 5-year period (August 2019 to July 2024) and 14 products between August 2023 and July 2024 (**Table S4**). The use trend of trifluoroacetyl tripeptide-2 cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for trifluoroacetyl tripeptide-2 is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported the use of this ingredient at a concentration range of 0.005% to 0.4% in makeup, skin care and

hair care products. A raw material supplier, Winkey Technology recommends using WKPep®Antiprogerin, a blend of water, glycerin, dextran and trifluoroacetyl tripeptide-2, at a concentration of 0.05-2%.[59] The exact amount of trifluoroacetyl tripeptide-2 within this mixture is not specified though.

Due to its skin protecting and conditioning properties, trifluoroacetyl tripeptide-2 containing products are predominantly applied topically to the skin, which makes dermal contact likely the primary route of consumer exposure. In addition, incidental ocular exposure to trifluoroacetyl tripeptide-2 may occur when using eye makeup products.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of trifluoroacetyl tripeptide-2 by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S9** identified one *in vitro* dermal permeation study of trifluoroacetyl tripeptide-2 (searched on 9/6/2024). In this study (Shariati Pour, Oddis et al. 2023), trifluoroacetyl tripeptide-2 was formulated in a hydrogel, consisting of the two peptide components Boc-L-Dopa(Bn)2OH and Boc-L-Ala-Aib-L-Val-OH, at a concentration of 0.1%. Dermal permeation was evaluated using Franz diffusion cells with pig ear skin membranes. After 24 hours, approximately 40% of the applied trifluoroacetyl tripeptide-2 permeated the skin and was detected in the receptor fluid after 24 hours, indicating significant dermal absorption. The actual absorption could be higher considering that the portion of trifluoroacetyl tripeptide-2 retained in the skin during the experiment may eventually pass through the skin and become systemically available in prolonged use scenarios. No other information regarding the toxicokinetics of trifluoroacetyl tripeptide-2 is available.

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of trifluoroacetyl tripeptide-2. We also did not identify a REACH dossier for trifluoroacetyl tripeptide-2 in the ECHA database (searched on 09/6/2024). According to the SDS from Cayman Chemical Company,[61] trifluoroacetyl tripeptide-2 is not considered a skin or eye irritant and has no known sensitizing effects. Additionally, it is not listed as a carcinogen by IARC, NTP or OSHA. Importantly, we note that the specific data regarding these health effects are unavailable for our independent evaluation.

Review Summary/Conclusion

Uses: Based on the mandatory cosmetic product listing data submitted to the FDA, trifluoroacetyl tripeptide-2 is used as a cosmetic ingredient in 164 cosmetic products, in particular skin care products for improving skin firmness and elasticity. The ingredient is also used in eye makeup such as lotions, and non-eye makeup such as liquid foundations. Additionally, it is used in hair care products and shaving

creams. The use concentration of trifluoroacetyl tripeptide-2 may vary depending on the specific product formulations and their intended uses.

Data from the VCRP and Mintel's GNPD do not indicate a clear trend of the usage change for trifluoroacetyl tripeptide-2. In addition, due to the lack of a baseline in the mandatory cosmetic product listing data submitted to the FDA, a trend cannot be demonstrated at this time.

Safety: Based on the type of products that contain trifluoroacetyl tripeptide-2, dermal contact is expected to be the primary route of consumer exposure to this ingredient. However, ocular exposure may also occur due to its presence in eye makeup products. Ingestion and inhalation are less likely exposure routes due to the ingredient's typical use in topical products.

The toxicokinetics of trifluoroacetyl tripeptide-2 have not been extensively investigated. One *in vitro* study examined the dermal permeation of trifluoroacetyl tripeptide-2 using Franz diffusion cells with pig ear skin (Shariati Pour, Oddis et al. 2023). When formulated in a hydrogel at a concentration of 0.1%, approximately 40% of the trifluoroacetyl tripeptide-2 permeated through the skin, indicating a significant absorption. Considering the structure, composition and mechanical similarities between pigs and humans (Surnmerfield, Meurens et al. 2015), it is reasonable to anticipate that upon dermal exposure a substantial portion of trifluoroacetyl tripeptide-2 can be absorbed into the bloodstream leading to systemic exposure, especially in the presence of absorption enhancers.

The actual level of systemic exposure to trifluoroacetyl tripeptide-2 would be influenced by the product type, e.g., leave-on products generally pose a higher risk compared to rinse-off products due to prolonged skin contact, amount of application, frequency and duration of use, and the product concentration.

While a raw material supplier's SDS indicates that trifluoroacetyl tripeptide-2 is not a skin or eye irritant, or a skin sensitizer, published or publicly available toxicity data is substantially lacking. Additionally, the potential for long-term organ toxicity, reproductive and development toxicity, or increased risk of cancer from prolonged exposure to trifluoroacetyl tripeptide-2 from using cosmetic products remains unknown.

Due to the lack of sufficient toxicity data and high-quality exposure information, the FDA cannot determine the safety of trifluoroacetyl tripeptide-2 from its use in cosmetic products or risks associated with such use.

4. Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate

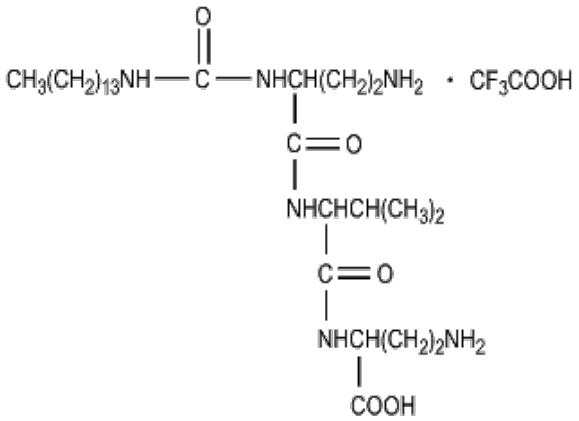
Introduction

Tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate (CAS No. 934368-60-2; PubChem CID: 137528195) is a synthetic tripeptide. **Table A.4.1** shows the chemical structure and physicochemical properties. According to a single raw material supplier, it appears as a white powder.[62] It is soluble in water and reportedly stable at room temperature. Other physicochemical properties, such as particle size, potential impurities, partition coefficient, vapor pressure, melting point and boiling point are currently unknown or have not been reported in the available literature.

Table A.4.1. Physical and Chemical Properties of Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate

Element	Description
Name	Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate
INCI name	Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate
Synonyms	(2S)-4-amino-2-[[(2S)-2-[[(2S)-4-amino-2-(tetradecylcarbamoylamino)butanoyl]amino]-3-methylbutanoyl]amino]butanoic acid;2,2,2-trifluoroacetic acid Tetradecyl aminocarbonyl-Dab-Val-Dab Tetradecylaminocarbonyl-dab-Val-dab bistrifluoroacetate Syn-Hycan 2,8-bis(2-aminoethyl)-5-(1-methylethyl)-4,7,10-trioxo-3,6,9,11-tetraazapentacosanoate 2,2,2-trifluoroacetate (1:1), (2S,5S,8S)-3,6,9,11-Tetraazapentacosanoic acid, 2,8-bis(2-aminoethyl)-5-(1-methylethyl)-4,7,10-trioxo-, (2S,5S,8S)-, 2,2,2-trifluoroacetate (1:2)
CAS#	934368-60-2

[62] https://www.chemicalbook.com/ProductDetail_EN_tetradecyl-aminocarbonyl-dab-val-dab-_1758195.htm (accessed 9/23/2024).

Element	Description
Structure	
Molecular formula	$C_{32}H_{58}F_6N_6O_9$ or $C_{28}H_{56}N_6O_5.2C_2HF_3O_2$
Molecular weight	784.8 g/mol
Particle size	NA
Physical form	White powder[62]
Density	NA
Solubility	Soluble in water[62]
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	NA
Boiling point	NA
Topological polar surface area	263 Å²
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	NA

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate is used as a skin-conditioning agent in face and neck preparations (excluding shaving preparations) and moisturizing preparations.

Based on the mandatory cosmetic product listing data submitted to the FDA, tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate is currently used in 156 cosmetic products, 142 (91.0%) of which fall under the skin care product category, particularly those for face and neck care (66.0%, n=103), followed by moisturizing products (9.6%, n=15). Eye lotions comprise 4.5% of the total products. Makeup products, including various facial cosmetics such as blushers and rouges, foundations, lipsticks and lip glosses, represent a smaller portion (1.9%). Other categories like suntan preparations

and other preparations each account for a minor percentage (0.6% and 1.9%, respectively) (**Table A.4.2**). Please see **Table S2** for a full list of cosmetic product categories.

Table A.4.2. Frequency of Use of Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (As of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Eye makeup		
Eye lotions	**7**	**4.5**
Makeup preparations (not eye) (other than makeup preparations for children)		
Blushers and rouges	1	0.6
Foundations	1	0.6
Lipsticks and lip glosses	1	0.6
Makeup (not eye) total	**3**	**1.9**
Skin care		
Moisturizing	15	9.6
Night	3	1.9
Paste masks (mud packs)	5	3.2
Cleansing, leave-on	8	5.1
Cleansing, rinse-off	2	1.3
Face and neck, leave-on	100	64.1
Face and neck, rinse-off	3	1.9
Body and hand, leave-on	3	1.9
Skin fresheners	1	0.6
Other makeup preparations, leave-on	2	1.3
Skin care total	**142**	**91.0**
Suntan, indoor tanning preparations	**1**	**0.6**
Other preparations	**3**	**1.9**
Grand total	**156**	**100.0**

There was no reported use of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate in cosmetic products between 2019 and 2021 in the VCRP, but there were 39 uses in 2023 in the VCRP (**Table S4**). Mintel's GNPD data revealed that the ingredient was used in 69 products in the U.S. market over a 5-year period (August 2019 to July 2024) and 11 products between August 2023 and July 2024, suggesting a possible decline in use (**Table S4**). The use trend of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported the use of this ingredient at a concentration range of 0.00025% to 0.025% in skin care products. In addition, based on information obtained from UL Prospector, the ingredient is used in SYN®-HYCAN CB, a mixture of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate, glycerin, water, and magnesium chloride by DSM-Firmenich.[63] SYN®-HYCAN CB is recommended to be used at 2.5% in cosmetic formulations. However, manufacturers or formulators may use a higher or lower concentration than suppliers' recommendations at their discretion.

Given the prevalence of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate in leave-on skin care products, consumer exposure is likely to occur through daily skin care routines, particularly to the facial and neck regions. Exposure to the eyes may occur when using eye makeup cosmetics. Incidental ingestion through lip makeup is also possible. Inhalation exposure is unlikely due to the absence of reported use of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate in powders, sprays, nail polishes, dry shampoos or fragrances. Prolonged exposure from skin contact remains a potential primary concern.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as outlined in **Table S5** did not identify any assessments of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate by government regulatory bodies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S9** did not identify any published data on the toxicokinetics of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate (searched on 9/11/2024). We also did not identify a REACH dossier for tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate in the ECHA database (searched on 09/11/2024). However, based on the ingredient's molecular weight of 784 g/mol, which is relatively large for passive skin penetration, some absorption may still be expected to occur, particularly in the presence of skin penetration enhancers such as glycerin.

Hazard Assessment

[63] SYN®-HYCAN CB is a trade name by DSM-Firmenich Company. See the following link for more information regarding this product: https://www.ulprospector.com/documents/1188113.pdf?bs=473&b=302762&st=20&r=na&ind=personalcare (accessed 9/23/2024. Login is required for access).

A literature search in PubMed and Web of Science using the query outlined in **Table S9** revealed no publicly available information regarding the toxicity of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate.

According to the DSM-Firmenich's SDS[64] for SYN®-HYCAN CB (product code 5017794), tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate is not acutely toxic, with an LD_{50} >5000 mg/kg body weight. While it may irritate eyes, it is neither a skin irritant nor a skin sensitizer based on human patch tests. It is not mutagenic based on an Ames test conducted in accordance with OECD TG 471. Further, the SDS does not indicate any concerns regarding carcinogenicity or reproductive toxicity, and no information is available for specific target organ toxicity following repeat exposure. Importantly, we note that the specific data regarding these health effects are unavailable for our independent evaluation.

Review Summary/Conclusions

Uses: Based on the mandatory cosmetic product listing data submitted to the FDA, tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate, a synthetic tripeptide, is currently used as a cosmetic ingredient in 156 cosmetic products, primarily for skin care, in particular face and neck care. It is also used in eye area cosmetic product such as eye lotions, and non-eye makeup such as lipsticks and lip glosses.

Mintel's GNPD data suggests a declining trend in the use of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate in cosmetic products. However, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, this trend cannot be demonstrated at this time.

Safety: Based on the types of products containing tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate, consumers can be exposed to the ingredient via multiple routes. Dermal contact is expected to be the primary route of consumer exposure to this ingredient from the use of skin care products. Ocular exposure is also possible due to the ingredient's presence in eye makeup. In addition, oral exposure may occur through incidental ingestion of lipsticks that contain tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate.

Despite its common use in cosmetic products, there is a significant lack of publicly available studies regarding the systemic or local toxicity of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate.

An SDS from a raw material supplier suggests that while tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate is not acutely toxic, doesn't cause skin irritation or sensitization, and is not mutagenic, it may potentially irritate the eyes. However, as the FDA does not have premarket authority over cosmetic ingredients or products, other than color additives which are subject to FDA approval before use, we do not have specific data to review or evaluate the test information included in this supplier's SDS. Additionally, the FDA does not have sufficient information to assess the toxicokinetics, including its potential for absorption, and subsequent systemic exposure and toxicity.

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[64] Obtained from UL prospector website: https://www.ulprospector.com/documents/1188114.pdf?bs=473&b=302762&st=1&sl=495353986&crit=a2V5d29yZDpbU3luLUh5Y2FuXQ%3d%3d&k=Syn-Hycan&r=na&ind=personalcare (accessed 9/23/2024. Login is required for access).

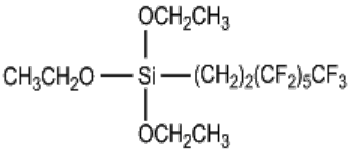
Given the insufficient data, the FDA cannot determine the safety of tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate from its use in cosmetic products or risks associated with such use.

5. Perfluorohexylethyl Triethoxysilane

Introduction

Perfluorohexylethyl triethoxysilane, also known as perfluorooctyl triethoxysilane (CAS No. 51851-37-7; PubChem CID: 103991) is a fluorinated alkyl silane. **Table A.5.1** shows the chemical structure and physicochemical properties. Under normal conditions, it is a colorless liquid, with a density of 1.34 g/ml. The very high partition coefficient (Log K_{ow}) of 7.2 indicates that perfluorooctyl triethoxysilane is highly hydrophobic and poorly soluble in water. Perfluorohexylethyl triethoxysilane has a relatively low volatility as indicated by its vapor pressure and boiling point. It is chemically stable under standard room temperature, however, perfluorohexylethyl triethoxysilane will hydrolyze moderately rapidly in contact with water to produce [2-(perfluorohexyl)ethyl]silanetriol and ethanol (ECHA 2018).

Table A.5.1. Physical and Chemical Properties of Perfluorohexylethyl Triethoxysilane

Element	Description
Name	Perfluorooctyl Triethoxysilane
INCI name	Perfluorohexylethyl Triethoxysilane
Synonyms	2-(Perfluorohexyl)ethyl Triethoxysilane Fluoro Silane (FS) 1H,1H,2H,2H-Perfluorooctyltriethoxysilane Perfluorooctyltriethoxysilane Triethoxy(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane 3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyltriethyoxysilane
CAS#	51851-37-7
Structure	
Molecular formula	$C_{14}H_{19}F_{13}O_3Si$
Molecular weight	510.36 g/mol
Particle size	Not applicable
Physical form	Colorless liquid
Density	1.34 g/ml at 20 °C
Solubility	<2 mg/L at 20 °C and pH 6.29 in water
Partition coefficient (Log K_{ow})	7.2 at 20 ℃ (predicted)
Vapor pressure	9.8 Pa at 25 ℃ (predicted)
Melting point	<-100 °C
Boiling point	225°C at 1007 hPa

Element	Description
Topological polar surface area	27.7 Å^2[65]
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	It is chemically stable under standard ambient conditions (room temperature). In contact with water under dilute conditions, it produces [2-(perfluorohexyl)ethyl]silanetriol and ethanol.

Notes: NA, not available. Sources: REACH registration dossier for perfluorohexylethyl triethoxysilane (ECHA 2018); specified otherwise.

Use in Cosmetic Products

According to INCI, perfluorohexylethyl triethoxysilane is a cosmetic ingredient that functions as a binder and skin-conditioning agent. The ingredient is used in various makeup formulations including eye shadows, lipsticks, foundations, and other miscellaneous makeup preparations (excluding eyes) such as nose shadow maker and bronzer.

Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorohexylethyl triethoxysilane is currently used in a total of 124 cosmetic products (**Table A.5.2)**. Nearly 70% of its applications are in makeup categories such as face powders, foundations, blushers and rouges, lipstick and lip glosses. Additionally, perfluorohexylethyl triethoxysilane is used in 14 types of eye makeup, 20 skin care products, one bath soap and body wash, and three suntan products. Please see **Table S2** for a full list of cosmetic product categories.

Table A.5.2. Frequency of Use of Perfluorohexylethyl Triethoxysilane in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Makeup		
Face powders	53	42.7
Foundations	12	9.7
Blushers and rouges	8	6.5
Lipstick and lip glosses	2	1.6
Others	11	8.9
Makeup total	**86**	**69.4**

[65] Available at: https://pubchem.ncbi.nlm.nih.gov/compound/103991#section=Computed-Properties (accessed 9/12/2024).

Product Category	Number of Products	Percentage of Total (%)
Eye makeup		
Eye shadows	6	4.9
Eyebrow pencils	5	4.0
Eyeliners	2	1.6
Other eye makeup preparations	1	0.8
Eye makeup total	**14**	**11.3**
Skin care		
Moisturizing	8	6.5
Face and neck	6	4.8
Cleansing	1	1.6
Others	5	4.0
Skin care total	**20**	**16.1**
Bath soaps and body washes	**1**	**0.8**
Suntan	**3**	**2.4**
Grand total	**124**	**100.0**

In contrast to PTFE and perfluorononyl dimethicone, which showed a steady decline in their usage in cosmetic products from 2019 to 2023 according to the VCRP data, the usage of perfluorohexylethyl triethoxysilane seems to have increased during the same period, rising from only 19 in 2019, to 105 in 2021, and 172 in 2023 before the discontinuation of the VCRP (**Table S4**). However, data obtained from Mintel's GNPD suggests a possible decline in its use, with 33 perfluorohexylethyl triethoxysilane containing products launched in the U.S. market over a 5-year period (August 2019 to July 2024) and only 1 product launched between August 2023 to July 2024 (**Table S4**). The use trend of perfluorooctyl triethoxysilane cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for perfluorohexylethyl triethoxysilane is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported the use concentration of perfluorohexylethyl triethoxysilane at a range between 0.06% and 0.82% in cosmetic products. However, actual use concentrations may vary depending on the raw material suppliers and the specific formulation.

The product categories indicate that consumers can be exposed to perfluorohexylethyl triethoxysilane via dermal, inhalation (incidental), and oral (incidental ingestion) routes. Ocular exposure is also possible when using perfluorohexylethyl triethoxysilane-containing products, such as eye shadows and eyebrow pencils.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of perfluorohexylethyl triethoxysilane by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

An extensive literature search in PubMed and Web of Science did not identify any published data on the toxicokinetics of perfluorohexylethyl triethoxysilane (searched on 9/18/2024).

Based on the limited publicly available information from a registrant dossier submitted to ECHA (2018) (accessed on 9/18/2024), perfluorohexylethyl triethoxysilane hydrolyzes moderately in water to 2-(perfluorohexyl)ethyl]silanetriol and ethanol with a hydrolysis half-life of 12.5 hours at pH 7 and 20 °C. The toxicokinetics of perfluorohexylethyl triethoxysilane through oral, inhalation, or dermal routes has been evaluated using computational models. Significant oral absorption is not expected for perfluorohexylethyl triethoxysilane based on prediction using computational models (details are not available for review in the REACH dossier). However, an oral repeated dose toxicity study confirms that oral absorption occurs, leading to systemic effects. The low water solubility and high log K_{ow} of perfluorohexylethyl triethoxysilane are unfavorable for dermal absorption. Therefore, dermal absorption into the blood is likely minimal. In addition, the predicted blood:air partition coefficient for perfluorohexylethyl triethoxysilane is extremely low (1.6E-06:1), indicating negligible to no systemic uptake via lung exposure. This could be supported by an acute inhalation test that did not reveal signs of systemic toxicity as stated in the REACH dossier. However, the report of the inhalation study is not publicly available and cannot be reviewed by the FDA.

Based on the Log K_{ow} of 7.2 and predicted much higher fat to blood partition coefficients of perfluorohexylethyl triethoxysilane compared to tissue to blood partition coefficients of other tissues, the ingredient would primarily distribute into adipose tissue. There is no direct data on metabolism of perfluorohexylethyl triethoxysilane, and if it is likely to accumulate due to low solubility in blood.

In summary, while direct data is lacking, the physicochemical properties suggest limited but possible oral absorption supported by experimental study results. Dermal and inhalation absorption are expected to be minimal. Systemic distribution is predicted to be primarily into adipose tissue, while no metabolism data exists. Excretion is limited for perfluorohexylethyl triethoxysilane, while the hydrolysis product is likely eliminated via the kidneys.

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of perfluorohexylethyl triethoxysilane. However, a registrant's dossier on the ECHA website provides some relevant information, which is summarized below in the corresponding subsections (ECHA 2018).

It is important to note that the REACH dossier provides only limited publicly available information and the original study reports were inaccessible for review. Thus, the quality of the data cannot be independently and fully evaluated.

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

An acute dermal toxicity study was conducted in 5 male and 5 female rats according to good laboratory practice (GLP) and current OECD TG 403 (ECHA 2018). Rats were exposed to 2000 mg/kg bw undiluted perfluorohexylethyl triethoxysilane for 24 hours. There were no signs of systemic reaction to treatment and no local dermal irritations at the treatment site following removal of the dressings. The LD_{50} value was determined to be >2000 mg/kg.

Oral

An acute oral toxicity study was conducted in 3 male and 3 female rats according to OECD TG 423 and in compliance with GLP (ECHA 2018). Rats were given a single dose (2000 mg/kg bw) of undiluted perfluorohexylethyl triethoxysilane via gavage and observed for 14 days. There were no deaths and no signs of systemic reaction to treatment. The LD_{50} value was determined to be >2000 mg/kg.

Inhalation

No data.

In summary, the results of the acute studies indicated a low risk of acute toxicity from exposure to perfluorohexylethyl triethoxysilane in cosmetics.

Repeated Dose Systemic Toxicity

Dermal

No data.

Oral

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test was conducted according to OECD TG 422 and in compliance with GLP (ECHA 2018). Wistar rats (10-11 weeks old), 10/group/sex (additional 6 rats/sex were used in the control and high dose recovery groups), were treated with perfluorohexylethyl triethoxysilane in liquid paraffin (vehicle) via oral gavage 7 days/week for 28 days (males) or up to 54 days (females) at 50, 100, 150 mg/kg bw/day. Due to observed morbidity and mortality in 150 mg/kg bw/day group, the dose was reduced to 125 mg/kg bw/day after premating day 14/mating day 1.

Clinical signs, such as progressive ataxia, paresis, and hypotonia in hind limbs related to the neuromuscular system, were observed dose-dependently in males and females of the two higher dose groups. Males appear to have been affected earlier and more severely when compared to females, leading to an earlier interim euthanasia of males than females. These signs partially remained in surviving animals in the high dose group (125 mg/kg bw) during the recovery period (14 days for males

and 16 days for females) except for one female rat. Upon histopathological examination, polyneuropathy was noted in peripheral nerves including the brachial, femoral, and sciatic nerves and distal extensions (tibial, peroneus, and soleus nerves). There were no clinical signs of toxicological relevance in the low dose group (50 mg/kg bw/day) during the treatment period of this study. In addition, significant treatment-related body weight loss was also observed in the two higher dose groups. The NOAEL was therefore reported to be 50 mg/kg bw/day based on effects on the peripheral nervous system.

Inhalation

No data.

Genotoxicity

Two Ames tests were performed according to OECD 471 and in compliance with GLP (ECHA 2018). Perfluorohexylethyl triethoxysilane was tested up to 1000 ug/plate in one test and 5000 ug/plate in another test in Salmonella typhimurium (ECHA 2018). No test substance-related increase in the number of revertants was observed with and without metabolic activation. The dossier concludes that the ingredient is negative for mutagenicity to bacteria under the conditions of the test.

An *in vitro* chromosome aberration study in mammalian cells was conducted according to OECD Guideline 473 and in compliance with GLP (ECHA 2018). Chinese hamster lung fibroblasts (V79) were exposed to perfluorohexylethyl triethoxysilane up to 200 µg/mL without metabolic activation and up to 500 µg/mL with metabolic activation. The ingredient is negative for the induction of chromosome aberrations under the conditions of this study.

A mammalian cell gene mutation assay was conducted according to OECD 490 and in compliance with GLP (ECHA 2018). Mouse lymphoma L5178Y cells were exposed to perfluorohexylethyl triethoxysilane at 0.05, 0.10, 0.25, 0.50, 1.00, 1.50, 1.75 and 2.0 mg/mL. No increase in the number of mutations was observed. The dossier concludes that the ingredient is negative for mutagenicity to mammalian cells under the conditions of the study.

Carcinogenicity

No data.

Developmental and Reproductive Toxicity (DART)

We identified a reproductive toxicity study in the REACH dossier for perfluorohexylethyl triethoxysilane (ECHA 2018). This was a combined repeated dose oral toxicity study with the reproduction/developmental toxicity screening test as described under the “Repeated Dose Systemic Toxicity” section. Perfluorohexylethyl triethoxysilane was administered daily via gavage at doses of 50, 100 and 125 mg/kg bw/day for a treatment period of up to 54 days. After 14 days of treatment, male and female rats were mated (1:1) for a maximum of 14 days, potential effects on their reproduction and development were also evaluated. The fertility index (number of pregnant females/number of copulated females x 100) was lower in the mid-dose group (100 mg/kg bw/day) but not in the low (50 mg/kg bw/day) or the high dose (125 mg/kg bw/day) groups when compared to the control group. No histological findings in reproductive organs were observed. Sperm staging did not reveal abnormalities in maturation. The copulation index (no. of animals copulated/no. of pairs x 100) was markedly reduced in the high dose group when compared to control. However, the authors concluded that the reduced copulation index was secondary to the more generalized physical debilitation (polyneuropathy) and was not considered as an adverse reproductive effect. There were no adverse effects observed in F1 offsprings. The study authors reported a NOAEL value of ≥125 mg/kg bw/day for reproductive toxicity for perfluorohexylethyl triethoxysilane.

In this study, a slightly and not statistically significantly higher percentage of pre-implantation loss was noted in the high dose group, but the effect was considered not toxicologically relevant. No adverse effects were noted on male and female fertility at any dose tested. Slightly lower mean total litter weight was observed in the two higher dose groups. Since values for litter weight in these two groups were within the normal range of biological variation and historical control data, the slight differences to controls were not considered toxicologically relevant. There were no treatment-related changes in fetus survival, pregnancy duration, and number of pregnancies. No adverse developmental effects were observed in F1 offspring. The study authors reported a NOAEL value of ≥125 mg/kg bw/day for developmental toxicity for perfluorohexylethyl triethoxysilane.

Neurotoxicity

Neurotoxicity was observed in rats in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (see previous description under Repeated Dose Systemic Toxicity). The NOAEL and LOAEL are 50 and 100 mg/kg bw/day, respectively after 28 days (males) or 54 days (females), based on polyneuropathy in the peripheral nerves including the brachial, femoral, and sciatic nerves and distal extensions (tibial, peroneus, and soleus nerves) (ECHA 2018).

Site of Contact Effects

No studies on the dermal irritation or sensitization, ocular irritation, respiratory irritation, or phototoxicity of perfluorohexylethyl triethoxysilane were found in the public literature. Available studies regarding dermal sensitization, irritation, and ocular irritation in the REACH dossier are summarized below.

Dermal Sensitization

The skin sensitization potential of perfluorohexylethyl triethoxysilane was tested in guinea pigs using Buehler method according to OECD Test Guideline 406 and in compliance with GLP. After the induction phase of three weekly occlusive applications of undiluted perfluorohexylethyl triethoxysilane, the animals were challenged with a 50% solution of perfluorohexylethyl triethoxysilane in corn oil. Observations were made at 30 and 54 hours after the challenge. No sensitization reactions were observed in any of the 20 test animals or the 10 negative control animals. The dossier concludes that perfluorohexylethyl triethoxysilane is not sensitizing under the conditions of the Buehler test (ECHA 2018).

Dermal Irritation

Perfluorohexylethyl triethoxysilane was also evaluated for acute skin irritation in a semi-occlusive study conducted in accordance with OECD TG 404 and GLP guidelines. In two of the three small white Russian rabbits exposed to undiluted perfluorohexylethyl triethoxysilane for 4 hours, very slight erythema was observed at 30-60 minutes, as well as at 2, 48, and 72 hours. One animal developed a very slight edema 48 and 72 hours after the bandage was removed. All signs of irritation were resolved within 6 days after application. One animal showed no signs of skin irritation throughout the observation period. Based on these findings, perfluorohexylethyl triethoxysilane was determined to be non-irritating to the skin (ECHA 2018).

Ocular Irritation

In an eye irritation study performed in compliance with OECD 405 guidelines and GLP standards, perfluorohexyl ethyl triethoxysilane (undiluted) caused only minimal and temporary irritation to the eyes of small white Russian rabbits. Within one hour of application, pronounced hyperemia in several blood vessels was observed in all animals. In one animal, this redness in the connective tissue was

accompanied by mild swelling, including the nictitating membrane. The cornea and iris remained unaffected. At the 24-hour mark, only one animal displayed slight redness in the connective tissue, marked by distinct hyperemia of the blood vessels. No additional changes in the eye or conjunctiva were observed. By 48 and 72 hours, the eyes of all three animals appeared normal. As a result, perfluorohexylethyl triethoxysilane was not classified as an eye irritant (ECHA 2018).

Potential Hazard on Workers and General Population

By using the NOAEL value of 50 mg/kg bw/day determined from the repeated dose toxicity study, the REACH dossier also calculated the derived no effect level (DNEL) for both workers and the general population. The DNELs for workers were estimated to be 1.17 mg/m³ and 0.17 mg/kg bw/day for inhalation and dermal exposure respectively. For the general population, it was 0.083 mg/kg bw/day for both oral and dermal exposure routes, and 0.29 mg/m³ for inhalation exposure (ECHA 2018).

Summary of Hazard Assessment

According to the REACH dossier, perfluorohexylethyl triethoxysilane exhibits low acute toxicity based on the oral and dermal studies in rats, both showing LD_{50} values >2000 mg/kg. *In vitro* mutagenicity testing was negative. In addition, perfluorohexylethyl triethoxysilane was not found to be a skin sensitizer or irritant in a guinea pig Buehler test (OECD TG 406) or a rabbit acute dermal irritation/corrosion test (OECD TG 404). Eye irritation was not observed following exposure to undiluted perfluorohexylethyl triethoxysilane (OECD TG 405). However, data on respiratory effects, phototoxicity, and carcinogenicity is lacking.

A combined repeated dose oral toxicity study with reproduction/developmental toxicity screening tests in rats revealed peripheral nervous system toxicity after 28 days (males) or 54 days (females), with a NOAEL and LOAEL of 50 and 100 mg/kg bw/day, respectively. Additionally, no treatment related reproductive or developmental toxicity was observed. The NOAEL was determined to be ≥125 mg/kg bw/day, which was the highest dose tested.

Dermal contact is expected to be the primary and most relevant route of consumer exposure to perfluorohexylethyl triethoxysilane from the use of cosmetic products containing it. However, due to the lack of relevant dermal studies, the NOAEL derived from the only available oral toxicity study is used as the POD (point of departure) for risk characterization.

For systemic endpoints, the POD needs to be converted from an external exposure dose to an internal (systemic) POD by considering exposure duration and bioavailability. While no oral absorption study exists for perfluorohexylethyl triethoxysilane, the REACH dossier suggests low oral exposure based on computational models. However, the observed peripheral nervous system toxicity in the repeated dose toxicity study indicates some oral absorption. SCCS recommends "in the absence of data, 50% of the administered dose is used as the default oral absorption value for a cosmetic ingredient and the PODsys [systemic POD] is derived from the POD by dividing with a factor 2. If there is information to suggest poor oral bioavailability, a default value of 10% oral absorption could be considered."(SCCS 2023).

Given the lack of experimental oral absorption data and an animal study's support for oral absorption, we assume 50% oral absorption for perfluorohexylethyl triethoxysilane. Therefore, the systemic POD (PODsys) is calculated as 25 mg/kg bw/day (50 mg/kg bw/day divided by 2), which is used for risk characterization described after the Exposure Assessment section below.

Since the existing data suggests that perfluorohexylethyl triethoxysilane is not sensitizing, a No Expected Sensitization Induction Level (NESIL) was not identified. Similarly, due to the lack of data or non-irritating properties, no POD was derived for site-of contact irritation or phototoxicity.

Exposure Assessment

Exposure Scenario

Based on the product categories (**Table A.5.2)**, a consumer can be exposed to perfluorohexylethyl triethoxysilane via multiple exposure routes including dermal, oral, inhalation, and potentially ocular. Given that these cosmetic products are intended to be used topically, dermal contact is considered the primary exposure route and likely leads to the most significant exposure.

Oral, inhalation, and ocular exposures, while possible, are considered incidental. The REACH dossier indicates that there is negligible systemic uptake through inhalation considering the extremely low predicted blood:air partition coefficient (1.6E-06:1) for perfluorohexylethyl triethoxysilane (ECHA 2018). As such, an inhalation exposure assessment is not warranted. Similarly, while oral exposure is possible, the daily exposure to a product that may be ingested such as lipstick is 100 fold lower than exposure through using a body lotion (0.90 mg/kg bw/day vs 123.2 mg/kg bw/day) based on data in the SCCS Notes of Guidance, 12 revision (SCCS 2023). In addition, due to the lack of toxicity data for ocular exposure, the potential risk via this route cannot be determined. Furthermore, because none of these products appear to be intended for babies or children, only adults are considered in this assessment.

Considering all the above, the current exposure assessment will focus on dermal applications, which represents the most significant exposure route for perfluorohexylethyl triethoxysilane in these cosmetic products. Body lotion is selected as a conservative exposure scenario for this ingredient due to its high application frequency, full-body coverage, prolonged contact time and maximum application amount, leading to significant and repeated exposure.

Calculation of Systemic Exposure Dose (SED)

Under the body lotion exposure scenario, the level of systemic exposure from dermal application can be calculated using the following formula:

SED = CRDE * C * DAF

Where:

CRDE represents calculated relative daily exposure, i.e. the amount of body lotion applied that is available for dermal exposure

C represents concentration of perfluorohexylethyl triethoxysilane in the body lotion

DAF represents the dermal absorption factor (rate)

For adults, a default CRDE value of 123.2 mg/kg bw/day for body lotion, as established by the SCCS Notes of Guidance (SCCS 2023), is used in this calculation. This CRDE value has incorporated factors including the amount of product per use, frequency of use per day, and a retention factor (RF)[66] (RF=1 for leave-on products). Additionally, it has been adjusted based on body weight.

Due to the fact that information on ingredient use concentration is not required to be submitted to the FDA as part of the product listing data, the specific concentration of perfluorohexylethyl triethoxysilane in this product category is unknown. As such, we apply a conservative approach and assume the highest

[66] Retention factor (RF) represents the fraction (ranges from 0.01 to 1) of applied ingredient available for uptake. A retention factor of 1.0 may be incorporated if the product is applied directly to the skin and left on after use (such as body lotion, deodorant, or makeup), 0.1 if the product is rinsed shortly after use (such as mouthwash) or left on but not applied directly to the skin (hair styling products), or 0.01 if the product is rinsed off immediately after use (such as shampoo or shower gel).

recommended concentration of 0.82%, as described in the "Use in Cosmetic Products" section (Balan, Bruton et al. 2024), is used in the body lotion. This assumption is supported by a reported concentration of only 0.03% in a leave-on product.

Given the absence of experimental data, the DAF for perfluorohexylethyl triethoxysilane is undetermined. In the absence of experimentally determined dermal absorption data, we adopt a DAF of 50%, as recommended by the SCCS (SCCS 2023). Considering the results from computational modeling in the REACH dossier that suggests minimal dermal absorption due to the compound's relatively high molecular weight (510.36 g/mol), low water solubility, and high partition coefficient (log Know=7.2), the assumption of 50% DAF is conservative.

Therefore, the systemic exposure to perfluorohexylethyl triethoxysilane is determined to be 0.505 mg/kg bw/day based on the following calculation:

SED = 123.2 mg/kg bw/day * 0.0082 (equivalent to 0.82%) * 0.5 (equivalent to 50%) = 0.505 mg/kg bw/day

Risk Characterization

Risk characterization is the final step of a risk assessment, quantitively evaluating whether the level of exposure to a specific ingredient in a product or product type of interest poses potential health risks to the consumers. As noted in the hazard assessment section, the potential of acute toxicity for perfluorohexylethyl triethoxysilane is low. In addition, it does not appear to be sensitizing to skin or irritating to the skin or eyes. Due to lack of data, the potential for phototoxicity cannot be determined. Therefore, this current risk characterization focuses solely on the potential risk of systemic toxicity.

In risk characterization, Margin of Exposure (MOE) is used as a tool to assess possible health concerns. MOE is the ratio between a safety-based POD and the estimated exposure level, i.e., SED. The larger the margin, the lower the risk. Typically, a calculated MOE smaller than the target MOE (e.g. the default of 100) indicates a concern for potential health risk, while a calculated MOE larger than the target MOE does not indicate a health concern.

The target MOE and the calculated MOE for perfluorohexylethyl triethoxysilane are derived as described below.

Target MOE

Target MOEs are determined by the composite uncertainty factor (UF) applied in a risk assessment, i.e. the multiplication of all individual applicable UFs. The default target MOE for non-cancer endpoints is typically set at 100 when the POD is a NOAEL derived from high quality 90-day animal studies. This MOE equals a composite UF that is made up of a factor of 10 for interspecies variability, i.e., animal to human extrapolation, and a factor of 10 for intraspecies variability, i.e., interindividual variation in the human population. However, modifications to the default value of 100 can be applied. For example, an UF of 10 is applied for animal to human, or human to human extrapolation. If a LOAEL, rather than a NOAEL, is derived from a toxicity study, a default UF of 3 to 10 may be applied when using a LOAEL. Similarly, if a key toxicity study is a 28-day study, instead of the desired 90-day study, an UF of 3 may be applied (SCCS 2023). Typically, a composite UF of 3,000 is considered to be a maximum that should be used in an assessment (Stedeford, Zhao et al. 2007).

Given that the POD in this assessment was derived from a relatively short-term animal study of 28-54 days as opposed to a 90-day repeated dose toxicity study, an additional uncertainty factor of 3 is applied. Thus, the target MOE for perfluorohexylethyl triethoxysilane is determined to be ≥300. A calculated MOE of 300 or higher is indicative of low concern for health risk for perfluorohexylethyl triethoxysilane.

Calculated MOE

To characterize the risk of systemic toxicity endpoints, an MOE is calculated by dividing a POD (specifically, PODsys) with an estimated exposure, i.e., SED. Based on the PODsys and SED values calculated in the hazard assessment and exposure assessment sections, respectively, the MOE for perfluorohexylethyl triethoxysilane used in body lotion by adults is determined to be 50 as calculated below.

MOE = PODsys/SED = 25 mg/kg bw/day ÷ 0.505 mg/kg bw/day = 50

In this conservative use scenario, the calculated MOE (50) is smaller than the target MOE of ≥300, indicating a potential safety concern regarding the use of this ingredient in cosmetic products under this use scenario (body lotion).

Characterization of Uncertainty

This risk assessment for perfluorohexylethyl triethoxysilane was carried out based on a worst-case scenario and is subject to significant uncertainties due to limited data availability. First, the actual concentration of perfluorohexylethyl triethoxysilane in cosmetic products is unknown, and the assumed concentration of 0.82% may be an overestimation. Second, there is a lack of experimental data on oral or dermal absorption. While the toxicity effects from the repeated dose study support oral absorption, the actual absorption rate was not reported. The default absorption rate of 50% for both oral and dermal absorption could be an overestimate. Third, there is no dermal toxicity study which is most relevant to the exposure of cosmetic products. The extrapolation from oral to dermal introduces uncertainty as dermal toxicokinetics, in particular, absorption, distribution, and metabolism, may differ significantly from oral exposure, potentially affecting the toxicity profile. Fourth, the quality for the only available oral toxicity study used to derive the NOAEL, cannot be independently evaluated due to lack of a full report. The additional uncertainty factor of 3 may not be necessary or it could be reduced depending on the quality of the toxicity data. Fifth, the mechanism or mode of action by which perfluorohexylethyl triethoxysilane induced peripheral nervous system toxicity is not known, making it impossible to evaluate whether the observed effects in rats would also occur in humans, i.e., its human relevance cannot be assessed. Finally, the assessment considered exposure to one cosmetic product (body lotion), which could underestimate exposure because individuals may use more than one cosmetic product containing perfluorohexylethyl triethoxysilane given that the mandatory cosmetic product listing data submitted to the FDA indicates there are about 124 cosmetic products that contain this ingredient sold in the U.S. and available data indicates an increasing market over time in the VCRP.

By addressing these knowledge gaps, we can refine this assessment and ensure the safety of perfluorohexylethyl triethoxysilane containing cosmetic products.

Review Summary and Conclusion

Uses: Perfluorohexylethyl triethoxysilane, a fluorinated alkyl silane, is a cosmetic ingredient currently reported to be used in 124 products according to the mandatory cosmetic product listing data submitted to the FDA as of August 30, 2024. It is primarily used in makeup, in particular face powders and foundations. While limited data from the VCRP suggests an increasing trend and Mintel's GNPD suggests a possible decline in the use of perfluorohexylethyl triethoxysilane in cosmetic products, a trend cannot be demonstrated at this time due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA.

Safety: Based on the product types, consumers may be exposed to perfluorohexylethyl triethoxysilane through various routes when using cosmetic products. While dermal contact is likely the primary route of consumer exposure, the presence of perfluorohexylethyl triethoxysilane in face powders, foundations, lipstick, lip glosses, and eye makeup, such as eye shadow, could also lead to potential inhalation, oral, or ocular exposure.

The toxicokinetics of perfluorohexylethyl triethoxysilane remain largely unstudied. Limited information publicly available in a REACH dossier suggests perfluorohexylethyl triethoxysilane is absorbed orally, while dermal absorption is minimal, and inhalation absorption is negligible (ECHA 2018).

We did not identify any published and peer reviewed toxicity data for perfluorohexylethyl triethoxysilane via a literature search. However, a REACH dossier that summarizes unpublished toxicity studies is available. The available REACH data indicates that perfluorohexylethyl triethoxysilane is not acutely toxic, skin sensitizing, or irritating to the skin or eyes (ECHA 2018). A combined repeated dose and reproduction/developmental toxicity study revealed peripheral nervous system toxicity in rats with a NOAEL and LOAEL of 50 and 100 mg/kg bw/day, respectively. No reproductive or developmental toxicity was observed at the highest dose (125 mg/kg bw/day) tested. Assuming oral absorption of 50%, the NOAEL (i.e., POD) was converted to a PODsys of 25 mg/kg bw/day.

Systemic exposure (i.e., SED) to perfluorohexylethyl triethoxysilane from using cosmetic products was estimated to be 0.505 mg/kg bw/day for a worst-case use scenario. This estimation assumed the highest recommended use level of 0.82% perfluorohexylethyl triethoxysilane in body lotion, a dermal absorption rate of 50%, and the SCCS recommended product use amount of 123.2 mg/kg bw/day (SCCS 2023).

The calculated MOE of 50 in body lotion is below the target MOE of ≥300, which considers a factor of 10 for interspecies variation, 10 for intraspecies variation, and 3 for extrapolating toxicity data from a 28–54-day short-term study to 90-day subchronic study. This indicates a potential safety concern for perfluorohexylethyl triethoxysilane in body lotion under the most conservative or worst-case use scenario.

It is important to note that this assessment is preliminary and subject to significant uncertainties. These uncertainties stem from limited data on use concentration, lack of dermal and oral absorption, insufficient mechanistic information, absence of dermal toxicity data, and lack of co-exposure information (i.e., exposure to the ingredient from multiple cosmetic products).

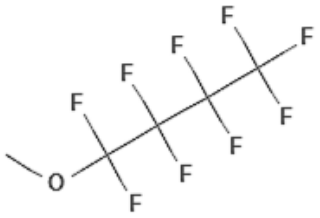
As more data becomes available, this assessment could be refined to provide a more accurate evaluation of the safety and potential risks of perfluorohexylethyl triethoxysilane's use in cosmetic products.

6. Methyl Perfluorobutyl Ether

Introduction

Methyl perfluorobutyl ether (CAS No. 163702-07-6; PubChem CID: 164514) is an asymmetric fluorinated ether compound with the chemical formula $C_5H_3F_9O$. It is also known as methyl nonafluorobutyl ether. It consists of a methyl group attached to a perfluorobutyl ether backbone. **Table A.6.1** shows the chemical structure and physicochemical properties. Methyl perfluorobutyl ether is typically a clear, colorless liquid with a mild ethereal odor. Its water solubility is not reported. However, the relatively high partition coefficient of 4.67 indicates that methyl perfluorobutyl ether is highly hydrophobic and poorly soluble in water. The high vapor pressure of 202 mmHg and a relatively low boiling point of 60 °C suggest that this chemical is highly volatile. While flammable, methyl perfluorobutyl ether is chemically stable. It is resistant to oxidation and does not readily react with common reagents under normal storage conditions.

Table A.6.1. Physical and Chemical Properties of Methyl Perfluorobutyl Ether

Element	Description
Name	Methyl Perfluorobutyl Ether
INCI name	Methyl Perfluorobutyl Ether
Synonyms	Methyl Nonafluorobutyl Ether Nonafluorobutyl methyl ether Perfluorobutyl Methyl Ether 1,1,1,2,2,3,3,4,4-nonafluoro-4-methoxybutane 1-methoxynonafluorobutane 1H,1H,1H-Nonafluoro-2-oxahexane Butane, 1,1,1,2,2,3,3,4,4-nonafluoro-4-methoxy-
CAS#	163702-07-6
Structure	
Molecular formula	$C_4F_9OCH_3$ (or $C_5H_3F_9O$)
Molecular weight	250.06 g/mol
Particle size	Not applicable
Physical form	Liquid, clear colorless with a mild ethereal odor

Element	Description
Density	1.529 g/ml at 20 °C; 1.52 g/ml at 25 °C[67]
Solubility	NA
Partition coefficient (Log K_{ow})	3.3 (predicted)
Vapor pressure	202 mmHg
Melting point	-135 °C[67]
Boiling point	60 °C[67]
Topological polar surface area	9.2 Å²
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Chemically stable. Resistant to oxidation and does not react readily with common reagents under normal condition.[67]

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, methyl perfluorobutyl ether, like its isomer methyl perfluoroisobutyl ether, is used as solvents and viscosity decreasing agents. The ingredient is used in three main product categories including cleansing products (cold creams, cleansing lotions, liquids and pads), face and neck preparations (excluding shaving preparations), and miscellaneous skin care preparations. According to a cosmetic ingredient supplier AE Chemie, methyl perfluorobutyl ether and its isomer, methyl perfluoroisobutyl ether, are used in AE CosmoFluor® 61, a brand name by AE Chemie, functioning as a fragrance enhancer, foam booster and cleansing agent for use in skin- and hair care formulations.[68]

Based on the mandatory cosmetic product listing data submitted to the FDA, methyl perfluorobutyl ether is currently used as an ingredient in 112 cosmetic products (**Table A.6.2)**. Similar to its isomer methyl perfluoroisobutyl ether, methyl perfluorobutyl ether is predominantly used in skin care products, accounting for 96.4% (n=108) of the ingredient's total usage in cosmetic products. It is commonly found in face and neck care products, both rinse-off (n=51, 45.5%) and leave-on (n=20, 17.9%). Cleansing products constitute 24.1% (n=27) of methyl perfluorobutyl ether's usage, while paste masks and other rinse-off skin care preparations represent 2.7% and 6.3%, respectively. Hair care products and non-eye makeup contribute to a smaller portion of its usage, at 2.7% and 0.9%, respectively (**Table A.6.2**). Please see **Table S2** for a full list of cosmetic product categories.

Table A.6.2. Frequency of Use of Methyl Perfluorobutyl Ether in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)

[67] Obtained from Chemical Book at https://www.chemicalbook.com/ProductChemicalPropertiesCB1328596_EN.htm (accessed 11/20/2024)

[68] See: https://cosmetics.specialchem.com/product/i-ae-chemie-ae-cosmofluor-61 (accessed 11/20/2024).

Skin care		
Face and neck, rinse-off	51	45.5
Face and neck, leave-on	20	17.9
Cleansing	27	24.1
Paste masks (mud packs)	3	2.7
Other skin care preparations, rinse-off	7	6.3
Skin care total	**108**	**96.4**
Hair care		
Hair conditioners, leave-on	1	0.9
Other hair preparations, leave-on	1	0.9
Other hair preparations, rinse-off	1	0.9
Hair care total	**3**	**2.7**
Makeup (not eye, traditional applications)	**1**	**0.9**
Grand total	**112**	**100.0**

Historical data from the VCRP revealed a slight increase in the use of methyl perfluorobutyl ether in cosmetic products, from 13 in 2019 to 17 in 2021 and 23 in 2023 (**Table S4**). However, the Mintel GNPD indicated a relatively stable use, with 28 products containing methyl perfluorobutyl ether launched in the U.S. market over a 5-year period (August 2019 to July 2024), including 5 launched in between August 2023 and July 2024 (**Table S4**). The use trend of methyl perfluorobutyl ether cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for methyl perfluorobutyl ether is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported the use of methyl perfluorobutyl ether at a range of 2% to 9% in cosmetic products. Additionally, a company reported using methyl perfluorobutyl ether at a concentration of 6.75% in facial masks according to a recent FDA survey.

Due to its predominant use in skin care products, consumers can be exposed to methyl perfluorobutyl ether primarily via dermal exposure from using cosmetic products. Oral and inhalation exposure are considered less likely based on the products in which this ingredient is used.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of methyl perfluorobutyl ether by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

One previous assessment, conducted by the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) in 2020 appears to be relevant to the safety of methyl perfluorobutyl ether (NICNAS 2020). This assessment, following the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework, is a tier II assessment of the human and environmental health of methyl perfluorobutyl ether along with a group of 15 other short chain perfluorocarboxylic acids (PFCAs) precursors. This NICNAS assessment concluded that the risk to the public from use of methyl perfluorobutyl ether is not considered to be unreasonable based on the low toxicity profile for this chemical (NICNAS 2020).

However, upon further examination of the citations used to support the safety of this ingredient, it was noted that all studies were conducted using HFE-7100 (or Cosmetic Fluid CF-61, a marketing name of HFE-7100 by 3M) as presented in another assessment (NICNAS 2006). As described earlier in this review, HEF-7100 is a mixture of methyl perfluorobutyl ether and methyl perfluoroisobutyl ether at a ratio of 40%: 60% (NRC 2007).

Given that this review is for a discrete individual chemical, i.e., methyl perfluorobutyl ether, these reports are not adopted for supporting the safety of either methyl perfluorobutyl ether or methyl perfluoroisobutyl ether in the current report.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no results in PubMed and 63 publications in Web of Science. After a title/abstract screening, we did not identify any publications relevant to the toxicokinetics of methyl perfluorobutyl ether. We also did not identify a REACH dossier for methyl perfluorobutyl ether in the ECHA database (9/16/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of methyl perfluorobutyl ether. However, we reviewed SDS from several raw material suppliers[69,70,71]. While these SDS reveal a general lack of toxicity data on acute toxicity, genotoxicity, repeated dose toxicity, carcinogenicity, and developmental and reproductive toxicity for this chemical, the SDS from AK Scientific Inc.[72] mentions a potential for health hazards associated with methyl perfluorobutyl ether exposure. These include skin, eye, and respiratory irritation. It may also cause drowsiness or dizziness as indicated by another supplier, SynQuest Laboratories, Inc.[73] Importantly, we note that the specific data regarding these health effects are unavailable for our independent evaluation.

Review Summary/Conclusion

[69] https://www.chemicalbook.com/msds/methyl-nonafluorobutyl-ether.pdf (accessed 1/2/2025).

[70] https://www.spectrumchemical.com//media/sds/M3112_AGHS.pdf (accessed 1/2/2025).

[71] https://www.tcichemicals.com/JP/ja/sds/M1345_JP_EN.pdf (accessed 1/2/2025).

[72] https://aksci.com/sds/J57155_SDS.pdf (accessed 1/2/2025).

[73] https://www.chemblink.com/MSDS/MSDSFiles/163702-07-6Syn-Quest.pdf (accessed 1/0/2025).

Uses: Based on the mandatory cosmetic product listing data submitted to the FDA, methyl perfluorobutyl ether is currently used in 112 cosmetic products. It is primarily used in skin care products, in particular face and neck care, including both rinse-off and leave-on types of products. The use of methyl perfluorobutyl ether in cosmetic products has shown a slight increase according to the VCRP data and stable usage trend per Mintel's GNPD. However, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, these trends cannot be demonstrated at this time.

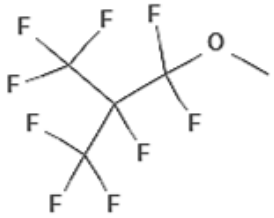
Safety: Based on the products that use methyl perfluorobutyl ether as an ingredient, consumers may be exposed to this ingredient primarily via dermal contact. In addition, due to the volatile nature of the chemical, inhalation exposure is possible. However, there is a significant lack of publicly available information regarding the toxicokinetics and toxicity of methyl perfluorobutyl ether. The FDA lacks the necessary information to assess its potential for eye and skin irritation, its ability to cause skin sensitization, and whether it can be absorbed into blood circulation and cause systemic toxicity. Due to these significant data gaps, the FDA cannot determine the safety of methyl perfluorobutyl ether from its use in cosmetic products or risks associated with such use.

7. Methyl Perfluoroisobutyl Ether

Introduction

Methyl perfluoroisobutyl ether, also known as methyl nonafluoroisobutyl ether (CAS No. 163702-08-7; PubChem CID: 4156734) is a fluorinated solvent used in various applications. It is synthesized from dimethyl ether and perfluoro(2-methylpropanoyl) fluoride. Methyl perfluoroisobutyl ether is the isomer of methyl perfluorobutyl ether that is reviewed in the previous section of this report (CAS No. 163702-07-6). **Table A.7.1** shows the chemical structure and physicochemical properties. Methyl perfluoroisobutyl ether is a clear, colorless liquid with a mild ethereal odor. It is slightly water soluble but is highly volatile owing to its high vapor pressure and low boiling point. In addition, methyl perfluoroisobutyl ether is highly stable chemically under normal laboratory conditions. It is also resistant to hydrolysis and oxidation.

Table A.7.1. Physical and Chemical Properties of Methyl Perfluoroisobutyl Ether

Element	Description
Name	Methyl Perfluoroisobutyl Ether
INCI name	Methyl Perfluoroisobutyl Ether
Synonyms	Methyl Nonafluoroisobutyl Ether Perfluoroisobutyl Methyl Ether 2-[difluoro(methoxy)methyl]-1,1,1,2,3,3,3-heptafluoropropane 2-(difluoromethoxymethyl)-1,1,1,2,3,3,3-heptafluoropropane 1,1,1,2,3,3-hexafluoro-3-methoxy-2-(trifluoromethyl)propane Propane, 2(difluoromethoxymethyl)1,1,1,2,3,3,3heptafluoro 1,1,2,3,3,3-hexafluoro-1-methoxy-2-(trifluoromethyl)propane
CAS#	163702-08-7
Structure	
Molecular formula	$CF_3CF(CF_3)CF_2OCH_3$ (or $C_5H_3F_9O$)
Molecular weight	250.06 g/mol
Particle size	Not applicable
Physical form	Liquid, clear colorless with a mild ethereal odor
Density	1.53 g/cm^3 at 20 °C (ECHA 1997)
Solubility	8.47 mg/L (ECHA 1997)
Partition coefficient (log K_{ow})	3.54 (ECHA 1997)
Vapor pressure	202.0 mmHg

Element	Description
Melting point	<0 °C (ECHA 1997)
Boiling point	≥60.5 °C ~ ≤62 °C at 101.3 kPa (ECHA 1997)
Topological polar surface area	9.2 Å²
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Highly stable under normal laboratory conditions; resistant to hydrolysis and oxidation.[74] Reflective index 1.27[75]

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, methyl perfluoroisobutyl ether is used as solvents and viscosity decreasing agents in two main cosmetic product categories including cleansing products (cold creams, cleansing lotions, liquids and pads), and face and neck preparations (excluding shaving preparations). Methyl perfluoroisobutyl ether and its isomer methyl perfluorobutyl ether are used in AE CosmoFluor® 61, a brand name by AE Chemie, acting as a fragrance enhancer, foam booster and cleansing agent. AE CosmoFluor® 61 is used in skin- and hair care formulations.[68]

Based on FDA's cosmetic product listing data, methyl perfluoroisobutyl ether is currently used as an ingredient in 106 cosmetic products. A substantial majority (n=105, 97.2%) of these products were categorized under the skin care product category (**Table A.7.2)**. Within the skin care product category, face and neck care products, including both rinse-off (n=49, 46.2%) and leave-on (n=13, 12.3%), are the most common, followed by cleansing products (n=27, 25.5%). While less common, methyl perfluoroisobutyl ether is also found in paste masks (2.8%), body and hand products (0.9%), and other miscellaneous skin care products (9.4%). Hair care products represent a small fraction (2.8%) of total use of methyl perfluoroisobutyl ether in cosmetic products as shown in **Table A.7.2**. Please see **Table S2** for a full list of cosmetic product categories.

Table A.7.2. Frequency of Use of Methyl Perfluoroisobutyl Ether in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Skin care		
Face and neck, rinse-off	49	46.2
Face and neck, leave-on	13	12.3
Cleansing	27	25.5

[74] Obtained from https://www.evitachem.com/product/evt-333518 (accessed 11/20/2024).

[75] Obtained from https://www.bocsci.com/product/methyl-perfluoroisobutyl-ether-cas-163702-08-7-72292.html (accessed 11/20/2024).

Paste masks (mud packs)	3	2.8
Body and hand	1	0.9
Other skin care preparations, rinse-off	10	9.4
Skin care total	**103**	**97.2**
Hair care		
Tonics, dressings, and other hair grooming aids	1	0.9
Other hair preparations, leave-on	1	0.9
Other hair preparations, rinse-off	1	0.9
Hair care total	**3**	**2.8**
Grand total	**106**	**100.0**

Like methyl perfluorobutyl ether, the use of methyl perfluoroisobutyl ether in cosmetic products saw a slight uptick in the VCRP before its sunsetting, increasing from 11 products in 2019 to 16 products in 2021, and to 22 products in 2023 (**Table S4**). According to the Mintel GNPD, 20 products containing methyl perfluoroisobutyl ether were launched in the U.S. market over a 5-year period (August 2019 to July 2024), with 4 products launched between August 2023 and July 2024 (**Table S4**). The use trend of methyl perfluoroisobutyl ether cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for methyl perfluoroisobutyl ether is not available. However, a recent publication by Balan, Bruton et al. (2024) reported a use range of 1% to 8% for methyl perfluoroisobutyl ether in cosmetic products. This was calculated based on a recommended use of 10% of AE CosmoFluor® 61, which contains methyl perfluoroisobutyl ether at a concentration of 10-80%. The actual concentration of methyl perfluoroisobutyl ether in a final product will vary depending on the specific product type and usage.

Given that the majority of the methyl perfluoroisobutyl ether-containing products (>97%) are used for skin care, dermal contact is expected to be the primary route of exposure to this ingredient from cosmetic use. Inhalation exposure is also possible due to the volatile nature of this ingredient. Other exposure routes, such as oral and ocular, are less likely.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of methyl perfluoroisobutyl ether by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A comprehensive literature search in PubMed and Web of Science did not identify any published data on the toxicokinetics of methyl perfluoroisobutyl ether (searched on 9/16/2024). We identified two REACH dossiers for methyl perfluoroisobutyl ether with limited publicly available information in the ECHA database (searched on 9/16/2024). However, no ADME/toxicokinetics data appears in these dossiers (ECHA 1997, ECHA 2011). The REACH dossiers (ECHA 1997, ECHA 2011) included toxicokinetic analyses of methyl perfluoroisobutyl ether based on the physicochemical properties such as molecular weight, lipophilicity, water solubility and vapor pressure. The dossiers stated that the absorption of methyl perfluoroisobutyl ether is expected to be high via inhalation, moderate via the oral, and low via the dermal routes. However, the FDA is unable to evaluate the quality and validity of the study due to the lack of critical details.

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of methyl perfluoroisobutyl ether. Relevant information pertaining to this review, as found in the two REACH dossiers, is summarized below in the corresponding sections.

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

No data.

Oral

An oral LD_{50} of >5,000 mg/kg bw was reported in one REACH dossier for methyl perfluoroisobutyl ether (ECHA 2011). The acute oral toxicity study, conducted in accordance with OECD TG 401 and GLP principles, involved 5 male and 5 female Crl:CD (SD)BR rats administered a single oral dose of 5,000 mg/kg bw undiluted methyl perfluoroisobutyl ether. Neither mortality nor visible lesions were observed during a 14-day observation period.

Inhalation

An inhalation LC_{50} of >361.8 mg/L air was reported in a 4-hour whole body inhalation exposure study in male and female Sprague-Dawley rats, as detailed in the REACH dossier for methyl perfluoroisobutyl ether (ECHA 1997). The dossier did not provide specific information on the number of animals, effects observed, or adherence to guidelines. Another study in the same dossier (ECHA 1997) reported an inhalation LC_{50} of >1,022.7 mg/L air in a 4-hour inhalation study in male Sprague-Dawley rats. No other details of the study were provided.

In summary, the above information indicates the acute toxicity for methyl perfluoroisobutyl ether is low.

Repeated Dose Systemic Toxicity

Dermal

No data.

Oral

No data.

Inhalation

A NOAEL of 77.1 mg/L in air was reported in a repeated dose inhalation toxicity study in rats in the REACH dossier for methyl perfluoroisobutyl ether (ECHA 1997). However, the dossier did not provide specific information on animal age and gender, dose levels, treatment duration, guideline compliance, or the critical effect (and the affected organ) associated with the NOAEL or a LOAEL.

Genotoxicity

An *in vitro* chromosome aberration test in V79 cells and an *in vivo* mammalian erythrocyte micronucleus test in mice were noted in the REACH dossier for methyl perfluoroisobutyl ether (ECHA 1997). Both studies reported negative in genotoxicity. However, details of the studies (e.g. concentration/dose, exposure route) were not reported.

An *in vitro* gene mutation study in bacteria was performed in accordance with OECD Guideline 471 (Bacterial Reverse Mutation Assay) and GLP principles (ECHA 2011). This study reported negative genotoxicity for methyl perfluoroisobutyl ether as well.

Carcinogenicity

No data.

Developmental and Reproductive Toxicity (DART)

The REACH dossier for methyl perfluoroisobutyl included a one-generation reproductive toxicity study in rats via nose only inhalation according to OECD TG 415, and a developmental toxicity study in rats via whole body inhalation according to OECD TG 414 (ECHA 1997). A NOAEL of 129.1 mg/L for parental rats (P0) and the first generation offsprings (F1), and a NOAEL of 304.5 mg/L for maternal and fetuses were determined. The study designs were not specified.

It is important to note that only very limited details regarding the studies were provided. Notably, the key effects associated with the NOAELs are missing, making it challenging to use these NOAELs for a quantitative risk assessment for this ingredient.

Neurotoxicity

The FDA did not identify any neurotoxicity data in the public literature. However, the information in the PubChem for methyl perfluoroisobutyl ether indicates it's a neurotoxin and may cause acute solvent syndrome. However, no citations were provided to support this claim.[76]

Site of Contact Effects

Dermal Irritation

An *in vivo* skin irritation study was conducted, according to OECD TG 404 (Acute Dermal Irritation / Corrosion) and GLP principles, in 3 male rabbits. Results of this study indicated that methyl perfluoroisobutyl ether was not a skin irritant (ECHA 2011).

[76] https://pubchem.ncbi.nlm.nih.gov/compound/4156734#section=Toxicity (accessed 11/21/2024).

Dermal Sensitization

Two skin sensitization tests, i.e., Guinea Pig Maximization Test and Buehler Test, were performed according to OECD 406 and GLP principles using undiluted methyl perfluoroisobutyl ether. Both studies reported negative results. Therefore, methyl perfluoroisobutyl ether was not classified as a skin sensitizer (ECHA 2011).

Ocular Irritation

An eye irritation test, according to OECD TG405 (Acute Eye Irritation / Corrosion) and GLP principles, was conducted in 3 male rabbits using undiluted methyl perfluoroisobutyl ether. Results indicated that methyl perfluoroisobutyl ether was not an eye irritant (ECHA 2011).

Respiratory irritation

No data.

Photo-induced toxicity

No data.

Others

None identified.

Review Summary/Conclusion

Uses: Methyl perfluoroisobutyl ether, an isomer of methyl perfluorobutyl ether, is used as an ingredient in 106 cosmetic products, according to the mandatory cosmetic product listing data submitted to the FDA. These products are predominantly for skin care (particularly face and neck care). Like methyl perfluorobutyl ether, the VCRP data indicated a slight increase in the use of methyl perfluoroisobutyl ether in cosmetic products, while Mintel's GNPD data suggested relatively stable usage in recent years. However, due to the lack of a baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend cannot be demonstrated at this time.

Safety: Given the primary use of methyl perfluoroisobutyl ether in skin care products, dermal contact is likely the most significant route of consumer exposure to this ingredient. In addition, due to its volatility, inhalation exposure may also be a potential exposure pathway.

However, there is no publicly available information on the toxicokinetics of methyl perfluoroisobutyl ether. Therefore, the potential for this ingredient to be absorbed via either dermal or inhalation routes cannot be determined. Furthermore, no published data relevant to the toxicity of methyl perfluoroisobutyl ether is available.

Limited information in the two REACH dossiers for this compound indicates a low concern for acute toxicity via either oral or inhalation exposure. It is not classified as a skin sensitizer, skin or ocular irritant. Additionally, both *in vitro* and *in vivo* genotoxicity studies did not produce any positive genotoxicity findings. There are no data available on respiratory irritation, phototoxicity, repeated dose dermal or oral toxicity, or carcinogenicity. While NOAELs were identified for a repeated dose inhalation study and developmental and reproductive studies, they cannot be used for a quantitative risk assessment. This is because the available REACH dossiers lack significant study details, such as critical effects related to the NOAELs, which prevents a proper assessment of study quality and reliability.

Given the limited data available, particularly related to toxicokinetic and long-term effects, the FDA cannot determine the safety of methyl perfluoroisobutyl ether from its use in cosmetic products or risks associated with such use.

8. Perfluorodecalin

Introduction

Perfluorodecalin (CAS No. 306-94-5; PubChem ID 9836) is a fluorocarbon, a derivative of decalin in which all of the hydrogen atoms are replaced by fluorine atoms. **Table A.8.1** shows the chemical structure and physicochemical properties. It is a colorless, odorless and tasteless liquid and is insoluble in water but soluble in low polar solvents like acetone and ethanol. It has a melting point of -5 °C, boiling point of 142 °C at 101 kPa and a vapor pressure of 0.88 kPa at 25 °C, indicating a low tendency to evaporate. In addition, perfluorodecalin is heat-resistant and stable up to 400 °C (ECHA 2016). The relatively high partition coefficient of 5.7 indicates that perfluorodecalin is highly hydrophobic and poorly soluble in water.

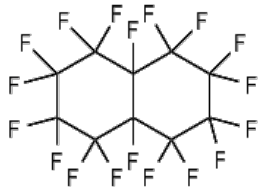
Perfluorodecalin has many medical applications. It is known for its exceptional ability to dissolve oxygen, making it a potential blood substitute for oxygen transport in the body. Perfluorodecalin was an ingredient in Fluosol-DA, an artificial blood substitute that was developed in the 1970s. It was approved for use in the U.S. in 1989 but discontinued due to side effects in 1994 (Zhao, Liu et al. 2024). It is also an ingredient in Perftoran, an emulsion of perfluorocarbons in a surfactant and electrolyte mixture, approved for use in some countries for hemorrhagic anemia and ischemic conditions (Latson 2019). However, it is not currently approved for human use in the U.S., and its long-term benefits and risks remain to be established with more extensive studies.

Highly purified perfluorodecalin has been extensively used in vitreoretinal surgery, particularly for retinal detachment treatment by acting as an ocular tamponade agent, holding the retina in place. Perfluorodecalin is generally well tolerated by patients, however, complete removal of perfluorodecalin is recommended at the end of surgical procedures to minimize the risk of potential retinal toxicity (Orzalesi, Migliavacca et al. 1998, Yu, Liu et al. 2014, Chehade, Guo et al. 2021). In addition, perfluorodecalin has been evaluated for use as a liquid ventilation agent for treating acute lung injury and respiratory failure (Suh, Chung et al. 2000, Dimmitt, Beckman et al. 2002, Guo, Lu et al. 2009); in cancer therapy for delivering oxygen to hypoxic tumors and enhancing the efficacy of radiotherapy and photodynamic therapy (Teicher and Rose 1984, Cheng, Cheng et al. 2015); in wound healing by topical application to provide extra oxygen to a specific location and accelerate the wound healing process (Li, Pang et al. 2022, Yang, Chen et al. 2022); and other uses such as organ preservation (Matsumoto and Kuroda 2002) and medical imaging as a contrast agent (Holman, Lorton et al. 2021).

In addition, perfluorodecalin has emerged as a promising clearing agent in laser tattoo removal procedures, showing notable safety and benefits over conventional methods. Reported advantages include better tolerability, increased efficacy, reduced particle emission, and fewer and less severe adverse effects such as epidermal whitening, thermal injury to epidermis, pain, swelling and scarring (Reddy, Brauer et al. 2013, Biesman and Costner 2017, Vangipuram, Hamill et al. 2019, Danysz, Becker et al. 2020). However, the long-term safety of using perfluorodecalin in tattoo removal requires further investigation.

Table A.8.1. Physical and Chemical Properties of Perfluorodecalin

Element	Description
Name	Perfluorodecalin

Element	Description
INCI name	Perfluorodecalin
Synonyms	Perflunafene Octadecafluorodecalin Naphthalene, octadecafluorodecahydro- Octadecafluorodecahydronaphthalene Decalin Perfluoride Perfluorodecahydronaphthalene Octadecafluorodecaline 1,1,2,2,3,3,4,4,4a,5,5,6,6,7,7,8,8,8a-Octadecafluorodecahydronaphthalene
CAS#	306-94-5
Structure	
Molecular formula	$C_{10}F_{18}$
Molecular weight	462.08 g/mol
Particle size	Not applicable
Physical form	Clear colorless, odorless liquid
Density	1.941 g/cm³ at 25 °C
Solubility	Insoluble in water; soluble in low polarity solvents such as acetone and ethanol.
Partition coefficient (Log K_{ow})	5.7 (predicted)
Vapor pressure	0.88 kPa at 25 °C
Melting point	-5 °C at 101 kPa
Boiling point	142 °C at 101 kPa
Topological polar surface area	0 Å² (computed)
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Stable up to 400 °C.

Notes: NA, not available. Sources: REACH registration dossier for perfluorodecalin (ECHA 2016); specified otherwise.

Use in Cosmetic Products

According to INCI, perfluorodecalin is a cosmetic ingredient functioning as miscellaneous skin-conditioning agents and solvents. It is reported to be used in various categories of cosmetic products including miscellaneous eye makeup preparations, moisturizing preparations, miscellaneous skin care preparations, face and neck preparations (excluding shaving preparations), and nail polish and enamels.

Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorodecalin is currently used in 71 cosmetic products (**Table A.8.2)**. Skin care products make up the largest category, accounting for 67.6% (N=48) of the total. Eye makeup is the second-largest category at 14.1% (N=10). Other categories include hair care, makeup (not eye), manicuring, and suntan, each representing less than 10% of the total products. Within skin care, face and neck leave-on products are the most prevalent, comprising 35.2% (N=25) of the total (**Table A.8.2**). Please see **Table S2** for a full list of cosmetic product categories.

Table A.8.2. Frequency of Use of Perfluorodecalin in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Eye makeup		
Eye shadows	7	9.9
Eye lotions	1	1.4
Other eye makeup	2	2.8
Eye makeup total	**10**	**14.1**
Hair care		
Other hair preparations, leave-on	**3**	**4.2**
Makeup preparations (not eye) (other than makeup preparations for children)		
Foundations, traditional application	2	2.8
Foundations, airbrush application	1	1.4
Fixatives	2	2.8
Makeup (not eye) total	**5**	**7.0**
Manicuring		
Basecoats and undercoats	1	1.4
Nail polishes and enamels	1	1.4
Manicuring total	**2**	**2.8**
Skin care		
Cleansing	1	1.4
Moisturizing	5	7.0
Face and neck, leave-on	25	35.2

Product Category	Number of Products	Percentage of Total (%)
Face and neck, rinse-off	4	5.6
Body and hand, leave-on	1	1.4
Body and hand, rinse-off	1	1.4
Paste masks (mud packs)	1	1.4
Other skin care, leave-on	6	8.5
Other skin care, rinse-off	4	5.6
Skin care total	**48**	**67.6**
Suntan		
Indoor tanning	2	2.8
Other suntan preparations	1	1.4
Suntan total	**3**	**4.2**
Grand total	**71**	**100.0**

Data from the VCRP and Mintel's GNPD indicated that the use of perfluorodecalin in cosmetic products in the U.S. market has remained relatively consistent. There were 36 perfluorodecalin-containing products in 2019 in the VCRP and 35 in 2021, decreasing to 28 in 2023 before the VCRP's discontinuation (**Table S4**). Mintel's GNPD data revealed that a total of 29 perfluorodecalin containing cosmetic products were launched in the U.S. market over a 5-year period (August 2019 to July 2024), with 6 of these launched between August 2023 and July 2024 (**Table S4**). The use trend of perfluorodecalin cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for perfluorodecalin is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) and a cosmetic ingredient supplier's datasheet,[77] reported the use concentration of 0.02% to 3.75% for perfluorodecalin in cosmetic products. It is important to note that this is the recommendation from one supplier; the actual use concentrations likely vary depending on specific suppliers and product types. As an example, one company reported using perfluorodecalin at 0.001% in a shave cream product, according to a recent FDA survey.

[77] https://cosmetics.specialchem.com/selectors?q=%20perfluorodecalin (accessed 10/10/2024). Based on information on the webpage, Innovation Company's Fiflow® products contain 1-25% perfluorodecalin. The suggested use concentration of these ingredients in final products is 2-15%. The use concentration for perfluorodecalin is thus calculated to be in the range of (1-25%)*(2-15%) = 0.02-3.75%.

Consumers can be exposed to perfluorodecalin primarily through dermal contact from using skin care products. Other routes of exposure, such as ingestion of lip products, inhalation of face powders, and ocular contact with eye makeup (including eye shadows and eyebrow pencils) are considered incidental.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of perfluorodecalin by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

We conducted a literature search for the ADME/toxicokinetics of perfluorodecalin using the query outlined in **Table S7** (searched on 10/15/2024)**.** The search yielded 336 publications. After the title, abstract and full text screening, 25 studies were deemed relevant. In addition, three extra publications were included from the review for the general toxicity of perfluorodecalin. We did not identify any toxicokinetic studies in the REACH dossier for perfluorodecalin (ECHA 2016). The REACH dossier (ECHA 2016) included a read-across study to evaluate ADME properties of perfluorodecalin based on a category approach using perfluorocarbons as analog. The study authors stated that saturated perfluorocarbons are well established as a class of compounds with very similar toxicological properties. The study authors concluded that perfluorodecalin is not expected to be absorbed significantly and tends to distribute to the liver and spleen. In addition, perfluorodecalin is not metabolized and is rapidly excreted by exhalation without bioaccumulation. However, we were unable to evaluate the quality and validity of the study due to the lack of critical details.

Animal studies are available for the distribution of perfluorodecalin though pulmonary and non-pulmonary exposure. For pulmonary administration routes, an animal study with male Wistar rats and rabbits indicated perfluorodecalin had extremely low bioavailability (no more than 0.2%), following the route of endotracheal administration (Zhurkovich, Utsal' et al. 2022). The lungs were identified as the main depot organ for perfluorodecalin. The study also shows that perfluorodecalin is rapidly eliminated through exhaled air with more than 200-fold decrease of perfluorodecalin concentration in the lungs (Zhurkovich, Utsal' et al. 2022). Similar results were found in another study with pre-term lambs, which also showed that the highest levels of the perfluorodecalin were found in the lungs (Shaffer, Wolfson et al. 1996). For non-pulmonary administration routes, a rat study using perfluorodecalin emulsions in a partial blood exchange procedure reported extensive uptake by the reticuloendothelial system, with preferential distribution to the liver and spleen (Shrewsbury, White et al. 1986). Similar findings were observed in a study involving dogs, where perfluorodecalin emulsion particles were taken up by phagolysosomes in various tissues. In the liver, particles were captured predominantly in Kupffer cells and macrophages (Mitsuno, Ohyanagi et al. 1984). In another study, the distribution of perfluorodecalin emulsions was observed to be primarily to the liver and spleen, followed by the kidney, bone marrow and lungs (Shrewsbury, Oliver et al. 1989). In a rat study with intraperitoneal administration of perfluorodecalin emulsions, the maximal concentration of perfluorodecalin in the spleen was identified 24 hours after treatment and the maximal concentration in the liver occurred 72 hours after treatment (Lowe and Bentley 1992).

Most perfluorodecalin is eliminated through the lungs by expiration, and small amounts are eliminated through the skin. Perfluorodecalin particles are mostly captured in the reticuloendothelial system and

then return to the blood vessels and transfer to the lungs for expiration with a half-life of 7.2 days in rats (Ohyanagi and Saitoh 1986). Based on a mouse study with intravenous injection of perfluorodecalin, the half-life of perfluorodecalin is 9 days, which is comparable to the half-life from rats (Jacoby, Temme et al. 2014). Another rat study with perfluorodecalin emulsion administered intravenously to rats suggested that perfluorodecalin is mainly eliminated through exhalation (Audran, Krafft et al. 2000). The biological half-life was reported to be 7 days in male rats following intravenous administration (Yokoyama, Yamanouchi et al. 1978). A review paper (Ravis, Hoke et al. 1991) analyzing the distribution and elimination of perfluorochemicals stated that perfluorodecalin is engulfed by phagocytic cells in the blood, liver, spleen, lymph nodes, lungs, and bone marrow. Perfluorodecalin does not undergo renal excretion due to its water insolubility and particle size.

In summary, perfluorodecalin exhibits minimal absorption according to available toxicokinetic studies discussed above. Once absorbed, perfluorodecalin distributes to tissues through the reticuloendothelial system. It is quickly eliminated from the body through exhalation without undergoing significant metabolic processing, as confirmed by studies and medical application investigations.

Hazard Assessment

We conducted a literature search on the acute and repeated dose toxicity of perfluorodecalin using the query outlined in **Table S7**. The search yielded 179 publications. After an initial title and abstract screening, we selected two of these publications deemed pertinent to the hazard assessment for inclusion in this section. In addition, we consulted a REACH dossier for perfluorodecalin available on the ECHA website (ECHA 2016) to supplement the existing literature. Relevant information from both the literature and the REACH dossier is summarized in the corresponding sections of this review. It is important to note that the REACH dossier provides only limited publicly available information and the original study reports were inaccessible for review. Thus, the quality of the data cannot be independently and fully evaluated.

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

The REACH dossier (ECHA 2016) included a read-across study to evaluate the acute dermal toxicity of perfluorodecalin using perfluoroperhydrofluorene as an analogue based on their justification that saturated perfluorocarbons are well established as a class of compounds with very similar toxicological properties. The study authors concluded that perfluorodecalin is not acutely toxic via dermal exposure. However, we were unable to evaluate the quality and validity of the study due to the lack of critical details.

Oral

The REACH dossier (ECHA 2016) includes two acute oral studies in rats. In one study, male and female Crj: CD(SD) rats (5/sex) were administered a single dose of 2,000 mg/kg bw perfluorodecalin by oral gavage, according to OECD TG420. No deaths or significant clinical signs of toxicity were observed in either sex. Based on these results, the LD_{50} was determined to be >2,000 mg/kg body weight, indicating a low concern for acute oral toxicity. In the second study, male and female Sprague-Dawley rats (5/sex) were treated with a single dose of 100 ml/kg bw perfluorodecalin following OECD TG401 and observed for 2 weeks. No deaths, clinical signs, or gross pathological abnormalities were observed in either male

or female rats. The LD_{50} was estimated to be >100 ml/kg (equivalent to 160,000 mg/kg, or more than 16% of rats' body weight), indicating very low acute oral toxicity.

Inhalation

The REACH dossier (ECHA 2016) presents an acute inhalation toxicity study conducted in Sprague-Dawley rats (guideline not specified). Rats (5/sex) were exposed to 8,647 ppm of perfluorodecalin vapor for approximately 60 minutes. No deaths, clinical signs, or adverse effects on body weight were observed. Post-mortem examinations revealed no abnormalities attributed to perfluorodecalin exposure. The acute inhalation LC_{50} was estimated to be >8,647 ppm. These results indicate that perfluorodecalin is considered to have no significant acute inhalation toxicity in rats at the tested concentration. The REACH dossier (ECHA 2016) also included a read-across study to evaluate the acute inhalation toxicity of perfluorodecalin using perfluoroperhydrofluorene as an analogue. The study authors concluded that perfluorodecalin is not acutely toxic via inhalation exposure. However, the FDA was unable to evaluate the quality and validity of the study due to the lack of critical details.

Other routes

A published abstract reported an LD_{50} of 13 ml/kg in rabbits for intravenously injected perfluorodecalin emulsion (10% v/v) stabilized with 4% Proxanol 268 (Sklifas, Obraztsov et al. 1991). The authors suggested that the observed animal death was likely due to pulmonary thrombosis resulting from the emulsion's instability in the circulatory system. However, specific methodology and detailed findings of the study were not provided.

In summary, the available data indicate that perfluorodecalin has low acute toxicity potential. The findings from studies involving intravenously administered perfluorodecalin are considered irrelevant to cosmetics use scenarios due to significant difference in exposure routes and extremely high dose levels used, which would not be encountered from typical use of cosmetic products.

Repeated Dose Systemic Toxicity

Dermal

No data.

Oral

No data.

Inhalation

The REACH dossier (ECHA 2016) included a read-across study to evaluate repeated dose inhalation toxicity of perfluorodecalin using octafluoropropane as an analogue. This study concluded that octafluoropropane is not chronically toxic, even at high concentrations, suggesting a low risk of chronic toxicity for perfluorodecalin based on the read-across approach. However, the FDA was unable to evaluate the quality and validity of the study due to the lack of critical details.

Other Routes of Exposure

In an animal study, emulsified perfluorodecalin was intravenously administered to male Wistar rats (average body weight 180-240 g), at doses of 0.1, 1 or 3 g/kg body weight (4-5 animals/group). Results showed a dose-dependent decrease in cytoplasmic motility of hepatic macrophages, attributing to

alterations in the cytoskeleton. The effect was not observed in rats receiving the lowest dose (0.1 g/kg bw) (Augustin, Spitznas et al. 1995).

Genotoxicity

We conducted a literature search on the genotoxicity potential of perfluorodecalin using the query outlined in **Table S7.** The search yielded five publications. After an initial abstract screening, we identified one paper as relevant to the current review.

Perfluorochemicals are generally considered biologically inert and can carry oxygen to organs and tissues. A study examined the effect of Perftoran® (perfluorodecalin) on the resistance of human lung cancer A549 cells to a chemotherapy drug (Gamal-Eldeen, Alrehaili et al. 2022). Perftoran (oxygenated) alone was found to not induce a significant increase in cell death and DNA damage in A549 cells when compared to control.

The REACH dossier for perfluorodecalin includes an Ames test that was performed four decades ago. The test showed that perfluorodecalin is not mutagenic (ECHA 2016).

Carcinogenicity

No data.

Developmental and Reproductive Toxicity (DART)

We conducted a literature search on the DART of perfluorodecalin using the query outlined in **Table S7**. The search yielded three publications with a focus on the efficacy of perfluorodecalin as an oxygen carrier. After an initial abstract screening, we identified one paper as relevant to the current review.

This study investigated the effect of perfluorodecalin on testicular endocrine function by determining the testosterone secretion rate (Chubb and Draper 1987). The testes of rats and mice were removed and perfused *in vitro* with medium containing perfluorodecalin. The testosterone secretion rate was not significantly different compared to control.

Neurotoxicity

We conducted a literature search on the neurotoxicity of perfluorodecalin using the query outlined in **Table S7.** The search yielded 22 publications. However, most of the studies focused on the therapeutic effects of perfluorodecalin in neurological diseases or injury. There was only one study that reported a potential neurotoxicity effect. This study investigated toxic effects of perfluorodecalin on ganglion cells *in vitro* (Meller, Augustin et al. 1998). Dorsal root ganglion (DRG) cells from chicken embryos were exposed to perfluorodecalin emulsion (consisted of 19% perfluorodecalin (w/v)) at 0.5%, 1% and 10% with particle size between 0.18 and 0.25 µm. The cells were evaluated after 30 hours and 120 hours for 0.5 and 1% and after 5 hours for 10%. Emulsified perfluorodecalin was shown to alter neuronal cell populations after brief exposure. Perfluorodecalin at concentrations of 0.5% and 1% did not change immunohistochemical labeling of DRG cells. A concentration of 10% led to degenerative alterations with a markedly reduced number of DRG cells and macrophages within 5 hours. The authors speculated that the toxicity may be caused by mechanical alteration and other pathophysiological mechanisms. The authors noted certain limitations of the study, such as physiological differences between the cell model and target tissue. This exposure route is not considered relevant to cosmetics usage.

Site of Contact Effects

Dermal Irritation

A PubMed and Web of Science literature search on dermal irritation, using the queries outlined in **Table S7** yielded a total of six publications. A thorough review of the full text identified no direct toxicity studies or reports of perfluorodecalin toxicity relevant to cosmetics use. However, four publications described the benefit of using perfluorodecalin, such as attenuating atopic dermatitis and reducing side effects in different dermal procedures, including tattoo removal. These studies provide indirect evidence to support that perfluorodecalin is unlikely to be a skin irritant. (Kim, Kim et al. 2014, Biesman and Costner 2017, Vangipuram, Hamill et al. 2018, Moustafa, Suggs et al. 2020).

Perfluorodecalin was evaluated for acute skin irritation in a semi-occlusive study conducted in accordance with OECD TG 404. In the three New Zealand White rabbits exposed to 0.5 ml of the undiluted test substance for 4 hours, no erythema or edema were observed throughout the 72-hour observation period (ECHA 2016).

Dermal Sensitization

We conducted a literature search on the skin sensitization of perfluorodecalin using the query outlined in **Table S7**. The search yielded 50 publications and after a title and abstract screening, none of the publications were identified as relevant to the current review. In most of the studies, perfluorodecalin emulsions, due to their favorable oxygen transporting properties, were proposed as a tumor sensitizer for application in radiation therapy (Zhitnukhin, Litvinenko et al. 1997).

The REACH dossier (ECHA 2016) included read-across studies to evaluate the skin sensitization of perfluorodecalin based on a category approach. It claimed that saturated perfluorocarbons, used as analogs, are well established as a class of compounds with very similar toxicological properties, and concluded that perfluorodecalin does not cause skin sensitization. However, the FDA was unable to evaluate the quality and validity of the studies due to the lack of critical details.

Ocular Irritation

A PubMed and Web of Science literature search on ocular irritation using the queries in **Table S7** yielded a total of two publications. Only one publication was identified as relevant after title and abstract screening. This study (Zhu, Wilson et al. 1999) tested a carbon-perfluorodecalin suspension in human eyes, finding it non-irritating and significantly better at retaining particles on the ocular surface than a saline suspension.

In an eye irritation study performed in compliance with OECD 405 guidelines, 0.1 ml perfluorodecalin (undiluted) did not cause irritation to the eyes of three New Zealand White rabbits throughout the 72-hour observation period (ECHA 2016).

The above information suggests that perfluorodecalin is non-irritating to the eyes.

Respiratory irritation

No data.

Photo-induced toxicity

No data.

Others:

The effects of perfluorodecalin were tested in an *in vitro* system using human peripheral leukocytes, erythrocytes, umbilical cord venous endothelial cells (ECV 304) and acute monocytic leukemia cells (MonoMac6). Perfluorodecalin did not cause hemolysis and had only mild effects on cell proliferation. Specifically, perfluorodecalin slightly increased the proliferation of endothelial cells (ECV 304) but decreased proliferation of monocytic cells (MonoMac6). In addition, it slightly suppressed the production of interleukin-1β (by 26%) and interleukin-6 (by 22%). Perfluorodecalin induced a low toxicity toward monocytes and granulocytes, causing approximately 20% and 12% cell death, respectively (Dinkelmann, Röhlke et al. 2001). These *in vitro* findings indicate that perfluorodecalin, under the tested conditions, exhibited minimal hemolytic activity, mild effects on cell proliferation and cytokine modulation, and relatively low toxicity in the specific cell types examined. It is important to note that these *in vitro* findings cannot be directly extrapolated to *in vivo* responses or used to predict the effects of perfluorodecalin in humans using cosmetics.

Review Summary/Conclusion

Uses: Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorodecalin is currently used in 71 cosmetic products as skin-conditioning agents and solvents. It is primarily used in skin care products, particularly for face and neck care, followed by eye cosmetic products such as eye shadows and lotions. The use concentration of perfluorodecalin in cosmetic products has been reported to range from 0.02% to 3.75%. Its frequency of use in cosmetic products has remained largely stable during the last several years, based on historical data from the VCRP and Mintel's GNPD. However, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, this trend cannot be demonstrated at this time.

Safety: Because the majority of the products containing perfluorodecalin are for skin care, dermal contact is considered the primary route for consumer exposure to this ingredient. Incidental exposure through ingestion, inhalation or ocular contact is also possible when using lip products, face powders, or eye makeup, respectively.

The dermal absorption rate of perfluorodecalin has not been previously reported but is expected to be minimal. Studies from other exposure routes, such as endotracheal and intravenous injection, indicate that any absorbed perfluorodecalin distributes to tissues through the reticuloendothelial system. Available data indicates that perfluorodecalin has no bioaccumulation potential and is quickly eliminated from the body through exhalation without undergoing significant metabolism. Notably, perfluorodecalin activates detoxification pathways, including the induction of xenobiotic transformation enzymes, such as CYP450 and glutathione-S-transferase. It also stimulates antioxidant defense mechanisms, such as activation of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase.

Based on available toxicity data, perfluorodecalin does not exhibit acute toxicity via dermal, oral or inhalation exposure routes. It is neither a skin sensitizer nor an irritant to the skin or eyes. We did not identify any relevant studies related to developmental, reproductive, or neurotoxic effects. Further, we did not identify any studies suggesting that perfluorodecalin is genotoxic. While limited to no data pertaining to repeated dose toxicity, respiratory irritation, phototoxicity, or carcinogenicity were identified in the available literature, the fact of low bioavailability in combination with rapid elimination suggests minimal concerns in these areas.

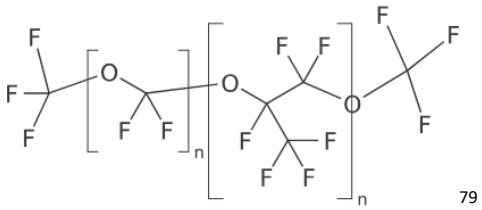
In summary, perfluorodecalin is a fluorocarbon skin-conditioning agent and solvent commonly used in skin care products. Its hydrophobic and lipophobic nature limit systemic absorption following dermal, oral or inhalation exposures. Available data indicate low concerns of acute, systemic and local toxicity.

Therefore, based on the limited data available, there is a low concern for safety associated with perfluorodecalin when used as an ingredient in cosmetic products under intended conditions of use.

9. Polyperfluoromethylisopropyl Ether

Introduction

Polyperfluoromethylisopropyl ether (CAS No. 69991-67-9; PubChem SID: 481176525), formerly known as perfluoropolymethylisopropyl ether, is a fluorine-based synthetic polymer. **Table A.9.1** shows the chemical structure and major physicochemical properties. Polyperfluoromethylisopropyl ether is a clear colorless liquid that is insoluble in water, highly hydrophobic due to a high Log K_{ow} (8.26) and is essentially involatile. Its molecular weight, density, viscosity, melting point and boiling points vary depending on the number of repeating units. It is stable under normal storage conditions and may decompose at temperatures above 350°C (662°F), forming hazardous fluorinated compounds.**Table A.9.1. Physical and Chemical Properties of Polyperfluoromethylisopropyl Ether**

Element	Description
Name	Polyperfluoromethylisopropyl Ether
INCI name	Polyperfluoromethylisopropyl Ether
Synonyms	1,1,2,3,3,3-Hexafluoro-1-Propene, Oxidized, Polymd 1-Propene, 1,1,2,3,3,3-hexafluoro-, oxidized, polymd Poly(1,1,2,3,3,3-hexafluoro-1-propene)[78] Perfluoropolymethylisopropyl ether[79] GALDENR HT230[78] GALDEN HT70[78] FOMBLIN YM-2700[78] FOMBLIN YR-1800[78] FOMBLIN HC (Trade Name)[80]
CAS#	69991-67-9
Structure	 79
Molecular formula	$[CF(CF_3)CF_2O]_x(CF_2O)_y$[81]
Molecular weight	Vary based on number of repeating units

[78] MOLBASE | Chemical Search and Share: https://www.molbase.com/cas/69991-67-9.html (accessed 1/4/2025).

[79] FDA's Global Substance Registration System (GSRS): https://gsrs.fda.gov/ginas/app/ui/substances/dbb769df-50a9-4eaa-b302-656d551dcc2b (accessed 1/4/2025)

[80] https://www.solvay.com/sites/g/files/srpend221/files/2018-10/Fomblin-HC-Transformative-Specialty-Ingredient_EN-v1.5_0.pdf (accessed 1/4/2025).

[81] Chemical Book-Product information for GALDEN HT70 from GALDEN (TM) HT70 CAS#: 69991-67-9 (accessed 1/4/2025).

Element	Description
Particle size	Not applicable
Physical form	Clear colorless liquid, Clear viscous odorless liquid[82]
Density	1.90-1.92 g/cm^3 at 0 °C[83]
Solubility	Insoluble in water[82]
Partition coefficient (Log K_{ow})	8.26[78]
Vapor pressure	0.00000004 mmHg
Melting point	-20 °C[78]
Boiling point	70 °C[78]
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	Thermal decomposition: 350ºC (662 °F)[82]
Additional properties	Flash point >230 °F[78]

Notes: NA, not available. Sources: PubChem; Specified otherwise.

Use in Cosmetic Products

According to INCI, polyperfluoromethylisopropyl ether functions as occlusive skin-conditioning agents and other miscellaneous skin-conditioning agents in cosmetic products. It is reported to be used in a variety of product categories including blushers (all types), eye lotions and shadows, face powders, indoor tanning preparations, makeup bases, miscellaneous manicuring preparations, miscellaneous skin care preparations, body and hand preparations (excluding shaving preparations), miscellaneous eye makeup preparations, face and neck preparations (excluding shaving preparations), foundations, lipsticks, miscellaneous makeup preparations (not eye), moisturizing preparations, suntan gels, creams, and liquids.

We note that Fomblin-HC is a commonly used trade name for polyperfluoromethylisopropyl ether of varying chain length. Based on raw material suppliers' information, Fomblin-HCs including HC/04, HC/25, HC/R, etc., are used in skin care and color cosmetics.[80]

Based on the mandatory cosmetic product listing data submitted to the FDA, polyperfluoromethylisopropyl ether is currently used as an ingredient in 54 cosmetic products (**Table A.9.2)**. The 54 products are categorized in the following four main product categories: eye makeup preparations (other than children's eye makeup preparations) (n=21, 38.9%); makeup preparations (not eye) (other than makeup preparations for children) (n=18, 33.3%); skin care preparations (creams, lotions, powder, and sprays) (n=14, 25.9%); and suntan preparations (n=1, 1.9%). Please see **Table S2** for a full list of cosmetic product categories.

[82] Material Safety Data Sheet for PFPE Oil TOPDA C Grades from https://www.fluorochemie.com/download/2469/?tmstv=1736255512 (accessed 1/4/2025).

[83] Technical Data Sheet for PFPE Oil TOPDA C Grades (C40, C250, C1250) from https://www.fluorochemie.com/products/pfpe-lubricants/fluorinated-oil-for-cosmetics (accessed 1/4/2025).

Table A.9.2. Frequency of Use of Polyperfluoromethylisopropyl Ether in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Eye makeup preparations (other than children's eye makeup preparations)		
Eyebrow pencils	4	7.4
Eyeliners	5	9.3
Eye shadows	11	20.4
Other eye makeup preparations	1	1.9
Eye makeup total	**21**	**38.9**
Makeup preparations (not eye) (other than makeup preparations for children)		
Blushers and rouges (all types)	1	1.9
Face powders	8	14.8
Foundations, traditional applications	2	3.7
Lipsticks and lip glosses	2	3.7
Makeup bases, traditional applications	1	1.9
Other makeup preparations, traditional applications	4	7.4
Makeup (not eye) total	**18**	**33.3**
Skin care preparations		
Cleansing	1	1.9
Face and neck, leave-on	11	20.4
Face and neck, rinse-off	1	1.9
Other skin care preparations, leave-on	1	1.9
Skin care total	**14**	**25.9**
Suntan preparations		
Suntan gels, creams, and liquids	**1**	**1.9**
Grand total	**54**	**100.0**

Available historical data suggests a stable use of polyperfluoromethylisopropyl ether in cosmetic products in the last several years. For example, it was present in 11 products in 2019, 10 in 2021 and 12

in 2023, according to the VCRP (**Table S4**). In addition, it appeared in 11 products launched in the U.S. market over a 5-year period (August 2019 to July 2024) and 3 products launched between August 2023 and July 2024 (**Table S4**). The use trend of polyperfluoromethylisopropyl ether cannot be demonstrated currently using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for polyperfluoromethylisopropyl ether is not available to the FDA. However, a recent publication by Balan, Bruton et al. (2024) reported a use concentration of 0.05-3% in cosmetic products.

Depending on the product categories, consumers can be exposed to polyperfluoromethylisopropyl ether through various routes. While dermal contact is considered the primary concern, ocular exposure can occur with products such as eye shadows applied near the eyes. Incidental ingestion is possible with products such as lipsticks and lip glosses. Similarly, incidental inhalation may occur during the use of face powders.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

In 2019, NICNAS of the Australian government conducted a Tier I assessment of the use of polyperfluoromethylisopropyl ether in cosmetic products following their IMAP (Inventory Multi-tiered Assessment and Prioritization) framework. They concluded that this ingredient is a low concern polymer and poses no unreasonable risk to human health based on a Tier I assessment under the NICNAS IMAP assessment framework (NICNAS 2019). The actual report is not accessible for review.

ADME/Toxicokinetics

We conducted a literature search in PubMed and Web of Science using the query outlined in **Table S9** (searched on 8/24/2024). The search retrieved six publications in both databases. None of these publications directly addressed the toxicokinetics of polyperfluoromethylisopropyl ether. However, the authors of one study concluded that Fomblin HC/25 might not be absorbed orally based on the negative results in a repeated dose toxicity study in rats (Malinverno, Pantini et al. 1996). Based on this, the authors speculated that dermal absorption in humans would also be minimal (Malinverno, Pantini et al. 1996). We did not identify a REACH dossier for polyperfluoromethylisopropyl ether in the ECHA database (searched on 8/24/2024).

Hazard Assessment

Using the literature search method described under the ADME/toxicokinetics section, we identified two articles relevant to the toxicity endpoints pertaining to polyperfluoromethylisopropyl ether. Relevant information is summarized in the corresponding sections below.

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

An acute dermal toxicity study was conducted in 5 male and 5 female rats according to EC guidelines (Annex to Commission Directive 92/69/EEC, part B: methods for the determination of toxicity) (Malinverno, Pantini et al. 1996). Undiluted Fomblin HC products, HC/25 (MW 3200) and HC/01 (MW 650), were dermally administered to the rats at a dose of 5 g/kg for 24 hours under occlusive dressings (HC/25) or semi-occlusive dressings (HC/01). Animals were observed for 14 days after dosing. Neither HC/25 nor HC/01 produced significant signs of reaction (clinical signs, body weight change or macroscopic abnormality at autopsy). This indicates a low acute dermal toxicity concern for polyperfluoromethylisopropyl ether.

Oral

An acute oral toxicity study was conducted in 5 male and 5 female rats according to EC guidelines (Malinverno, Pantini et al. 1996). Undiluted Fomblin HC products, HC/25 and HC/01, were given to the rats at doses of 15 g/kg orally. Animals were observed for 14 days after dosing. Neither HC/25 nor HC/01 produced significant signs of reaction (clinical signs, body weight change or macroscopic abnormality at autopsy). This indicates a low acute oral toxicity concern for polyperfluoromethylisopropyl ether.

Inhalation

No data.

Other Exposure Route

An acute toxicity study was conducted in 5 male and 5 female rats according to EC guidelines (Malinverno, Pantini et al. 1996). Fomblin HC/25, without dilution, at a dose of 5 g/kg, was intraperitoneally injected (IP) to animals and observed for 14 days after dosing. HC/25 did not produce significant signs of reaction (clinical signs, body weight change or macroscopic abnormality at autopsy). This indicates polyperfluoromethylisopropyl ether is not acutely toxic via IP injection.

Repeated Dose Systemic Toxicity

Dermal

No data.

Oral

A 28-day repeated dose toxicity test was conducted in 5 male and 5 female rats according to EC guidelines (Malinverno, Pantini et al. 1996). Fomblin HC/25 was dosed without dilution orally by gavage each day for 28 days at a dose of 1000 mg/kg bw/day. The animals showed no visible changes in behavior after daily dosing. The authors did not observe any clinical signs. Biochemical and hematological measurements showed no significant changes compared to the controls. Autopsy examination and microscopic examination of the selected organs and macroscopic abnormalities also revealed no changes considered to be treatment related, except that microscopic finding in the kidney tubules of four out of five test group males showed some basophilic and/or dilated tubules, compared to none in control. However, the study authors concluded that the observed kidney tubule effect was of no toxicological importance because it was for one sex only, without accompanying effects on kidney weight and blood chemistry parameters indicating kidney damage (Malinverno, Pantini et al. 1996).

Inhalation

No data

Genotoxicity

The mutagenicity of Fomblin HC/25 and HC/01 was tested using Ames assay at concentrations of 50 to 5000/µg/plate according to EC guidelines. Both chemicals were negative for mutagenicity (Malinverno, Pantini et al. 1996).

Carcinogenicity

No data.

Developmental and Reproductive Toxicity (DART)

No Data.

Neurotoxicity

No data.

Site of Contact Effects:

Dermal Irritation

The skin irritancy of polyperfluoromethylisopropyl ether in Fomblin HC/25 and HC/01 was investigated in New Zealand White rabbits (number and sex not specified). Results showed the two Fomblins tested are non-irritating to rabbit skin (Malinverno, Pantini et al. 1996). Two repeated-dose dermal irritation tests performed on human volunteers in Japan and Europe confirmed the non-irritancy of Fomblin HC/25 and HC/01 (Malinverno, Pantini et al. 1996). The fact that Fomblin HC are protective of irritant contact dermatitis further supports the non-irritancy of this ingredient (Pantini, Forestieri et al. 1990).

Dermal Sensitization

The skin sensitizing potential of four different Fomblin HC products (HC/25, HC/01, HC/04 and HC/R) was evaluated in guinea pigs. No evidence of skin sensitization was observed. Fomblin products were also tested in human volunteers to investigate the effects of prolonged skin contact, and the authors did not observe any sensitization (Malinverno, Pantini et al. 1996).

Ocular Irritation

Ocular irritancy of Fomblin HC/25 and HC/01 was investigated in six and three New Zealand White rabbits, respectively. No reactions to test materials were noted and examinations at 1 to 72 hours after treatment found no conjunctival, iridial or corneal changes, indicating the two Fomblins tested were non-irritating to rabbit eyes.

Respiratory irritation

No data.

Photo-induced toxicity

The photosensitizing potentials of Fomblin HC/25 and HC/R were evaluated in Dunkin-Hartley albino guinea pigs. Results indicated the two Fomblins were negative for photosensitization (Malinverno, Pantini et al. 1996).

Others

None identified.

Review Summary/Conclusion

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, polyperfluoromethylisopropyl ether is currently used as an ingredient in 54 cosmetic products, predominantly makeup preparations and skin care products. Available information from the VCRP and Mintel's GNPD indicates a relative stable use of polyperfluoromethylisopropyl ether in cosmetic products in the past several years. However, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a definitive trend cannot be demonstrated at this time.

Safety: Given the primary use of polyperfluoromethylisopropyl ether in eye makeup and skin care products, ocular and dermal exposures are likely the most significant routes of consumer exposure to this ingredient. In addition, incidental ingestion, such as from using lipsticks and lip glosses, and incidental inhalation exposure from using face powders may also be potential exposure pathways. Limited data suggests polyperfluoromethylisopropyl ether may not be absorbed orally and dermal absorption is minimal.

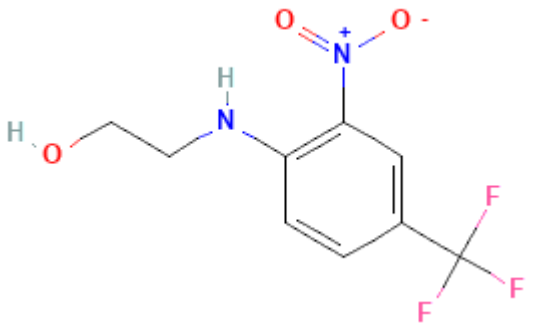
Available animal toxicity studies conducted via dermal, oral and IP routes indicate polyperfluoromethylisopropyl ether does not exhibit acute toxicity. It has been observed to be non-mutagenic in bacteria assays, non-irritating to the skin or eyes of rabbits, and non-sensitizing to human skin. Further, oral administration of polyperfluoromethylisopropyl ether at a dose of 1,000 mg/kg bw/day for 28 days did not reveal any significant toxicity in rats. These data collectively suggest a low potential for toxicity of this ingredient. However, available data is limited. In particular, there is insufficient information regarding the long-terms effects, including potential developmental and reproductive toxicity. Therefore, the FDA cannot determine the safety of polyperfluoromethylisopropyl ether from its use in cosmetic products or risks associated with such use based on the currently available data.

10. HC Yellow No. 13

Introduction

HC Yellow No. 13 (CAS No. 10442-83-8; PubChem CID: 2799157) is a secondary alkanolamine which is prone to nitrosation. **Table A.10.1** shows its chemical structure and limited information on physicochemical properties. HC Yellow No. 13 is a yellow crystalline powder with moderate solubility in water and high solubility in DMSO. It is generally stable in aqueous and organic solutions at room temperature. HC Yellow No. 13 consists of more than 99% of N-(2-hydroxyethyl)-2-nitro-4trifluormethylaniline. The chemical has trade names including Fluorgelb II, Cos 128, and COLIPA B102 (SCCS 2011).

Table A.10.1. Physical and Chemical Properties of HC Yellow No. 13

Element	Description
Name	HC Yellow No. 13
INCI name	HC Yellow No. 13
Synonyms	2-((2-Nitro-4-(trifluoromethyl)phenyl)amino)ethanol 2-[2-nitro-4-(trifluoromethyl)anilino]ethanol 2-{[2-nitro-4-(trifluoromethyl)phenyl]amino}ethanol N-(2-Hydroxyethyl)-2-nitro-5-(trifluoromethyl)aniline 4-(2-Hydroxyethylamino)-3-nitrobenzotrifluoride
CAS#	10442-83-8
Structure	
Molecular formula	$C_9H_9F_3N_2O_3$
Molecular weight	250.17 g/mol
Particle size	NA

Element	Description
Physical form	Yellow crystalline powder[84]
Density	Relative: 1.45 (20 °C)[84], 1.486±0.06 g/cm^3(Predicted)[85]
Solubility	Water solubility: 506 mg/L (20 °C) determined by EC –A.6 method DMSO solubility: 50 mg/ml[84]
Partition coefficient (Log K_{ow})	2.54 (pH 6.5 -7.1, 23 °C) determined by EC –A.8 method,[84] 2.520 (est),[85] 2.614[86]
Vapor pressure	3.1 x 10-8 hPa (20 °C),[84] 1.52E-05 mmHg at 25 °C[86]
Melting point	74.7 °C,[84] 78-79 °C[85]
Boiling point	227.1 °C,[84] 351.5±42.0 °C (predicted)[85]
Topological polar surface area	78.08 Å^2 [86]
UV light absorption spectrum	Absorption maxima at 240 nm and 408 nm[84]
Decomposes	NA
Additional properties	pKa: 14.54±0.10 (predicted),[85] flash point 166.4 °C,[86] reflective index 1.549[86]

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, HC Yellow No. 13 functions as hair colorants in cosmetic products. Based on the mandatory cosmetic product listing data submitted to the FDA, HC Yellow No. 13 is used as an ingredient in 40 cosmetic products (**Table A.10.2)**. All 40 products are categorized in the hair coloring preparations product category. Please see **Table S2** for a full list of cosmetic product categories.

According to the Mintel GNPD, no product containing HC Yellow No. 13 was launched in the past 5 years (August 2019 to July 2024). There was no reported use of HC Yellow No. 13 in cosmetic products in the VCRP in 2019 and 2021, but there were 6 reported uses in the VCRP before its sunsetting in 2023 (**Table S4**). The use trend of HC Yellow No. 13 cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Within the hair coloring preparations product category, HC Yellow No. 13 is predominantly used in hair dyes and colors, accounting for 75.0% of the ingredient's total usage in cosmetic products. It is also used in hair tints, hair rinses (coloring), and hair bleaches as shown in **Table A.10.2**.

[84] SCCS, 2010: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_044.pdf (accessed 12/4/2024).

[85] https://www.chemicalbook.com/ProductChemicalPropertiesCB4946856_EN.htm (accessed 12/4/2024)..

[86] https://m.molbase.com/moldata/133431.html (accessed 12/4/2024)..

Table A.10.2. Frequency of Use of HC Yellow No. 13 in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Hair coloring preparations		
Hair dyes and colors	30	75.0
Hair tints	2	5.0
Hair rinses (coloring), rinse-off	1	2.5
Hair bleaches	7	17.5
Total	**40**	**100.0**

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for HC Yellow No. 13 is not available to the FDA. SCCS reported a maximum on-head concentration of 2.5% in non-oxidative and oxidative hair dye formulations in its opinion report (SCCS 2011). According to the SCCS report, for non-oxidative hair dye formulations, it is common to apply 35 to 50 g of the product over a period of 30 minutes followed by rinsing off with water and shampoo. The application may be repeated at weekly intervals. For oxidative hair dye formulations, the coloring component and a developer (hydrogen peroxide) are mixed in ratios between 1:1 to 1:3 and up to 100 g of the finished mixed product is applied for a period of 30 to 45 minutes followed by rinsing off with water and shampoo. The application may be repeated at monthly intervals.

According to the product categories, HC Yellow No. 13 is used in hair coloring preparations. Thus, the primary exposure route to HC Yellow No. 13 for consumers would be dermal contact.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search within data sources listed in **Table S5** identified an SCCS opinion on HC Yellow No. 13. The SCCS committee assessed the use of HC Yellow No. 13 as a direct dye with a maximum on-head concentration of 2.5% in oxidative and non-oxidative hair dye formulations and concluded it does not pose a risk to the health of the consumer (SCCS 2011).

ADME/Toxicokinetics

A literature search in PubMed and Web of Science did not identify any published data on the toxicokinetics of HC Yellow No. 13 (searched on 12/4/2024). There was no ADME/Toxicokinetics information in the REACH dossier for HC Yellow No. 13 in the ECHA database (ECHA 2002) (accessed on 12/4/2024). Studies for the toxicokinetics of HC Yellow No. 13 were identified in the report from the SCCS of the European Commission (SCCS 2011). An *in vivo* study was conducted to investigate the absorption, distribution, and excretion of HC Yellow No. 13 in Sprague Dawley rats after both oral and dermal exposure. For oral administration, HC Yellow No. 13 was quickly absorbed and excreted within 72 hours, with the majority eliminated within 24 hours after application, mainly via urine (82% of the applied dose within 72 hours) and to a minor extent via feces (18%). Following dermal exposure, the absorption of HC Yellow No. 13 was low, ranging from 0.121% to 0.147% of the applied dose. The majority of the absorbed dose was excreted via urine (63-75%) and to a lesser extent via feces (25-37%).

The radioactivity remaining in the skin and other tissues was low, with the highest concentrations found in the thyroid, adrenals, and fat. The excretion pattern after dermal exposure was similar to that observed for the oral route, with the majority excreted via urine within 24 hours after administration. The low tissue residue levels and minimal skin retention suggest that bioaccumulation of HC Yellow No. 13 is unlikely.

In summary, while HC Yellow No. 13 is well-absorbed after oral exposure, it is poorly absorbed through the skin, with rapid excretion via urine and feces. The low tissue residue levels and minimal skin retention indicate that bioaccumulation is unlikely for HC Yellow No. 13.

Hazard Assessment

A literature search in PubMed and Web of Science using the queries outlined in **Table S9** yielded no published toxicity data for HC Yellow No. 13. We identified a dossier for HC Yellow 13 in ECHA, which contains the same toxicity information as mentioned in a report from SCCS (2011). The relevant toxicity information is summarized below. Note that the FDA does not have access to any of the original study reports.

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

An acute dermal toxicity study was conducted in 5 male and 5 female rats according to OECD TG 402 and in compliance with GLP (SCCS 2011). Fluorgelb II (Trade name of HC Yellow No. 13) was administered at a dose of 2000 mg/kg bw under an occlusive patch on the back of the rats for 24 hours. The animals were observed twice daily for 14 days. No mortalities were observed. The treatment caused chromodacryorrhea (red lacrimal secretion from the eyes) in 3 males and in 2 females. The LD_{50} was reported to be >2000 mg/kg bw.

Oral

An acute oral toxicity study was conducted in 5 male and 5 female rats according to OECD TG 401 and in compliance with GLP (SCCS 2011). The rats received a single oral dose of 2000 mg/kg bw Fluorgelb II in 2% gum Arabic and were observed daily for 14 days. No mortalities were observed. The treatment caused lethargy, piloerection, abnormal posture and reduced righting reflex for up to 6 hours after dosing. The LD_{50} was >2000 mg/kg bw.

Inhalation

No data.

Repeated Dose Systemic Toxicity

Dermal

No data.

Oral

A sub-chronic oral toxicity study was conducted in 15 male and 15 female rats according to OECD TG 408 and in compliance with GLP. Fluorgelb II in 0.5% aqueous sodium carboxymethylcellulose was administered by oral gavage at doses of 10, 30 and 90 mg/kg bw/day, 5 days per week for 90-92 days. No mortalities were observed during the study. Islet cell degeneration, accompanied by inflammation or fibrosis of the endocrine pancreas was observed in two of the male rats treated with 90 mg/kg bw/day.

A high but not statistically significant blood glucose level was also observed and considered to be treatment related. No other treatment related effects were reported. The authors suggested a dose of 90 mg/kg bw/day as the LOAEL and 30 mg/kg bw/day as the NOAEL. However, the NOAEL was adjusted to 21 mg/kg bw/day after considering that the rats only received treatment 5 days per week (SCCS 2011).

Inhalation

No data.

Genotoxicity

An Ames test was conducted in accordance with OECD TG 471 and GLP (SCCS 2011). HC Yellow 13 was tested at up to 5,000 µg/plate with and without S9-mix (a liver enzyme system for metabolic activation). The study authors concluded that this ingredient was not mutagenic after conducting the Ames test.

An *in vitro* study for induction of chromosomal aberrations in V79 cells was conducted in accordance with OECD TG 471 and in compliance with GLP (SCCS 2011). The cells were treated with Fluorgelb II at 50, 100, and 150 µg/ml in the presence and absence of S9-mix for 4 hours. A biologically relevant, statistically significant and dose-dependent increase in the number of cells with chromosome aberrations was found in the presence of S9-mix. No biologically relevant increase in the number of polyploid metaphases was recorded. Fluorgelb II was considered genotoxic in the *in vitro* test.

An *in vivo* study for the induction of micronuclei in bone marrow cells of mice was conducted in accordance with OECD TG 474 and in compliance with GLP (SCCS 2011). The mice were exposed to Fluorgelb II orally three times at 24-hour intervals at dose levels of 0, 375, 750 and 1500 mg/kg bw/day. An increased number of bone marrow cells with micronuclei was not found. Fluorgelb II was not considered genotoxic in bone marrow cells of mice. Although the study did not demonstrate that bone marrow was reached, clinical signs indicated systemic distribution and thus bioavailability of Fluorgelb II.

Carcinogenicity

No data.

Developmental and Reproductive Toxicity (DART)

A teratogenicity study was conducted in rats in accordance with OECD TG 414 and in compliance with GLP (SCCS 2011). Fluorgelb II dissolved in 0.5% sodium carboxymethylcellulose was administered by gavage to pregnant rats at dose levels of 10, 30 and 90 mg/kg bw/day on days 6-15 of gestation. The dams were euthanized on day 20 of gestation and the abdominal and thoracic cavities were examined. The fetuses were examined for external abnormalities, skeletal defects and visceral abnormalities. No treatment related adverse effects were observed in the dams. A slight decrease of viable fetuses per female and an increase in the number of post implantation losses were observed at 30 and 90 mg/kg bw/day. No gross, skeletal or visceral malformations were observed in fetuses, but there was delayed skeletal ossification of metacarpals and the sternum in fetuses at 30 and 90 mg/kg bw/day. The reproductive performance was not affected but slight increased embryolethality was observed. Based on the results, the study authors identified a NOAEL of 90 mg/kg bw/day for maternal toxicity, embryotoxicity and teratogenicity, and a NOAEL of 10 mg/kg bw/day and a LOAEL of 30 mg/kg bw/day for developmental anomalies.

Neurotoxicity

No data.

Site of Contact Effects:

Dermal Irritation

The SCCS report in 2010 cited a study in compliance with OECD TG 404, where a 5% solution of HC Yellow No. 13 did not cause skin irritation in rabbits (SCCS 2011). A 0.5 ml sample of a 5% HC Yellow No. 13 in propylene glycol was applied to the clipped backs of 6 New Zealand white rabbits under occlusion for 4 hours before the solution was washed off. Skin reactions were evaluated at 30–60 minutes and 24-, 48-, and 72-hours post-exposure. No erythema or edema was observed.

Dermal Sensitization

SCCS concluded in 2010 that a possible sensitizing effect of HC Yellow No. 13 cannot be excluded based on a Guinea pig maximization test of Magnusson and Kligman (SCCS 2011). However, the study was not fully in compliance with OECD guideline 406, which specifies that, when testing a non-irritating material, local irritation should be included 24 hours before the topical induction. The sensitization data in this study was generated without irritation during induction.

Ocular Irritation

SCCS concluded in 2010 that HC Yellow No. 13 is not an eye irritant under the cited experimental conditions (SCCS 2011). In a study performed in compliance with OECD TG 405, a 0.1 ml dose of a 5% solution of HC Yellow No. 13 in propylene glycol was instilled into the left eye of 6 New Zealand White rabbits, with 3 of the animals having the solution rinsed out after 4 seconds. The untreated right eye served as a control. Eye reactions were assessed at 1-, 24-, 48-, and 72-hours post-treatment. Mild redness and conjunctival chemosis were observed, but based on 83/467/EEC criteria, 5% HC Yellow No. 13 in propylene glycol was classified as a non-irritant. In another study under similar experimental conditions on three female New Zealand White rabbits using undiluted HC Yellow No. 13, only mild reactions were observed, including slight effects on the cornea, iris, and conjunctiva, where the undiluted material was also classified as a non-irritant.

Respiratory irritation

No data.

Photo-induced toxicity

No data.

Others

None identified.

Review Summary/Conclusion

Use: HC Yellow No. 13 functions as hair colorants in cosmetic products. Based on the mandatory cosmetic product listing data submitted to the FDA, the ingredient is used in 40 products, all categorized

in the hair coloring preparations product category. It is predominantly used in hair dyes and colors (75%). Other usages include hair tints, hair rinses (coloring), and hair bleaches. SCCS reported a maximum on-head concentration of 2.5% in both non-oxidative and oxidative hair dye formulations.

Available information from the VCRP and Mintel's GNPD does not reveal a trend of use in cosmetic products. Due to the lack of baseline or historical data, a definitive trend also cannot be demonstrated using the mandatory cosmetic product listing data submitted to the FDA.

Safety: Given that HC Yellow No. 13 is primarily used in hair dye products, dermal contact is expected to be the main route of consumer exposure from using products containing this ingredient. A skin penetration study indicated a maximum penetration of 0.15% (2.5 µg/cm^2) or 0.121% (2.9 µg/cm^2) for the formulation with or without oxidative H_2O_2, respectively, suggesting a low skin absorption. Incidental inhalation or ocular exposure may occur with a negligible level.

Based on the 2010 SCCS report, HC Yellow No. 13 exhibited low acute toxicity in rats following dermal or oral exposure. A NOAEL of 21 mg/kg bw/day for sub-chronic oral toxicity study, a NOAEL of 90 mg/kg bw/day for maternal toxicity, embryotoxicity and teratogenicity, and a NOAEL of 10 mg/kg bw/day for developmental anomalies were determined with HC Yellow No. 13 via oral gavage exposure. No dermal or ocular irritation was observed in laboratory animals. HC Yellow No. 13 was not mutagenic in a bacterial test. It was positive for clastogenicity in an *in vitro* chromosomal aberration test but gave negative results in the mammalian erythrocyte micronucleus test. We did not identify any cancer or neurotoxicity studies in the literature. SCCS concluded that the use of HC Yellow No. 13 as a direct dye with a maximum on-head concentration of 2.5% in oxidative and non-oxidative hair dye formulations does not pose a risk to the health of the consumers (SCCS 2011).

11. Perfluorohexane

Introduction

Perfluorohexane (CAS No. 355-42-0; PubChem CID: 9639), also known as perflexane or tetradecafluorohexane, is a fluorocarbon. It is a derivative of hexane in which all the hydrogen atoms are replaced by fluorine atoms. **Table A.11.1** shows the chemical structure and physicochemical properties. Perfluorohexane is a clear colorless liquid. It is very poorly water soluble but soluble in lipophilic reagents such as ethyl ether, benzene, and chloroform. The relatively high partition coefficient of 5.1 indicates that perfluorohexane is highly hydrophobic. Perfluorohexane exhibits a moderate evaporation rate with a melting point of -86.1 °C, boiling point of 57.2 °C, and a vapor pressure of 29.067 kPa at 25 °C. Compared to other perfluorinated alkanes, perfluorohexane has a relatively low boiling point and vapor pressure. Like perfluorodecalin, perfluorohexane demonstrates heat-resistance and can remain stable at temperatures as high as 450 °C (Arnold, Hartman et al. 2007).

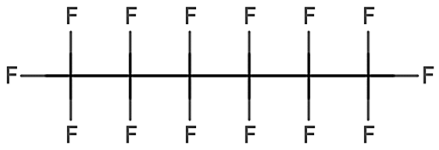
Perfluorohexane is one of the candidate fluids for blood substitute because of its high affinity for oxygen and it's not metabolized in the human body (Riess 2002, Dias, Bonifácio et al. 2003, Graziano 2017). Perfluorohexane has been recently investigated as a component of theranostic agents, which combines both diagnostic and therapeutic functions, through incorporation into nanodroplets or nanoemulsions (Yang, Li et al. 2014, Xiao, You et al. 2021, Abdipour, Abbasi et al. 2024). These formulations have been explored for cancer imaging and chemotherapeutic drug delivery for various types of cancers including melanoma (Maghsoudinia, Akbari-Zadeh et al. 2022), breast cancer (Cui, He et al. 2020, Fernandes, Fernandes et al. 2021), gastric cancer (Li, Fan et al. 2023), hepatocellular carcinoma (Maghsoudinia, Tavakoli et al. 2021), and ovarian cancer (Huang, Dong et al. 2019). Perfluorohexane is an active ingredient of an FDA approved drug, perfluorohexane-lipid microspheres (AFO150 or Imagent®, NDA 21-191), an ultrasound imaging contrast agent for use in echocardiograms for cardiac function and perfusion, and as an enhancer of the images of prostate, liver, kidney and other organs (2002).[87] It is also a component of an FDA-approved food additive at a concentration of 1% (21 CFR 173.342).[88]

Table A.11.1. Physical and Chemical Properties of Perfluorohexane

Element	Description
Name	Perfluorohexane
INCI name	Perfluorohexane
Synonyms	Perflexane Tetradecafluorohexane Perfluoro-n-hexane n-Perfluorohexane Flutec PP1 AF 0150

[87] See also drug approval package for Imagent: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-191_Imagent.cfm (accessed 10/23/2024).

[88] 21 CFR 173.342. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=173.342. (accessed 10/23/2024).

Element	Description
	Perfluoro-compound FC-72 1,1,1,2,2,3,3,4,4,5,5,6,6,6-Tetradecafluorohexane
CAS#	355-42-0
Structure	
Molecular formula	C_6F_{14}
Molecular weight	338.04 g/mol
Particle size	Not applicable
Physical form	Colorless, odorless liquid
Density	1.6910 g/cm³ at 20 °C
Solubility	≤0.1 mg/L in water at 20 °C (ECHA 2018); Soluble in ethyl ether, benzene, chloroform.
Partition coefficient (Log K_{ow})	5.1 (predicted)
Vapor pressure	218 mm Hg (equivalent to 29.067 kPa) at 25 °C
Melting point	-86.1 °C
Boiling point	57.2 °C
Topological polar surface area	0 Å² (computed)
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Chemically stable, nonflammable, and physiologically inert. Stable up to 450 °C (Arnold, Hartman et al. 2007).

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, perfluorohexane is a cometic ingredient used as a solvent in several categories of products including miscellaneous eye makeup preparations, moisturizing preparations, face and neck preparations (excluding shaving preparations), and miscellaneous skin care preparations.

Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorohexane is used in 40 cosmetic products of various product categories as shown in **Table A.11.2.** The ingredient is most commonly used in skin care products, particularly for face and neck care including both leave-on and rinse-off types. While less prevalent, perfluorohexane is also used in hair care products, primarily in leave-on treatments, accounting for 7.5% of all the ingredient's uses. Additionally, it is used in one eye lotion. Please see **Table S2** for a full list of cosmetic product categories.

Table A.11.2. Frequency of Use of Perfluorohexane in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Eye makeup		
Eye lotions	**1**	**2.5**
Hair care		
Other hair preparations, leave-on	**3**	**7.5**
Skin care		
Face and neck, leave-on	16	40.0
Face and neck, rinse-off	7	17.5
Body and hand, rinse-off	1	2.5
Moisturizing	1	2.5
Paste mask (mud packs), rinse-off	2	5.0
Other skin care preparations, leave-on	4	10.0
Other skin care preparations, rinse-off	5	12.5
Skin care total	**36**	**90.0**
Grand total	**40**	**100.0**

VCRP data revealed that the usage of perfluorohexane in cosmetic products in the U.S. market has remained largely stable over the past several years, fluctuating between 18 and 23 products from 2019 to 2023 (**Table S4**). Mintel's GNPD data demonstrated that the ingredient was used in a total of 21 products launched in the U.S. market over a 5-year period (August 2019 to July 2024), including 3 products introduced between August 2023 and July 2024 (**Table S4**). The use trend of perfluorohexane cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration of perfluorohexane is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) and a cosmetic ingredient supplier's datasheet[89] reported the typical use concentration of perfluorohexane

[89] https://cosmetics.specialchem.com/selectors?q=perfluorohexane (accessed on October 23, 2024). Based on information on the webpage, Innovation Company's Fiflow® products contain 45-95% perfluorohexane. The suggested use concentration of these ingredients in final products is 2-15%. The use concentration for perfluorohexane is therefore calculated to be in the range of (45-95%)*(2-15%) = 0.9-14.25%.

from 0.9% to 14.25% in cosmetic products. However, recommended levels may vary depending on the specific product type and supplier.

Since the majority of products are intended for skin care, consumers are expected to be primarily exposed to perfluorohexane through skin contact. There is also a potential for incidental eye exposure when using eye makeup.

Existing Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

Upon a comprehensive search of the data sources as listed in **Table S5**, we found that perfluorohexane is an active ingredient in an FDA approved drug, AF0150 or Imagent (NDA 21-191), which is a perfluorohexane-lipid microsphere (FDA 2002), and a component of a secondary direct food additive permitted in food for human consumption (FR 1990). These represent FDA safety assessments conducted for drug and food additive approvals, which provide relevant toxicological data for understanding perfluorohexane's safety profile. It has not been assessed by other government agencies or scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search for ADME and toxicokinetics of perfluorohexane using the query from **Table S8** yielded 156 publications (searched on 8/24/2024). After abstract and full text screening, we deemed one publication relevant and included it in the review. In addition, since FDA approved perfluorohexane as a contrast agent for ultrasound imaging, its pharmacokinetic information is included in the drug label (FDA 2002). Furthermore, we identified a REACH dossier for perfluorohexane in the ECHA chemicals database which contain some toxicokinetic information on perfluorohexane (ECHA 2018) (accessed on 8/24/2024). Relevant information is reviewed and summarized below.

Following inhalation exposure in rats, perfluorohexane was detected in various tissues immediately after exposure, but after 24 hours, perfluorohexane was found only in the adipose tissue (Dodd, Brashear et al. 1993). In a study with rats following a single intravenous dose of 20 mg/kg, expired air analysis revealed that approximately 94% of perfluorohexane was excreted within the first 3 hours (ECHA 2018). In addition, its low solubility and low affinity for albumin binding indicates low protein binding potential (FDA 2002, ECHA 2018). The REACH dossier estimates the absorption of perfluorohexane to be 10% by oral and dermal routes, and 100% by the inhalation route (ECHA 2018).

Results from a clinical trial with volunteers suggest that perfluorohexane may be metabolized in the gastrointestinal tract and liver and excreted through bile and urine and can also be eliminated through exhaled air. Approximately 75% of an administered dose was eliminated within 3 hours, and 87% within 24 hours (FDA 2002).

No metabolite was identified in rat urine or tissues following inhalation exposure (Dodd, Brashear et al. 1993). The primary elimination route is exhalation, with a mean terminal elimination half-life of approximately 5.3 hours in blood and 9 hours in expired air. Females appear to eliminate perfluorohexane more slowly than males, with a longer terminal elimination half-life (13 ± 4 hours) compared to males (6 ± 3 hours) (FDA 2002).

Overall, systemic uptake of perfluorohexane following exposure is expected to be minimal due to its low solubility in blood and rapid elimination. Studies suggest that perfluorohexane is primarily eliminated through expired air. The clearance of perfluorohexane is rapid, with a terminal elimination half-life of 5.3 hours in blood.

Hazard Assessment

Acute and Repeated Dose Toxicity

We conducted a literature search on the acute and repeated dose toxicity of perfluorohexane using the query outlined in **Table S8**. The search yielded 44 publications. After an initial title and abstract screening, we selected four of these publications for inclusion in this review. Several articles discussing the application of perfluorohexane are cited in the introduction section. In addition, we consulted the REACH dossier for perfluorohexane available on the ECHA website (ECHA 2018) to supplement the existing literature. Relevant information from both the literature and the REACH dossier is summarized in the corresponding sections of this review.

It is important to note that the REACH dossier provides only limited publicly available information and the original study reports were inaccessible for review. Thus, the quality of the data cannot be independently and fully evaluated.

Acute Toxicity

Dermal

We did not identify any acute dermal toxicity studies for perfluorohexane in published literature. The REACH dossier for perfluorohexane indicates an acute dermal toxicity study was not necessary because the physicochemical and toxicological properties suggest no potential for a significant rate of absorption through the skin (ECHA 2018).

Oral

We did not identify any acute oral toxicity studies for perfluorohexane in published literature.

The REACH dossier for perfluorohexane includes an acute oral toxicity study (ECHA 2018). In this study, female Wistar rats (n=6) were administered a single oral (by gavage) dose of 2000 mg/kg bw undiluted perfluorohexane following OECD TG 423 under GLP. No mortality occurred; body weights were unaffected over a 2-week observation period and no abnormalities were observed upon macroscopic examination. Based on these findings, the dossier concluded that the LD_{50} value for perfluorohexane was >2,000 mg/kg bw, indicating a low oral toxicity concern.

Inhalation

In a study using female sheep (Bleyl, Ragaller et al. 2002), exposure to 18% perfluorohexane vapor for 30 minutes improved lung function in animals with oleic acid-induced lung. The vapor increased lung compliance, decreased peak inspiratory pressure, and led to better oxygen exchange in injured animals (n=7 for injury control group and n=7 for injury + perfluorohexane group). Importantly, there were no significant adverse effects on healthy animals (n=5). During the experiment, all animals were under anesthesia and ventilated in a volume-controlled intermittent positive pressure mode by using an anesthetic ventilator.

Perfluorohexane vapor-exposed rats were used as a control group (n=6) in a study aimed to examine the respiratory toxicity of soman, a chemical warfare nerve agent, diluted in perfluorohexane (Perkins, Wong et al. 2013, Perkins, Wong et al. 2015). All animals were exposed for 15 minutes and observed for 24 hours post exposure. The control animals showed no signs of toxicity, changes in breathing pattern, or abnormalities upon gross or histopathology examination following inhalation exposure to perfluorohexane (concentration unspecified).

Other Routes of Exposure

Extensive toxicity data on perfluorohexane is available for the intravenous route (IV) in the context of new drug application 21-191 (AF0150) for perfluorohexane in phospholipid microsphere (FDA 2002). Intravenous injection of AF0150 at doses of 50-400 mg/kg to Crj: CD(SD) rats did not result in treatment related mortality, signs of acute toxicity or effects on body weight gain and food consumption. Additionally, based on an estimated oral absorption rate of 10% (ECHA 2018), acute oral toxicity is not expected to occur at 4000 mg/kg.

Repeated Dose Systemic Toxicity

We did not identify any repeated dose systemic toxicity studies for dermal, oral or inhalation routes of exposure.

Other routes of exposure

A short-term repeated dose toxicity study by the intravenous route was conducted to support the approval of the drug AF0150 (FDA 2002). Male and female Crl:CD (SD) rats (20/sex/group) were intravenously given AF0150 at doses of 50, 200 or 400 mg/kg bw/day for 29 days followed by a 14-day recovery. The study was conducted in compliance with OECD TG407 and GLP. No mortality or significant clinical signs of toxicity were observed at any dose level. Body weight and food consumption were not affected. Macrophage vacuolation was observed at all dose levels upon histopathologic examination, which was deemed to be caused by the lipid-component in AF0150, rather than perfluorohexane (FDA 2002). In addition, increased eosinophil infiltration and extramedullary hematopoiesis were observed. The NOAEL was determined to be 50 mg/kg bw/day. Based on an estimated dermal absorption rate of 10% (ECHA 2018), the dermal NOAEL is estimated to be 500 mg/kg bw/day.

Genotoxicity

We conducted a literature search on the genotoxicity potential of perfluorohexane using the query outlined in **Table S8**. The search yielded one paper relevant to the current review.

The study authors investigated the possible application of perfluorocarbons (PFCs) as oxygen "reservoirs" for harvested organs in pancreas organ transplantation. Purified rat islets were cultured with or without oxygen-saturated PFCs, perfluorohexane and perfluorooctane, for 1 or 7 days. Caspase 3/7 activity and histone associated DNA fragments were measured as markers of apoptosis. After 1 day in culture, caspase activity and DNA fragmentation did not significantly differ between control and perfluorohexane islets. After 7 days in culture, however, the authors observed a significant increase of DNA fragmentation in the perfluorohexane islet group (Bergert, Knoch et al. 2005).

The REACH dossier for perfluorohexane included an Ames test at the doses of 1-20 mg/plate and a mammalian erythrocyte micronucleus test via IV injection of a single dose up to 800 mg/kg of AF0150, perfluorohexane in phospholipids. Both tests showed negative results. The dossier concluded that perfluorohexane has no genetic toxicity properties given the negative responses in standard genotoxicity battery tests (ECHA 2018).

Carcinogenicity

No data.

Developmental and Reproductive Toxicity (DART)

We conducted a literature search on the DART potential of perfluorohexane using the query outlined in **Table S8**. The search yielded three publications. After an initial abstract screening, we did not identify any publications relevant to the current review.

The REACH dossier for perfluorohexane included reproductive and developmental toxicity studies assessing the effects of AF0150 (perfluorohexane-lipid microspheres) via intravenous injection: (1) on pregnant/lactating female rats and on development of the conceptus and the offspring; (2) a developmental toxicity study assessing the teratogenicity of AF0150 in rabbits and rats; and (3) a reproduction toxicity study assessing effects of AF0150 on fertility and early embryonic development in rats (ECHA 2018). AF0150 (at 50, 100 or 200 mg/kg bw/day) did not significantly affect maternal toxicity, pregnancy rate or gestation duration at any dose level. No differences in fertility, physical and functional development were observed in offsprings. A NOAEL of 100 mg/kg bw/day for neonate toxicity in rats was determined based on decreased live birth index and increased stillbirth at 200 mg/kg bw/day. The NOAELs were determined to be 50 mg/kg bw/day based on slight increased fetal malformations, and 200 mg/kg bw/day (highest dose tested) for maternal toxicity in both rabbits and rats. Slight decreases in male fertility were observed at 200 mg/kg bw/day. A NOAEL of 100 mg/kg bw/day was determined for fertility and early embryonic development. However, the authors concluded that since AF0150 was administered by IV route in these studies (which dramatically increased systemic exposure), and only 10% is absorbed by oral exposure and then rapidly eliminated from the body, these DART effects are considered irrelevant for oral exposure.

Neurotoxicity

No data.

Site of Contact Effects:

Dermal Irritation

In the REACH dossier for perfluorohexane, the skin irritation potential of perfluorohexane was assessed using a human 3D epidermal model (EPISKIN-SMTM). Following OECD guideline 439, 25 µL of undiluted perfluorohexane was applied to the skin tissue for 15 minutes, with a post-incubation period of 42 hours. Cytotoxicity, measured by mitochondrial dehydrogenase activity (MTT assay), was used to assess cell viability. Perfluorohexane resulted in 108% cell viability, well above the 50% threshold for irritation. Thus, the study authors concluded that perfluorohexane is a non-irritant under the GHS guidelines (ECHA 2018).

Dermal Sensitization

As discussed in the REACH dossier for perfluorohexane, two GLP *in vivo* studies were conducted in guinea pigs, according to OECD TG 406 and GLP principles, to test the antigenicity and delayed hypersensitivity of AF0150 when injected intradermally. No indication of antigenicity or delayed hypersensitivity was observed in these studies (ECHA 2018).

Ocular Irritation

The REACH dossier for perfluorohexane notes that the eye irritation potential of perfluorohexane was evaluated using the Bovine Corneal Opacity and Permeability (BCOP) test. Following OECD guideline 437, 750 µL of perfluorohexane was applied to isolated bovine corneas for 10 minutes. Results showed no significant increase in opacity or permeability, with a mean irritancy score of -0.5. As perfluorohexane scored below the threshold for irritation (IVIS ≤3), it was not classified as an eye irritant or as causing serious eye damage in the study (ECHA 2018).

Respiratory irritation

No data.

Photo-induced toxicity

No data.

Others

An *in vitro* study investigated the potential effects of perfluorohexane on innate host defense (Haufe, Koenigshausen et al. 2008). Neutrophils and peripheral blood mononuclear cells isolated from whole blood were exposed to 25% (v/v) perfluorohexane for 1~4 hours and tested for phagocytosis activity toward bacteria (Escherichia coli). Results demonstrated that perfluorohexane did not impair the ability of human leukocytes to fight bacteria in *in vitro* settings. The treatment did not result in reduced phagocytosis capacity and reduced bacteria-induced respiratory burst, suggesting that key functions of the innate host defense are not compromised by perfluorohexane treatment.

Review Summary/Conclusion

Uses: Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorohexane, a fluorocarbon solvent that moderately evaporates, is currently used in 40 cosmetic products, primarily in skin care products, and particularly face and neck care. Available information indicates perfluorohexane is used in cosmetic products at concentrations ranging from 0.9% to 14.25%. Historical data from Mintel's GNPD and the VCRP suggests the use of perfluorohexane in cosmetic products has remained stable during the last several years. However, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, this trend cannot be demonstrated at this time.

Safety: Given that perfluorohexane is primarily used in skin care cosmetic products, dermal contact is expected to be the main route of consumer exposure from using products containing this ingredient. Eye exposure is also possible when using eye lotions containing perfluorohexane.

The absorption rates of perfluorohexane are estimated to be 10% for oral and dermal exposure, and 100% for inhalation exposure. However, due to its poor solubility in blood and rapid elimination via exhalation, systemic uptake of perfluorohexane following various exposure routes is expected to be minimal. In addition, the clearance of perfluorohexane is rapid and bioaccumulation potential is low. The relatively high partition coefficient of 5.1 indicates that perfluorohexane is highly lipophilic and will partition into fat tissue.

Based on limited published literature, the REACH dossier, and the data on AFO150, perfluorohexane is not a skin sensitizer, dermal or eye irritant, or acutely toxic via oral or inhalation exposure. Due to its physicochemical properties which suggest low skin absorption, an acute dermal toxicity study was deemed unnecessary. It is also not genotoxic.

We did not identify any data for respiratory irritation, phototoxicity, oral, dermal or inhalation repeated dose toxicity, carcinogenicity or neurotoxicity.

The REACH dossier for perfluorohexane reports a NOAEL of 50 mg/kg bw/day based on a short-term repeated dose toxicity study with AFO150 (perfluorohexane-lipid microsphere) administered intravenously to rats. In addition, NOAELs were determined for various reproductive and developmental endpoints following intravenous injection, including neonate toxicity (100 mg/kg bw/day), fetal malformations (50 mg/kg bw/day), maternal toxicity (200 mg/kg bw/day, highest dose tested), and fertility and early embryonic development (100 mg/kg bw/day). Based on an estimated dermal absorption rate of 10%, the dermal NOAEL is expected to be 500 mg/kg bw/day or higher.

While the intravenous studies of AF0150 provide valuable insight into the potential toxicity of perfluorohexane, their relevance to cosmetic use is considered limited due to the significant difference between intravenous administration and topical application. Additionally, it's important to note that AF0150 is a complex formulation of perfluorohexane, which includes 1,2-dimyristoyl-sn-glycero-3-phosphocholine, a phospholipid, hydroxyethyl starch, poloxamer 188, sodium chloride and sodium phosphate compared with pure perfluorohexane substance. Given this information, these NOAELs reported in the REACH dossier are not considered for risk characterization of perfluorohexane as an ingredient in cosmetic products.

In summary, perfluorohexane is a fluorocarbon solvent primarily used in skin care products. Due to its low blood solubility and rapid elimination via exhalation, systemic uptake of perfluorohexane following various exposure routes, in particular skin contact, is expected to be low. Additionally, perfluorohexane's low water solubility and moderate molecular weight limit its potential for bioaccumulation, although the partition coefficient indicates it is lipophilic. Based on the limited available data, there is a low concern for safety associated with perfluorohexane when used as an ingredient in cosmetic products under intended use conditions.

12. Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer

Introduction

Diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer is a copolymer of three chemicals: diethylaminoethyl methacrylate, HEMA, and perfluorohexylethyl methacrylate, crosslinked with PEG-3 dimethacrylate.[90] **Table A.12.1** shows the chemical structure and limited physicochemical properties. Diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer is a pale amber liquid that is dispersible in water, and it is chemically stable under normal storage conditions.

Table A.12.1. Physical and Chemical Properties of Diethylaminoethyl Methacrylate-HEMA-Perfluorohexylethyl Methacrylate Crosspolymer

Element	Description
Name	Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer
INCI name	Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer
Synonyms	Diethylaminoethyl Methacrylate/Hydroxyethyl Methacrylate/Perfluorohexylethyl Methacrylate Crosspolymer Trade name: Salus FP-100[91]
CAS#	NA
Structure	NA
Molecular formula	NA
Molecular weight	NA
Particle size	Not applicable
Physical form	Pale amber liquid solution with a mild characteristic glycol odor[91]
Density	1.08 g/ml (25 °C)[91]
Solubility	Water solubility: dispersible[91]
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	NA
Boiling point	NA
Topological polar surface area	NA
UV light absorption spectrum	NA

[90] The information can be found in the following INCI link: Monograph. Note: Membership/login is required to view the content.

[91] https://graybeardllc.com/wp-content/uploads/2022/07/Salus-FP-100-SDS-20180813.pdf (accessed 2/20/2025).

Element	Description
Decomposes	Chemical stability: stable under normal conditions[91]
Additional properties	Flash Point >100 °C closed cup pH: 2-6 Low viscosity[91]

Notes: NA, not available. Sources: See footnotes in the Table.

Use in Cosmetic Products

According to INCI, diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer functions as binders and surface modifiers in cosmetic products.[91]

Based on the mandatory cosmetic product listing data submitted to the FDA, diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer is used as an ingredient in 35 cosmetic products that are all categorized as manicuring preparations. The ingredient is primarily used in nail polishes and enamels, accounting for 65.7% (n=23) of the ingredient's total usage in cosmetic products as shown in **Table A.12.2**. Please see **Table S2** for a full list of cosmetic product categories.

Table A.12.2. Frequency of Use of Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Manicuring preparations		
Basecoats and undercoats	1	2.9
Nail creams and lotions	1	2.9
Nail extenders	2	5.7
Nail polishes and enamels	23	65.7
Other manicuring preparations	8	22.9
Total	**35**	**100.0**

To assess the trend of diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer use in cosmetic products, we searched historical data in the VCRP and the Mintel GNPD. We did not find any reported use of this ingredient in the VCRP or Mintel's GNDP over the past 5 years (August 2019 to July 2024) (**Table S4)**. The use trend of diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer is not available

to the FDA. However, the SDS for Salus FP-100 from a supplier indicates its concentration ranges between 10-15%.[91]

According to the product types containing diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer, consumers can be exposed to this ingredient primarily through dermal exposure. Other exposure routes such as incidental oral ingestion or inhalation may also occur.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources listed in **Table S5** did not identify any assessments of diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science did not identify any publications on the toxicokinetics of diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer. We did not identify a REACH dossier for diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer in the ECHA database (searched on 12/6/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publications on the toxicity of diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer. The SDS from the supplier Gray Beard Solutions,[91] notes that diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer may cause skin irritation with repeated or prolonged contact, and it may cause eye irritation. According to the SDS, this ingredient is classified as GHS Eye damage/irritation Category 2B at concentrations of 10-15%, however, it is not classified as sensitizing by skin contact. Importantly, we note that the specific data regarding these health effects are unavailable for our independent evaluation.

Review Summary/Conclusion

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer is currently used as an ingredient in 35 cosmetic products in the manicuring preparations product category. There was no reported use of diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer in cosmetic products in the VCRP or Mintel's GNPD in the past several years (2019-2024). Although there are 35 registered products in the mandatory cosmetic product listing data submitted to the FDA, due to its lack of baseline or historical data, a trend in use cannot be demonstrated at this time.

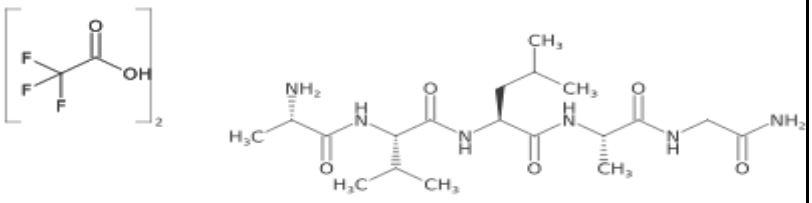
Safety: Given that diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer is used in manicuring preparations, dermal contact is considered the primary route of consumer exposure. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer. Given the limited data and information available to us, the FDA cannot determine the safety of diethylaminoethyl methacrylate/HEMA/perfluorohexylethyl methacrylate crosspolymer from its use in cosmetic products or risks associated with such use.

13. Pentapeptide-34 Trifluoroacetate

Introduction

Pentapeptide-34 trifluoroacetate (PubChem SID: 472421453) is a synthetic peptide compound composed of a chain with five amino acids. Pentapeptide-34 trifluoroacetate contains trifluoroacetate, which features multiple fluorine atoms attached to a carbon atom, making it a PFAS compound. **Table A.13.1** shows the chemical structure and physicochemical properties. Pentapeptide-34 trifluoroacetate is an odorless white powder[93] with the molecular weight of 430 Da. It is soluble in water or 1% acetic acid. According to a manufacturer, heavy metal impurities are not expected in the powder of pentapeptide-34 trifluoroacetate.[92]

Table A.13.1. Physical and Chemical Properties of Pentapeptide-34 Trifluoroacetate

Element	Description
Name	Pentapeptide-34 Trifluoroacetate
INCI name	Pentapeptide-34 Trifluoroacetate
Synonyms	Glycinamide, L-alanyl-L-valyl-L-leucyl-L-alanyl-, 2,2,2-trifluoroacetate (1:2) SQS1FA1FGW (UNII) PEPTIDE Q10 (trade name) PCEQ
CAS#	NA
Structure	
Molecular formula	$C_{19}H_{36}N_6O_5.2C_2HF_3O_2$[93]
Molecular weight	430 Da
Particle size	NA
Physical form	White powder,[93] no odor[94]
Density	NA

[92] https://cosmetics.alfa-chemistry.com/product/pentapeptide-trifluoroacetate-371921.html (accessed 12/19/2024).

[93] Product Specification for Pentapeptide-34 Trifluoroacetate: https://experchem.com/files/files/file/05a16a3d-6a1c-4f28-920e-95cf919c450b/Pentapeptide-34-Trifluoroacetate-Productinformation-ExperChem.pd f(accessed 12/19/2024).

[94] Chemical Book: Pentapeptide-34 Trifluoroacetate: https://www.chemicalbook.com/ProductDetail_EN_pentapeptide-34-trifluoroacetate_1791772.htm (accessed 12/19/2024).

Element	Description
Solubility	Soluble in water or 1% acetic acid[93]
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	NA
Boiling point	NA
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	NA

Notes: NA, not available. Sources: FDA-GSRS; specified otherwise.

Use in Cosmetic Products

According to INCI, pentapeptide-34 trifluoroacetate functions as a skin-conditioning agent in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, pentapeptide-34 trifluoroacetate is used in 33 cosmetic products as shown in **Table A.13.2**. The 33 products are categorized in the following two main product categories: hair preparations (non-coloring) (n=3, 9.1%) and skin care preparations (creams, lotions, powder, and sprays) (n=30, 90.9%). Please see **Table S2** for a full list of cosmetic product categories. Within the skin care preparations (creams, lotions, powder, and sprays) product category, pentapeptide-34 trifluoroacetate is predominantly used in the face and neck (excluding shaving preparations) leave-on product category, accounting for 72.7% (n=24) of the ingredient's total usage in cosmetic products (**Table A.13.2)**.

Table A.13.2. Frequency of Use of Pentapeptide-34 Trifluoroacetate in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Hair preparations (non-coloring)		
Hair conditioners, rinse-off	1	3.0
Shampoos (non-coloring), rinse-off	1	3.0
Other hair preparations, rinse-off	1	3.0
Hair preparations total	**3**	**9.1**
Skin care preparations (creams, lotions, powder, and sprays)		
Face and neck (excluding shaving preparations), leave-on	24	72.7
Moisturizing	1	3.0

Product Category	Number of Products	Percentage of Total (%)
Night	2	6.1
Other skin care preparations, leave-on	3	9.1
Skin care preparations total	**30**	**90.9**
Grand total	**33**	**100.0**

To assess the trend of pentapeptide-34 trifluoroacetate use in cosmetic products, we conducted a search of the historical data in the VCRP and Mintel's GNPD. No use data of pentapeptide-34 trifluoroacetate was reported in the VCRP from 2019 to 2023 (**Table S4)**. Data from Mintel's GNPD do not show a clear trend for change of use for pentapeptide-34 trifluoroacetate. In Mintel's GNPD, 9 products were launched in the U.S. market over a 5-year period (August 2019 to July 2024), and 4 of those products were launched between August 2023 and July 2024 (**Table S4)**. There are significantly more products in the mandatory cosmetic product listing data submitted to the FDA compared to the VCRP and Mintel's GNPD. However, due to the lack of historical data, the use trend of pentapeptide-34 trifluoroacetate cannot be determined at this time.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for pentapeptide-34 trifluoroacetate is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported the use of this ingredient at a concentration range of 0.001% to 1% in hair and skin care preparations.

Based on the product types that contain pentapeptide-34 trifluoroacetate, dermal contact is expected to be the primary route of exposure for this ingredient from use of cosmetic products, such as creams and lotions for skin care, and hair care products.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of pentapeptide-34 trifluoroacetate by government agencies and other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the queries outlined in **Table S9** did not identify any published data on the toxicokinetics of pentapeptide-34 trifluoroacetate. We did not identify a REACH dossier for pentapeptide-34 trifluoroacetate in the ECHA database (searched on 12/6/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of pentapeptide-34 trifluoroacetate. As the FDA does not have premarket authority over cosmetic ingredients or products, other than color additives which are subject to FDA approval before use, we do not have specific data to review.

Review Summary/Conclusion

Use: According to INCI, pentapeptide-34 trifluoroacetate functions as a skin-conditioning agent in cosmetic products. Based on the mandatory cosmetic product listing data submitted to the FDA, pentapeptide-34 trifluoroacetate, a synthetic peptide compound, is currently used as an ingredient in 33 cosmetic products, primarily in products for hair and skin care preparations. A recent publication reported a concentration range of 0.001% to 1% in hair and skin care preparations. The Mintel GNPD does not show a clear trend in use for pentapeptide-34 trifluoroacetate in the past several years, and usage was not reported in the VCRP. Due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend in use cannot be demonstrated at this time.

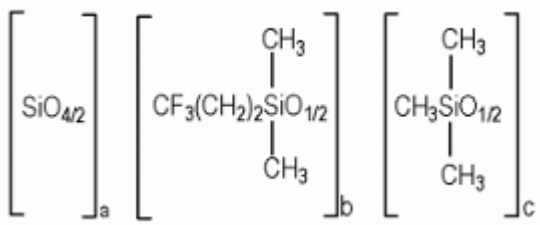
Safety: Based on the product types containing pentapeptide-34 trifluoroacetate, the main route of consumer exposure is through dermal contact. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of pentapeptide-34 trifluoroacetate. The FDA does not have information to assess the potential for skin irritation or sensitization, and whether it can be absorbed or could lead to systemic exposure and toxicity. Given the limited data and information available, the FDA cannot determine the safety of pentapeptide-34 trifluoroacetate from its use in cosmetic products or risks associated with such use.

14. Trifluoropropyldimethyl/trimethylsiloxysilicate

Introduction

Trifluoropropyldimethyl/trimethylsiloxysilicate is a co-condensed silica material prepared by the simultaneous reaction of condensable inorganic silica and silylated organic compound. This process is similar to random co-polymer synthesis, but it is non-linear (Becker, Bergfeld et al. 2013). **Table A.14.1** shows the chemical structure and limited physicochemical properties. According to the CIR, trifluoropropyldimethyl/trimethylsiloxysilicate is amorphous and practically insoluble in most common solvents much like un-modified silica (Becker, Bergfeld et al. 2013). It is generally stable under normal storage and handling conditions.

Table A.14.1. Physical and Chemical Properties of Trifluoropropyldimethyl/trimethylsiloxysilicate

Element	Description
Name	Trifluoropropyldimethyl/trimethylsiloxysilicate
INCI name	Trifluoropropyldimethyl/trimethylsiloxysilicate
Synonyms	NA
CAS#	NA
Structure	
Molecular formula	$C_8H_{17}F_3O_4Si_2$
Molecular weight	290.38
Particle size	NA
Physical form	NA
Density	NA
Solubility	NA
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	NA
Boiling point	NA
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	NA

Element	Description
Additional properties	Stable after five 2-day cycles of -10 °C and 45 °C for 24 hours at each temperature. Stable after 3 months storage at 45 °C.

Notes: NA, not available. Sources: (Becker, Bergfeld et al. 2013).

Use in Cosmetic Products

According to INCI, trifluoropropyldimethyl/trimethylsiloxysilicate functions as binders and skin-conditioning agents – emollient in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, trifluoropropyldimethyl/trimethylsiloxysilicate is used in 28 products as shown in **Table A.14.2**. The 28 products are categorized in the following two main product categories: eye makeup preparations (other than children's eye makeup preparations) (n=3, 10.7%) and makeup preparations (not eye) (other than makeup preparations for children) (n=25, 89.3%). Please see **Table S2** for a full list of cosmetic product categories.

Within the makeup preparations (not eye) (other than makeup preparations for children) product category, trifluoropropyldimethyl/trimethylsiloxysilicate is predominantly used in foundations (traditional applications), accounting for 78.6% (n=22) of the ingredient's total usage in cosmetic products as shown in **Table A.14.2**.

Table A.14.2. Frequency of Use of Trifluoropropyldimethyl/trimethylsiloxysilicate in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Eye makeup preparations (other than children's eye makeup preparations)		
Eyeliners	**3**	**10.7**
Makeup preparations (not eye) (other than makeup preparations for children)		
Foundations, traditional applications	22	78.6
Lipsticks and lip glosses	3	10.7
Makeup (not eye) total	**25**	**89.3**
Grand total	**28**	**100.0**

To assess the trend of trifluoropropyldimethyl/trimethylsiloxysilicate use in cosmetic products, we searched the historical data in the VCRP and the Mintel GNPD. For example, the VCRP data included 4 trifluoropropyldimethyl/trimethylsiloxysilicate-containing cosmetic products in 2023 (**Table S4**). The Mintel GNPD data showed a decline in use from 6 trifluoropropyldimethyl/trimethylsiloxysilicate-containing cosmetic products launched in the U.S. market over a 5-year period (August 2019 to July 2024) to 0 products launched between August 2023 and July 2024 (**Table S4**). Because these numbers are very low, a trend of use cannot be determined over time. A use trend of

trifluoropropyldimethyl/trimethylsiloxysilicate also cannot be currently demonstrated using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for trifluoropropyldimethyl/trimethylsiloxysilicate is not available to the FDA. CIR (Becker, Bergfeld et al. 2013) and a recent publication by Balan, Bruton et al. (2024) reported the use of this ingredient at a concentration range of 2.0% to 20% in leave-on products with the highest level in eyeliner products. It is important to note that different suppliers of raw material may recommend varying concentrations of use, and that manufacturers or formulators ultimately determine the final concentration in their cosmetic products, which may be outside the range of suppliers' recommendations.

Given that over 89% of the products that contain trifluoropropyldimethyl/trimethylsiloxysilicate are makeup preparation (not eye) products, the potential for dermal exposure is higher than for other routes of exposure. Additionally, the presence of trifluoropropyldimethyl/trimethylsiloxysilicate in eye makeup preparation products indicates a potential ocular exposure.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** identified a 2013 CIR Assessment document on the safety of trifluoropropyldimethyl/trimethylsiloxysilicate (Becker, Bergfeld et al. 2013). CIR assessed the safety of trifluoropropyldimethyl/trimethylsiloxysilicate as used in cosmetics and concluded that trifluoropropyldimethyl/trimethylsiloxysilicate is "safe as used when formulated and delivered in the final product not to be irritating or sensitizing to the respiratory tract." As the FDA does not have premarket authority over cosmetic ingredients or products, other than color additives which are subject to FDA approval before use, we do not have the full study report to review.

ADME/Toxicokinetics

Through a literature search in PubMed and Web of Science using the query outlined in **Table S9,** we found the CIR safety assessment of silylates and surface-modified siloxysilicates (searched on 12/6/2024). The CIR Assessment (Becker, Bergfeld et al. 2013) does not include information for ADME/toxicokinetics of trifluoropropyldimethyl/trimethylsiloxysilicate. We did not identify a REACH dossier for trifluoropropyldimethyl/trimethylsiloxysilicate in the ECHA database (searched on 12/6/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded the same CIR safety assessment of silylates and surface-modified siloxysilicates with unpublished data submitted by the Personal Care Products Council on the local effects of this ingredient (Becker, Bergfeld et al. 2013). No information was provided for other endpoints except for acute oral toxicity and local effects.

The CIR Assessment (Becker, Bergfeld et al. 2013) reported an oral LD_{50} of >2 g/kg for trifluoropropyldimethyl/trimethylsiloxysilicate in mice, based on unpublished data submitted by the PCPC. We did not identify any acute toxicity data for the dermal or inhalation routes. Additionally, we were unable to locate any repeated dose systemic toxicity, genotoxicity, carcinogenicity, DART or reproductive toxicity data for this ingredient.

Site of Contact Effects:

Dermal Irritation:

The CIR Assessment (Becker, Bergfeld et al. 2013) reported that in a cumulative dermal irritation test conducted on Japanese white rabbits (n = 3), trifluoropropyldimethyl/trimethylsiloxysilicate (50%) showed no signs of irritation when applied to normal, clipped skin for four consecutive days.

Skin sensitization:

In the unpublished study cited by CIR (Becker, Bergfeld et al. 2013), trifluoropropyldimethyl/trimethylsiloxysilicate (100%) was determined to be a weak sensitizer in a guinea pig maximization test using five subjects. A mixture containing 50% trifluoropropyldimethyl/trimethylsiloxysilicate was not sensitizing in a human patch test.

Ocular Irritation:

Trifluoropropyldimethyl/trimethylsiloxysilicate (100%; 0.1 ml) received a Draize score of 0 in a test conducted on Japanese white rabbits (n = 3), indicating no ocular irritation.

Respiratory irritation:

No data.

Photo-induced toxicity

No data.

Review Summary/Conclusion

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, trifluoropropyldimethyl/trimethylsiloxysilicate is currently used as an ingredient in 28 cosmetic products, primarily in makeup preparation (not eye) products, and has lesser use in eye makeup preparation products. A trend of use could not be determined in Mintel's GNPD due to the low number of new products launched in the past 5 years. Due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend of use cannot be demonstrated at this time.

Safety: Based on the product types containing trifluoropropyldimethyl/trimethylsiloxysilicate, this ingredient may have multiple routes of exposure from its use in certain cosmetic products. In addition to dermal contact, which is the primary route of consumer exposure, the ingredient's use in eye makeup products may lead to ocular exposure. Use of trifluoropropyldimethyl/trimethylsiloxysilicate in other cosmetic products, such as lipsticks and lip glosses, may also lead to oral exposure. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of trifluoropropyldimethyl/trimethylsiloxysilicate.

According to the CIR Assessment, trifluoropropyldimethyl/trimethylsiloxysilicate did not cause skin or eye irritation in rabbits. It was considered a weak skin sensitizer in guinea pigs at a 100% concentration but not sensitizing in humans at 50%. However, given the limited data and information available, the FDA cannot determine the safety of trifluoropropyldimethyl/trimethylsiloxysilicate from its use in cosmetic products or risks associated with such use.

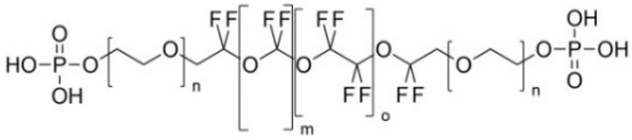
15. Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate

Introduction

Polyperfluoroethoxymethoxy difluoroethyl PEG phosphate (CAS No. 200013-65-6; PubChem SID: 472213584) has a long chain of fluorinated carbon atoms (perfluoroethoxymethoxy) attached to a difluoroethyl group, which is then linked to a PEG (polyethylene glycol) chain and finally esterified with phosphoric acid. **Table A.15.1** shows the chemical structure and physicochemical properties. Polyperfluoroethoxymethoxy difluoroethyl PEG phosphate is a viscous liquid with an amber color and odorless. Due to its high fluorination leading to extreme hydrophobicity, it is insoluble in water, mineral oil, dimethicone, and polar oils but highly soluble in alcohol, isopropanol, acetone, methylal, and propylene glycol. It has high thermal stability, remaining stable under normal storage and handling conditions while withstanding high temperatures with minimal degradation.

As polyperfluoroethoxymethoxy difluoroethyl PEG phosphate acts as a skin protectant, anti-irritant, skin feel improver, conditioning agent, emulsifier and water-proofing ingredient, it is recommended for use in hair care, skin care, makeup, creams, lotions, and gels.[95]

Table A.15.1. Physical and chemical properties of Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate

Element	Description
Name	Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate
INCI name	Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate
Synonyms	Diphosphoric acid, polymers with ethoxylated reduced Me esters of reduced polymd. oxidized tetrafluoroethylene DTXSID601026493 Fomblin® HC/P2-1000[95]
CAS#	200013-65-6[95]
Structure	 (Harris 2022)
Molecular formula	$PO_4H_2(C_2H_4O)_nC_2H_2F_2(OCF_2)_m(OC_2F_4)_oOC_2H_2F_2(OC_2H_4)_nPO_4H_2$ (Harris 2022)
Molecular weight	2500 (average)[95]
Particle size	Not applicable
Physical form	Amber liquid, viscous
Density	1.9 g/cm^3 at 20 °C[95]

[95] Fomblin® HC/P2-1000: Technical Datasheet from: https://cosmetics.specialchem.com/product/i-syensqo-fomblin-hc-p2-1000 (accessed 9/16/2024. Login is required for access).

Element	Description
Solubility	Insoluble in water, mineral oil, dimethicone, and polar oils. Soluble in alcohol, isopropanol, acetone, methylal, and propylene glycol. Dispersible in glycerin.[95]
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	NA
Boiling point	NA
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Odorless, thermal stability <250 °C, viscosity: 35000 cP at 20 °C, surface tension: 32 mN/m at 20 °C, difunctional content: 93%[95]

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, polyperfluoroethoxymethoxy difluoroethyl PEG phosphate functions as hair conditioning agents and miscellaneous skin-conditioning agents in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, polyperfluoroethoxymethoxy difluoroethyl PEG phosphate is used in 27 cosmetic products. The 27 products are categorized in the following six main product categories: eye makeup preparations (other than children's eye makeup preparations) (n=10, 37.0%), predominantly in eye shadows (n=7, 25.9%), hair preparations (non-coloring) (n=5, 18.5%), makeup preparations (not eye) (face powders, n=8, 29.6%), personal cleanliness (n=1, 3.7%), shaving preparations (n=2, 7.4%), and skin care preparations (creams, lotions, powder, and sprays) (n=1, 3.7%) as shown in **Table A.15.2**. Please see **Table S2** for a full list of cosmetic product categories.

Table A.15.2. Frequency of Use of Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Eye makeup preparations (other than children's eye makeup preparations)		
Eye shadows	7	25.9
Mascaras	2	7.4
Eyelash and eyebrow preparations (primers, conditioners, serums, fortifiers)	1	3.7
Eye makeup total	**10**	**37.0**

Product Category	Number of Products	Percentage of Total (%)
Hair preparations (non-coloring)		
Hair conditioners, rinse-off	1	3.7
Shampoos (non-coloring), rinse-off	1	3.7
Tonics, dressings, and other hair grooming aids	2	7.4
Other hair preparations, leave-on	1	3.7
Hair preparations total	**5**	**18.5**
Makeup preparations (not eye) (other than makeup preparations for children)		
Face powders	**8**	**29.6**
Personal cleanliness		
Deodorants (underarm), sticks, roll-ons, gels, creams, and wipes	**1**	**3.7**
Shaving preparations		
Aftershave lotions	**2**	**7.4**
Skin care preparations (creams, lotions, powder, and sprays)		
Face and neck (excluding shaving preparations), leave-on	**1**	**3.7**
Grand total	**27**	**100.0**

To assess the trend of the ingredient's use in cosmetic products, we searched the historical data in the VCRP and the Mintel GNPD. The retrieved data from both databases show declining trends of its use in cosmetic products. For example, the VCRP data showed that polyperfluoroethoxymethoxy difluoroethyl PEG phosphate was used in 29 products in 2019, 2 products in 2021, and further decreased to 1 product in 2023 (**Table S4**). According to Mintel's GNPD, the ingredient was used in 9 products that launched in the U.S. market over a 5-year period (August 2019 to July 2024) and 0 products launched between August 2023 and July 2024 (**Table S4**). However, the use trend of polyperfluoroethoxymethoxy difluoroethyl PEG phosphate cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the concentration of polyperfluoroethoxymethoxy difluoroethyl PEG phosphate used in listed cosmetic products is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported a use concentration of 0.1%-2% in various cosmetic products, including eye shadow, face powder, foundation and concealer,

hair care, lotions and moisturizers, and mascara. It is important to note that different raw material suppliers may recommend different usage concentrations and the final concentration in cosmetic products is ultimately determined by manufacturers or formulators, which may be outside the range of suppliers' recommendations.

Given that the majority of the products containing polyperfluoroethoxymethoxy difluoroethyl PEG phosphate are eye makeup products and face powders, dermal contact is expected to be the primary route of consumer exposure to this ingredient. Eye exposure may occur with eye cosmetic products, and incidental inhalation exposure may occur with products such as face powders.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of polyperfluoroethoxymethoxy difluoroethyl PEG phosphate by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using query outlined in **Table S9** did not identify any publications on the ADME/toxicokinetics of polyperfluoroethoxymethoxy difluoroethyl PEG phosphate (searched on 9/16/2024). We did not identify a REACH dossier for polyperfluoroethoxymethoxy difluoroethyl PEG phosphate in the ECHA database (searched on 9/16/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publications on the toxicity of polyperfluoroethoxymethoxy difluoroethyl PEG phosphate. Based on limited information from the ECHA's Classification and Labelling Inventory (which we understand to be based on the Classification, Labelling, and Packaging (CLP) Regulation), polyperfluoroethoxymethoxy difluoroethyl PEG phosphate is classified under Category 2, Eye Irritation with Hazard Statement Code (H319), indicating that the ingredient causes serious eye irritation. However, no specific data is provided to support the classification. Other hazard classification is not available.[96]

Review Summary/Conclusion

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, polyperfluoroethoxymethoxy difluoroethyl PEG phosphate is currently used as an ingredient in 27 cosmetic products, primarily in eye makeup products, and particularly in eye shadows and face powders. Additional data available to the agency, including information from the VCRP and Mintel's GNPD suggests a declining trend in the use of polyperfluoroethoxymethoxy difluoroethyl PEG phosphate in cosmetic products. However, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, this trend cannot be demonstrated at this time.

Safety: Based on the product types containing polyperfluoroethoxymethoxy difluoroethyl PEG phosphate observed in the mandatory cosmetic product listing data submitted to the FDA, this

[96] Classification and Labelling Inventory from ECHA website: https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/108615 (accessed 9/16/2024).

ingredient may have multiple routes of exposure from its use in certain cosmetic products. The use of polyperfluoroethoxymethoxy difluoroethyl PEG phosphate in eye makeup products may lead to dermal exposure in addition to potential ocular exposure. Additionally, the ingredient's use in face powders not only involves dermal exposure but also poses potential inhalation exposure. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of polyperfluoroethoxymethoxy difluoroethyl PEG phosphate. The FDA does not have information to assess the potential for eye irritation, skin irritation or sensitization, and whether it can be absorbed and could lead to systemic exposure and toxicity. Given the limited data and information available, the FDA cannot determine the safety of polyperfluoroethoxymethoxy difluoroethyl PEG phosphate from its use in cosmetic products or risks associated with such use.

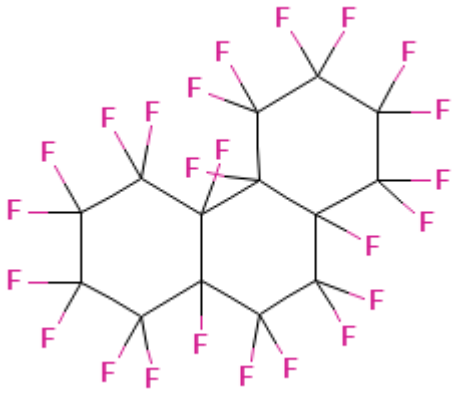
16. Perfluoroperhydrophenanthrene

Introduction

Perfluoroperhydrophenanthrene, also known as perfluorophenanthrene (CAS No. 306-91-2; PubChem CID: 78972), is a clear, colorless liquid with low surface tension. It has a high density of 2.03 g/ml and a boiling point of 215 °C. It is insoluble in water but dissolves in aliphatic and chlorinated hydrocarbons. **Table A.16.1** shows the chemical structure and physicochemical properties. Perfluoroperhydrophenanthrene is highly stable chemically under normal storage and handling conditions. Medically, it can be used as a surgical adjunct tool during ophthalmological operations. It has been used to manage certain cases of nonexpulsive suprachoroidal hemorrhages (Desai, Peyman et al. 1992).

Table A.16.1. Physical and chemical properties of Perfluoroperhydrophenanthrene

Element	Description
Name	Perfluoroperhydrophenanthrene
INCI name	Perfluoroperhydrophenanthrene
Synonyms	Perfluorophenanthrene PERFLUORINATED TETRADECAHYDROPHENANTHRENE Flutec PP11 Flutec PC-11 Fiflow 180 Fiflow 220 1,1,2,2,3,3,4,4,4a,4b,5,5,6,6,7,7,8,8,8a,9,9,10,10,10a-tetracosafluorophenanthrene Perfluorotetradecahydrophenanthrene Phenanthrene, tetracosafluorotetradecahydro- Phenanthrene,1,1,2,2,3,3,4,4,4a,4b,5,5,6,6,7,7,8,8,8a,9,9,10,10,10a-tetracosafluorotetradecahydro- ZZ3T53GWV9 (UNII) DTXSID1047029 Tetracosafluorotetradecahydrophenanthrene
CAS#	306-91-2

Structure	
Molecular formula	$C_{14}F_{24}$
Molecular weight	624.11 g/mol
Particle size	Not applicable
Physical form	Clear, colorless liquid[97]
Density	2.03 g/ml[97]; vapor density: 0.016 g/ml[97]
Solubility	Soluble in aliphatic hydrocarbons. Soluble in chlorinated hydrocarbons. Insoluble in water.[97]
Partition coefficient (Log K_{ow})	NA
Vapor pressure	0 kPa[97]
Melting point	-31 °C[97]
Boiling point	215 °C[97]
Topological polar surface area	0 Å²
UV light absorption spectrum	NA
Decomposes	Decomposition temperature: 400 °C[97]
Additional properties	XLogP3-AA: 7.2, viscosity (dynamic): 28.4 mPas,[97] viscosity (kinematic): 13.99 mm²/s,[97] surface tension: 19 mN/m,[97] not flammable, refractive index: 1.3348[97]

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

[97] Safety datasheet for Flutec P11, https://f2chemicals.com/pdf/sds/FLUTEC%20PP11(306-91-2).pdf (accessed 12/26/2024).

According to INCI, perfluoroperhydrophenanthrene functions as miscellaneous skin-conditioning agents and solvents in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, perfluoroperhydrophenanthrene is used as an ingredient in 25 cosmetic products. The 25 products are categorized in the following four main product categories: eye makeup preparations (other than children's eye makeup preparations) (n=1, 4.0%), hair preparations (non-coloring) (n=2, 8.0%), hair coloring preparations (n=1, 4.0%), and skin care preparations (creams, lotions, powder, and sprays) (n=21, 84.0%) (**Table A.16.2)**. Please see **Table S2** for a full list of cosmetic product categories.

Table A.16.2. Frequency of Use of Perfluoroperhydrophenanthrene in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Eye makeup preparations (other than children's eye makeup preparations)		
Eye lotions	**1**	**4.0**
Hair preparations (non-coloring)		
Other hair preparations, leave-on	**2**	**8.0**
Hair coloring preparations		
Other hair coloring preparations, leave-on	**1**	**4.0**
Skin care preparations (creams, lotions, powder, and sprays)		
Face and neck (excluding shaving preparations), leave-on	14	56.0
Face and neck (excluding shaving preparations), rinse-off	2	8.0
Body and hand (excluding shaving preparations), rinse-off	1	4.0
Moisturizing	1	4.0
Other skin care preparations, leave-on	3	12.0
Skin care total	**21**	**84.0**
Grand total	**25**	**100.0**

Historical data from the VCRP suggests a decline in the use of perfluoroperhydrophenanthrene in cosmetic products over the past several years. In the VCRP 2019 dataset, this ingredient was reported in 20 formulations, decreasing to 13 in 2021, and further to 7 in 2023 (**Table S4**). Mintel's GNPD does not

indicate a significant number of new products launched in the U.S. market containing perfluoroperhydrophenanthrene in recent years, with 10 in total over a 5-year period (August 2019 to July 2024) and only 3 introduced between August 2023 and July 2024 **(Table S4)**. The use trend of perfluoroperhydrophenanthrene cannot be currently determined using the cosmetic product listing data due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for perfluoroperhydrophenanthrene is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported the use of perfluoroperhydrophenanthrene at concentrations of 0.02% to 7.5% in cosmetic products.

Given its application in products used on the skin, dermal contact is expected to be the primary route of consumer exposure to perfluoroperhydrophenanthrene . Incidental inhalation may also occur when applying powder and spray-based products, particularly those designed for facial use.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of perfluoroperhydrophenanthrene by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

We conducted a literature search for ADME/toxicokinetics of perfluoroperhydrophenanthrene using the query outlined in **Table S9.** The search yielded 66 publications in PubMed and 112 publications from Web of Science (searched on 12/26/2024). After abstract screening, we did not identify any publications containing data on the toxicokinetics of perfluoroperhydrophenanthrene. Additionally, a search of the ECHA database for a REACH dossier on perfluoroperhydrophenanthrene found no toxicokinetic information (ECHA 1985) (searched on 12/26/2024).

Hazard Assessment

We conducted a literature search on the acute and repeated dose toxicity of perfluoroperhydrophenanthrene using the query outlined in **Table S9.** The search yielded no publicly available information regarding the toxicity of perfluoroperhydrophenanthrene. However, a registrant's dossier on the ECHA website provides some relevant information, which is summarized below in the corresponding subsections (ECHA 1985).

It is important to note that the REACH dossier provides only limited publicly available information and the original study reports were inaccessible for review. Thus, the quality of the data cannot be independently and fully evaluated.

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

An acute dermal toxicity study was conducted in rats under occlusive conditions according to OECD Guideline 402. An LD_{50} of >2000 mg/kg bw was determined (ECHA 1985).

The REACH dossier (ECHA 1985) also included a read-across study to evaluate the acute dermal toxicity of perfluoroperhydrophenanthrene based on a category approach. The study authors determined a LD_{50} of >2000 mg/kg bw in rats. However, we were unable to evaluate the quality and validity of the read-across study due to the lack of critical details.

Oral

Acute oral toxicity studies were conducted in mice and rats via gavage according to OECD Guideline 401. An LD_{50} of >5000 mg/kg bw in mouse and rat was determined (ECHA 1985).

The REACH dossier (ECHA 1985) also included a read-across study to evaluate the acute oral toxicity of perfluoroperhydrophenanthrene based on a category approach. The study authors determined an LD_0 (lowest lethal dose) of >2000 mg/kg bw in rats. However, we were unable to evaluate the quality and validity of the read-across study due to the lack of critical details.

Inhalation

No data.

Repeated Dose Systemic Toxicity

We did not locate any data regarding the dermal route, the inhalation route, carcinogenicity, DART, or neurotoxicity.

Oral

A 28-Day oral toxicity study was conducted in rats according to OECD Guideline 407. The study authors did not observe any mortality or critical effects. The study authors determined a no observed effect level (NOEL) of >1000 mg/kg bw/day (actual dose received) (ECHA 1985).

Genotoxicity

A mammalian erythrocyte micronucleus test was conducted in mice following oral gavage exposure according to OECD Guideline 474. Dose levels were not provided. A negative response was reported (ECHA 1985).

The REACH dossier (ECHA 1985) also included read-across studies to evaluate the genetic toxicity of perfluoroperhydrophenanthrene based on a category approach. The study authors concluded that the ingredient is negative in *in vitro* genetic toxicity studies. However, the FDA was unable to evaluate the quality and validity of the study due to the lack of critical details.

Site of Contact Effects

We did not locate any data for dermal, ocular or respiratory irritation, or photo-induced toxicity.

Dermal Sensitization

We did not find any studies on the skin sensitization of perfluoroperhydrophenanthrene in the public literature. The REACH dossier summarized a study on the skin sensitization potential of

perfluoroperhydrophenanthrene that evaluated female Dunkin-Hartley guinea pigs using a maximization test according to OECD Test Guideline 406. The authors concluded that perfluoroperhydrophenanthrene was not sensitizing under the test conditions (ECHA 1985).

Review Summary/Conclusion

Use: Perfluoroperhydrophenanthrene is used as a skin-conditioning agent and solvent in cosmetic products. Based on the mandatory cosmetic product listing data submitted to the FDA, the ingredient is used in 25 cosmetic products. Its most common application is in leave-on face and neck products. VCRP data shows that the use of perfluoroperhydrophenanthrene in cosmetic products has been declining, and Mintel's GNPD does not indicate a significant number of new products introduced to the market containing perfluoroperhydrophenanthrene in recent years. Due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, this trend cannot be demonstrated at this time.

Safety: Based on the product types containing perfluoroperhydrophenanthrene, dermal contact is expected to be the primary route of consumer exposure for its use in cosmetic products. The use of perfluoroperhydrophenanthrene in eye makeup may also lead to ocular exposure. A hazard assessment of perfluoroperhydrophenanthrene revealed limited data across various toxicological endpoints, mainly from the REACH dossier for this chemical. Acute toxicity studies in rats and mice and a 28-day oral toxicity study in rats indicate low systemic toxicity potential. An *in vivo* genotoxicity test and read-across studies suggest this ingredient is not genotoxic, and we did not identify any carcinogenicity data in the literature. There were also no data available for dermal or ocular irritation, but the substance was not sensitizing in a guinea pig dermal sensitization test. However, the FDA does not have access to the full study reports to assess the quality of the studies presented in the REACH dossier and therefore cannot fully evaluate and determine the safety of perfluoroperhydrophenanthrene from its use in cosmetic products or risks associated with such use.

17. Dimethiconol Fluoroalcohol Dilinoleic Acid

Introduction

Dimethiconol fluoroalcohol dilinoleic acid is a complex blend of silicones and siloxanes, combined with fluoroalcohol and dilinoleic acid. **Table A.17.1** shows the chemical structure and limited information on physicochemical properties. Dimethiconol fluoroalcohol dilinoleic acid is a soft, off-white paste with faint odor. It is insoluble in water. When applied to fiber, hair and skin, it is hydrophobic, non-occlusive and highly lubricious. It provides barrier properties when applied to these substrates. This substance is generally stable under normal storage and handling conditions.[98]

Table A.17.1. Physical and chemical properties of Dimethiconol Fluoroalcohol Dilinoleic Acid

Element	Description
Name	Dimethiconol Fluoroalcohol Dilinoleic Acid
INCI name	Dimethiconol Fluoroalcohol Dilinoleic Acid
Synonyms	Silwax F (trade name)
CAS#	NA
Structure	NA
Molecular formula	NA
Molecular weight	NA
Particle size	NA
Physical form	Mixture, soft paste,[99] wax/paste,[98] off-white[99]
Density	NA
Solubility	Insoluble in water[99]
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	48 °C[98]
Boiling point	NA
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Odor: faint,[98] flash point (PMCC): >100 °C

Notes: NA, not available. Sources: See footnotes.

[98] Safety datasheet for Silwax F, https://www.siltech.com/wp-content/uploads/2024/01/SDS-5702-Silwax-F_GHS.pdf (accessed 12/6/2024).

[99] Technical datasheet for Silwax F, https://www.siltech.com/wp-content/uploads/2017/11/TP5702.pdf (accessed 12/6/2024).

Use in Cosmetic Products

According to INCI, dimethiconol fluoroalcohol dilinoleic acid functions as an occlusive skin-conditioning agent in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, dimethiconol fluoroalcohol dilinoleic acid is used as an ingredient in 24 products. All 24 products are categorized in the makeup preparations (not eye) (other than makeup preparations for children) product category, which includes face powders (n=11, 45.8%) and foundations (traditional applications) (n=13, 54.2%), as shown in **Table A.17.2**. Please see **Table S2** for a full list of cosmetic product categories.

Table A.17.2. Frequency of Use of Dimethiconol Fluoroalcohol Dilinoleic Acid in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Makeup preparations (not eye) (other than makeup preparations for children)		
Face powders	11	45.8
Foundations, traditional applications	13	54.2
Total	**24**	**100.0**

To assess the trend of dimethiconol fluoroalcohol dilinoleic acid use in cosmetic products, we searched the historical data in the VCRP and Mintel's GNPD. We did not identify any reported use of this ingredient in the U.S. in the VCRP or Mintel's GNPD over the past 5 years (**Table S4**). The use trend of dimethiconol fluoroalcohol dilinoleic acid cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for dimethiconol fluoroalcohol dilinoleic acid is not available to the FDA. A manufacturer's technical data sheet reported that the typical usage levels are between 1.0-3.0% wt when used in cosmetic products.[99]

According to the product categories, consumers can be exposed to dimethiconol fluoroalcohol dilinoleic acid through various routes. While dermal contact is expected to be the primary concern, inhalation exposure could occur with products such as face powders.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of dimethiconol fluoroalcohol dilinoleic acid by government agencies and other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science did not identify any published data on the toxicokinetics of dimethiconol fluoroalcohol dilinoleic acid. We did not identify a REACH dossier for dimethiconol fluoroalcohol dilinoleic acid in the ECHA database (searched on 12/6/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of dimethiconol fluoroalcohol dilinoleic acid. An SDS from a raw material supplier[98] provided toxicological information such as potential irritation after ingestion or skin and ocular exposure. The SDS also noted suspicions that the ingredient may be damaging to fertility. It also suggested low toxicity following inhalation under normal conditions of handling and use. Importantly, we note that the specific data regarding these health effects are unavailable for our independent evaluation.

Review Summary/Conclusion

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, dimethiconol fluoroalcohol dilinoleic acid is currently used as an ingredient in 24 products that are categorized in the makeup preparations (not eye) (other than makeup preparations for children) product category. It functions as an occlusive skin-conditioning agent in cosmetic products. Dimethiconol fluoroalcohol dilinoleic acid is mainly used in face powders and traditionally applied foundation product categories. There was no reported use in either the VCRP or Mintel's GNPD. Due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend in use cannot be demonstrated at this time.

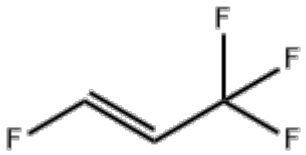
Safety: Based on the product types containing dimethiconol fluoroalcohol dilinoleic acid, this ingredient may have multiple routes of exposure from its use in cosmetic products. In addition to dermal exposure, the use of dimethiconol fluoroalcohol dilinoleic acid in face powder may lead to potential inhalation exposure or incidental oral exposure. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of dimethiconol fluoroalcohol dilinoleic acid. The FDA does not have enough information to assess the potential for dermal and inhalation irritation or sensitization, and whether it can be absorbed and could lead to systemic exposure and toxicity. Given the limited data and information available to us, the FDA cannot determine the safety of dimethiconol fluoroalcohol dilinoleic acid from its use in cosmetic products or risks associated with such use.

18. Tetrafluoropropene

Introduction

Tetrafluoropropene, also known as (1E)-1,3,3,3-tetrafluoroprop-1-ene (CAS No. 29118-24-9; PubChem CID: 5708720) is commonly used as a refrigerant and propellant due to its low global warming potential and favorable thermodynamic properties. It is a colorless liquefied gas (aerosol), has a slight ether-like odor, and exhibits a density of 1.17 g/cm³ at 21 °C in its liquid state. Tetrafluoropropene is only slightly soluble in water but is miscible with dimethyl ether, isobutane, lower alcohols, and ketones. **Table A.18.1** shows the chemical structure and physicochemical properties.

Table A.18.1. Physical and Chemical Properties of Tetrafluoropropene

Element	Description
Name	(1E)-1,3,3,3-tetrafluoroprop-1-ene
INCI name	Tetrafluoropropene
Synonyms	1,3,3,3-tetrafluoroprop-1-ene 1-Propene, 1,3,3,3-tetrafluoro-, (1E)- (E)-1,3,3,3-tetrafluoropropene (1E)-1H,2H-Perfluoroprop-1-ene trans-1,3,3,3-Tetrafluoroprop-1-ene HFO-1234ze Solstice Propellant (trade name)
CAS#	29118-24-9
Structure	
Molecular formula	$C_3H_2F_4$
Molecular weight	114.04 g/mol
Particle size	NA
Physical form	Liquefied gas (aerosol),[100] colorless
Density	1.17 g/cm³ at 21 °C (liquid state)[101]
Solubility	Solubility in water: 0.037 at 21.1 °C,[101] miscible in DME, isobutane, lower alcohols, and ketones[100]

[100] Technical datasheet for Solstice 1234ze, https://cosmetics.specialchem.com/product/i-honeywell-solstice-1234ze (accessed 12/11/2024).

[101] https://advancedmaterials.honeywell.com/us/en/products/propellant-and-solvents/industrial-propellant/solstice-propellant#specifications (accessed 12/11/2024).

Partition coefficient (Log K_{ow})	NA
Vapor pressure	3.4 bar at 21 °C, 10 bar at 54 °C[100]
Melting point	NA
Boiling point	-19 °C[100]
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Odor: slight, ether-like,[100] photochemical reactivity: 0.09 g O_3/g, dielectric strength: 0.12 kV/mil (vapor at 1 atm), dipole moment: 1.44 Debye, Global Warming Potential (GWP) vs. CO_2, 100 year ITH: <1, Volatile Organic Compound (VOC): no, expansion ratio: 247 at 1 ATM and 15.6 °C (liquid to gas), heat of gas: 0.224 Cp at 15.6 °C, cal/g, heat of vaporization: 195 KJ/g at BP, Kaurl-Butanol (KB) value: 12, liquid viscosity: 0.171 cP at 37.8 °C, specific gravity: 1.17 at 21 °C, surface tension: 8.95, vapor volume: 0.25 per liter of liquid at 16.6 °C, m^3, flashpoint: non-flammable[101]

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, tetrafluoropropene functions as a propellant in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, tetrafluoropropene is used in 23 products as shown in **Table A.18.2**. The 23 products are categorized in the following three main product categories: hair preparations (non-coloring) (n=16, 69.6%), makeup preparations (not eye) (other than makeup preparations for children) (n=4, 17.4%), and personal cleanliness (n=3, 13.0%). Please see **Table S2** for a full list of cosmetic product categories.

Within the three main product categories, tetrafluoropropene is predominantly used in hair sprays (aerosol fixatives), lip care products and deodorant sprays, respectively (**Table A.18.2**).

Table A.18.2. Frequency of Use of Tetrafluoropropene in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Hair preparations (non-coloring)		
Hair sprays (aerosol fixatives)	9	39.1
Shampoos (non-coloring), leave-on	3	13.0
Tonics, dressings, and other hair grooming aids	1	4.3
Other hair preparations, leave-on	2	8.7

Product Category	Number of Products	Percentage of Total (%)
Other hair preparations, rinse-off	1	4.3
Hair preparations total	**16**	**69.6**
Makeup preparations (not eye) (other than makeup preparations for children)		
Lipsticks and lip glosses	2	8.7
Makeup bases, traditional applications	1	4.3
Other makeup preparations, traditional applications	1	4.3
Makeup (not eye) total	**4**	**17.4**
Personal cleanliness		
Deodorants (underarm), sprays	**3**	**13.0**
Grand total	**23**	**100.0**

To assess the trend of tetrafluoropropene use in cosmetic products, we searched the historical data in the VCRP and the Mintel GNPD. In the VCRP database, tetrafluoropropene was identified in only 1 registered product in 2023. Mintel's GNPD shows that 21 cosmetic products containing tetrafluoropropene were launched in the U.S. market over a 5-year period (August 2019 to July 2024), with 4 of these introduced between August 2023 and July 2024 (**Table S4**). The use trend of tetrafluoropropene cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for tetrafluoropropene is not available to the FDA. However, in China, our understanding is that regulatory guidelines specify that the maximum allowable concentration of tetrafluoropropene in cosmetics is 90%. This limit appears to apply to both leave-on and rinse-off skin and hair care cosmetic products.[102]

According to the product categories that contain tetrafluoropropene, consumers may be exposed to this ingredient through multiple routes including dermal, inhalation, oral and ocular routes.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

[102] https://www.cirs-group.com/en/cosmetics/the-spring-of-new-cosmetic-ingredients-filing-in-china (accessed 8/20/2025)

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of tetrafluoropropene by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

We performed a literature search in PubMed and Web of Science using the query outlined in **Table S9**. The search yielded 55 publications in PubMed and 375 from Web of Science (searched on 12/11/2024). After screening the abstracts, we identified two papers relevant to the toxicokinetics of tetrafluoropropene. In addition, we found a REACH dossier containing animal studies related to toxicokinetics of tetrafluoropropene in the ECHA database (ECHA 2007) (accessed on 12/11/2024).

In an animal study (Schuster, Bertermann et al. 2009), male Sprague-Dawley rats were exposed to concentrations of 2000, 10,000, and 50,000 ppm of tetrafluoropropene through inhalation for 6 hours and male B6C3F1 mice were only exposed to a single concentration of 50,000 ppm through inhalation for 6 hours. Urine samples were collected and analyzed at alternating 6- and 12-hour intervals post exposure for 48 hours to identify tetrafluoropropene metabolites. The results identified S-(3,3,3-trifluoro-trans-propenyl)-mercaptolactic acid as the predominant metabolite in the urine of rats exposed to tetrafluoropropene, and 3,3,3-trifluoropropionamide as the predominant metabolite in the urine samples of mice. This study suggests that tetrafluoropropene undergoes a low extent of biotransformation, with less than 1% of the dose being metabolized, and the majority of metabolites being excreted within 18 hours after exposure.

Giffen, Kilgour et al. (2024) reported on toxicokinetic studies in mice, rats and dogs through inhalation exposure of tetrafluoropropene. The mouse study involved a 13-week inhalation exposure of CD-1 mice to tetrafluoropropene, 2 hours/day, at 5350, 11,900, 22,000 and 50,700 ppm with blood samples collected immediately after dosing and at 30, 60, and 120 minutes after each exposure during weeks 4, 9 and 13. Tetrafluoropropene was only detectable in blood samples immediately after dosing and increased with dose. The C_{max} values were higher in later weeks 9 and 13 than during week 4. The rat study consisted of a 7-day inhalation exposure of Wistar Han rats to tetrafluoropropene, 4 hours/day, at 1550, 5280, and 15,900 ppm with blood samples collected immediately after dosing, and at 15, 30, 60 and 90 minutes after exposure on days 1 and 7. Similarly to the mouse study, blood concentration of tetrafluoropropene was only detectable immediately after dosing and blood concentrations increased with dose. The blood concentrations declined rapidly and became undetectable after 30 minutes. The dog study involved 39 weeks of repeated inhalation exposure of Beagle dogs to tetrafluoropropene, 2 hours/day, at 1680, 4850 and 14,700 ppm with blood samples collected immediately after dosing and at 15, 30, 60, and 90 minutes after each exposure during weeks 2, 7, 14, 28, and 38 or 39. Tetrafluoropropene was detectable in blood samples for up to 30 minutes at two lower doses or 90 minutes at the highest dose after exposure. Blood concentrations increased proportionally with dose, and mean concentrations remained similar across different weeks. In all studies, tetrafluoropropene was rapidly eliminated from the blood, and its concentrations were generally not detectable after a short period following exposure. These studies suggest that tetrafluoropropene has a short half-life and is quickly cleared from the body.

The REACH dossier for tetrafluoropropene (ECHA 2007) describes an *in vitro* study that was conducted to evaluate the biotransformation of tetrafluoropropene using rat hepatocytes. The results showed that very little to no metabolism of tetrafluoropropene occurred *in vitro*, and none of the metabolites found

in vivo were detected. Another *in vitro* study was conducted to determine the tissue-to-air partition coefficients for tetrafluoropropene in rat and rabbit tissues and in human blood. The results showed that tetrafluoropropene had lower blood-to-air partition coefficients. Among all tissues, fat shows the highest tissue-to-air partition coefficient, which means tetrafluoropropene tends to distribute to the adipose tissue. The results suggested that tetrafluoropropene had relatively low solubility in blood and tissues, and that its partitioning between tissues was similar across different species. A PBPK modeling study was used to evaluate the concentrations of tetrafluoropropene in the arterial blood of adult female humans, pregnant rabbits, and rats following inhalation exposure. The models predicted rapid uptake and distribution of the chemical in humans, with a peak concentration in arterial blood of 45.7-74.8 mg/L after exposure times of 0.5-60 minutes. The area under the concentration curve (AUC) was approximately linear with the time of exposure, indicating rapid uptake and clearance of the chemical from blood.

Overall, available evidence indicates that tetrafluoropropene undergoes a low extent of biotransformation, with less than 1% of the dose being metabolized, and most metabolites being excreted within 18 hours after exposure. It has relatively low solubility in blood and tissues. Following inhalation exposure, a PBPK model predicted that the AUC for tetrafluoropropene is approximately linear with the time of exposure, indicating rapid uptake and clearance from blood. Tetrafluoropropene has a high fat to air partition coefficient, indicating it distributes to the adipose tissue.

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded two relevant publications regarding the toxicity of tetrafluoropropene. In addition, a REACH dossier on the ECHA website provides some relevant information (ECHA 2007). Relevant information from both the literature and the REACH dossier is summarized in the corresponding sections of this review.

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

No data.

Oral

No data.

Inhalation

An acute inhalation toxicity study (ECHA 2007, Rusch, Tveit et al. 2013) was conducted in rats according to OECD TG 403 and in compliance with GLP. The rats were exposed to tetrafluoropropene at 103,300 ppm (481,378 mg/m^3) and 207,000 ppm (964620 mg/m^3) via nose-only inhalation for 4 hours. The animals were observed for 14 days. No mortalities were observed. No clinical signs of toxicity and gross pathology were observed. The authors concluded that the LC_{50} was >207,000 ppm.

In addition, acute inhalation toxicity was assessed by exposing mice to 10000 ppm tetrafluoropropene via whole body inhalation for 4 hours. The study authors concluded that the ingredient is not toxic to mice following acute inhalation exposure (ECHA 2007, Rusch, Tveit et al. 2013).

Repeated Dose Systemic Toxicity

Dermal

No data.

Oral

No data.

Inhalation

A sub-chronic (90 day) inhalation toxicity study (ECHA 2007, Rusch, Tveit et al. 2013) was conducted in Sprague-Dawley rats according to OECD TG 413 and in compliance with GLP. The rats were exposed to tetrafluoropropene at 1,500, 5,000 and 15,000 ppm via nose-only inhalation for 6 hours/day, 5 days a week for 63 or 64 exposure days over a 91-92-day period. No mortalities were observed. Slight adverse effects in animals of the 15,000 ppm concentration group were observed, such as: (1) a number of monocytes and thrombocytes were increased in male animals; (2) Aspartate aminotransferase (AST), a liver function biomarker, was increased in males; and (3) urea, a kidney function biomarker, was increased in females. Treatment-related cell damage in the heart (multifocal mononuclear cell infiltrates, accompanied by increased eosinophilia and pyknotic nuclei) was observed in the 15,000 ppm concentration group. A histopathological exam did not find tumors. The study authors concluded that the No Observed Adverse Effect Concentration (NOAEC) for this study was 5,000 ppm, based on the cell damage in the heart of the 15,000 ppm animals.

A subacute inhalation toxicity study was conducted according to OECD TG 412 and in compliance with GLP. Rats were exposed to tetrafluoropropene at 0, 5,000, 20,000 and 50,000 ppm via nose-only inhalation for 6 hours/day, 5 days a week for 28 days. Treatment-related hematological effects were observed at 50,000 ppm. Treatment-related effects in the heart and liver in rats of the 20,000 ppm and 50,000 ppm groups and in the nasal passages of rats of the 50,000-ppm group were observed. A NOAEC of 5,000 ppm was determined (Rusch, Tveit et al. 2013).

In another study, rats were exposed to levels of 0, 1,000, 5,000, 10,000 or 15,000 ppm of tetrafluoropropene for 6 hours/day, 5 days/week for 4 weeks. Slight to moderate inflammation in male rats was observed in the hearts at 15,000 ppm. Thus, a NOAEC (referred to as NOAEL in the REACH dossier) of 10,000 ppm was determined (Rusch, Tveit et al. 2013).

A 14-day study and a 13-week study were reported in a recent publication by Giffen, Kilgour et al. (2024). In these studies, mice were exposed to tetrafluoropropene via nose-only inhalation at 6000, 12,500, 25,000, and 50,000 ppm for 2 hours/day for 14 days and 13 weeks. There were no exposure-related effects, including any microscopic findings, up to the highest estimated doses in the 14-day (28,000 mg/kg bw/day) and 13-week (29,000 mg/kg bw/day) studies in mice. The authors identified a NOEL of 29,000 mg/kg bw/day.

Giffen, Kilgour et al. (2024) reported a repeated dose study in rats that were exposed to tetrafluoropropene via nose-only inhalation at 1500, 5000 and 15,000 ppm (estimated achieved dose: 1,220, 4,280, and 12,000 mg/kg bw/day, respectively) for 4 hours/day for 26 weeks. Rats at the highest dose (12,000 mg/kg bw/day) showed effects in the heart, such as an increased incidence/severity of rodent progressive cardiomyopathy, with an increase in severity seen in males compared to females. No other adverse effects related to the exposure were observed. Based on the heart effects, the authors identified a NOAEL of 4,280 mg/kg bw/day.

Repeated dose toxicology studies in dogs were also reported by Giffen, Kilgour et al. (2024). In these studies, Beagle dogs were exposed to tetrafluoropropene via inhalation (whole body) at concentrations of 1,500, 5,000 and 15,000 ppm for 1 hour/day for 14 days, and 2 hours/day for 13 weeks and 39 weeks. There were no toxicology findings, including any microscopic findings, and no findings of effects on functional respiratory or cardiovascular safety pharmacology parameters at the highest estimated doses in the 14-day (1,740 mg/kg bw/day (15,000 ppm)), 13-week (3,620 mg/kg bw/day (15,000 ppm)) or 39-week studies (3,647 mg/kg bw/day (15,000 ppm)). The authors identified a NOEL of 3,647 mg/kg bw/day (15,000 ppm).

Genotoxicity

An *in vitro* human lymphocyte chromosome aberration test (ECHA 2007, Rusch, Tveit et al. 2013) was conducted according to OECD TG 473 and in compliance with GLP. Human lymphocytes were exposed to tetrafluoropropene (as a gas) in a modular incubator chamber to 0, 10, 20, 40, 60, and 76% in the atmosphere for 4 hours, with and without S9-mix. Tetrafluoropropene did not induce a statistically significant increase in the number of aberrant cells with or without metabolic activation. The test substance was considered not clastogenic in cultured human lymphocytes. An *in vitro* gene mutation study in bacteria was conducted following Japan Guidelines for Screening Mutagenicity Testing of Chemicals (ECHA 2007). Bacteria were exposed to 0.05, 0.1, 0.5, 1, 5 ,10 and 50% tetrafluoropropene in the atmosphere in a gas exposure chamber for 24-48 hours. The authors concluded that the test substance was not mutagenic under the test conditions with or without metabolic activation.

A mammalian erythrocyte micronucleus test (ECHA 2007, Rusch, Tveit et al. 2013) was conducted according to OECD TG 474 and in compliance with GLP. Mice were exposed via nose-only inhalation to tetrafluoropropene for 4 hours at 10,000 ppm. 24-48 hours after the treatment, mouse bone marrow cells were collected for the micronucleus analysis. No cytotoxicity to the bone marrow cells was observed. This ingredient did not cause an increase in micronuclei in bone marrow cells.

A mammalian erythrocyte micronucleus test (ECHA 2007, Rusch, Tveit et al. 2013) was conducted in rats according to OECD TG 474 and in compliance with GLP. Male rats were exposed to tetrafluoropropene at 0, 5,000, 10,000 and 15,000 ppm via nose-only inhalation for 6 hours/day, 5 days a week for 4 weeks. No damage to the chromosomes and/or mitotic spindle apparatus (micronuclei) in the bone marrow cells of male rats was observed.

An unscheduled DNA synthesis test (ECHA 2007, Rusch, Tveit et al. 2013) was performed in male rats according to OECD TG 486 and in compliance with GLP. The rats were exposed via nose-only inhalation to 5,000 and 15,000 ppm tetrafluoropropene for 6 hours/day, 5 days a week for 4 weeks. Within 24 hours of the last exposure, rat hepatocytes were isolated and tested for DNA damage. The test substance yielded net nuclear grains (NNG) <0, indicating it did not induce unscheduled DNA synthesis in rat hepatocytes. In this study, the positive control did not give a positive response but did show a higher NNG and % cells in repair compared to negative controls or test substance-tested cells.

Carcinogenicity

No data.

Developmental and Reproductive Toxicity (DART)

A two-generation reproductive toxicity study (ECHA 2007, Giffen, Kilgour et al. 2024) was conducted according to OECD TG 416 and in compliance with GLP. Rats were exposed to tetrafluoropropene gas via whole-body inhalation at concentrations of 2,000, 5,000, and 20,000 ppm (estimated achieved dose: 2400, 5800, and 23,000 mg/kg bw/day). The F0 generation (parental animals) were exposed to tetrafluoropropene gas 6 hours/day, 7 days/week for 10 weeks during the time before pairing, throughout pairing, gestation, lactation and until termination, except that exposure of pregnant females was not performed from gestation day 20 to lactation day 4. However, the authors did not provide justifications for the change of dosing schedule. For the F0 generation, there were 9 female decedents, 1 at 2,000 ppm and 8 at 20,000 ppm. The cause of death at 2,000 ppm was not determined and it was considered unrelated to the test article since no other effect was observed. Most of the deaths at 20,000 ppm were considered test article-related and all occurred in late lactation. Brain lesions were determined as the factor that contributed to one of the deaths in this treatment group. Histopathological examination found non-neoplastic effects in the heart, brain and spinal cord at 20,000 ppm. There were no effects on any reproductive parameters in the F0 generation. The NOEC (referred to as NOEL in the REACH dossier) for paternal (systemic) toxicity was therefore considered to be 5,000 ppm.

The F1 generation (litters) were also exposed to tetrafluoropropene gas from weaning through pairing, gestation and lactation, except that pregnant females were not exposed from gestation day 20 to lactation day 4. However, the authors did not provide justifications for the change of dosing schedule. There were 3 female decedents in the F1 generation at 20,000 ppm, all occurring in the lactation phase. The cause of death was not determined. There were no effects on development, sexual maturation, litter size, litter survival, litter sex ratio, clinical observations, organ weights or macroscopic findings in the pups from either generation. The NOEC (referred to as NOEL in the REACH dossier) for fertility and development was 20,000 ppm because no adverse effects on fertility parameters or offspring were observed.

A prenatal developmental toxicity (ECHA 2007, Rusch, Tveit et al. 2013) study was conducted in rats according to OECD guideline 414 and in compliance with GLP. The pregnant rats were exposed to tetrafluoropropene gas via nose-only inhalation at gestation days 6-19 for 6 hours/day at doses up to 15,000 ppm. For maternal rats, no mortality or remarkable clinical signs were observed in treated animals compared to controls. Non-treatment-related body weight loss during pregnancy was observed during gestation days 6-9 and 19-21. For maternal rats, no differences were noted in female fecundity index and corpora lutea. Weights of gravid uterus, carcass, empty uterus, and ovaries were not different from controls. The authors identified a NOEC of >15,000 ppm for maternal toxicity.

For fetuses, no statistically significant differences in the incidence of external observations and visceral malformations, anomalies, or variations were observed among the groups. Enlarged placenta was seen in all live fetuses in one high dose dam but no abnormalities were observed with microscopical evaluation. Placental weights were not different. A NOAEC of >15,000 ppm was identified for developmental toxicity due to absence of adverse toxic effects.

A prenatal developmental toxicity (ECHA 2007, Rusch, Tveit et al. 2013) study was conducted in rabbits in compliance with GLP and according to OECD guideline 414 and EPA OPPTS 870.3700. Pregnant rabbits were exposed to tetrafluoropropene gas via whole-body inhalation at gestation days 6-28 for 6 hours/day at doses of 0, 4,000, 10,000, and 15,000 ppm. For maternal rabbits, no treatment-related

effects on pregnancy rate, number of corpora lutea, number of implantations or sex ratio were reported. A decrease in pre-implantation loss at concentrations >4,000 ppm was noted but according to the authors, the observation was not considered to be treatment related since these parameters were established prior to exposure. An increase in post implantation loss was noted (dose level was not specified), however, the authors claimed that the effect was not dose dependent and was within historical controls, thus it was considered to not be treatment related. For fetuses, no adverse effects were observed. Thus, the authors identified a NOAEC of >15,000 ppm for both maternal systemic toxicity and for reproductive and developmental toxicity.

Another prenatal developmental toxicity (ECHA 2007) study was conducted in rabbits in compliance with GLP and according to OECD guideline 414. The rabbits were exposed to tetrafluoropropene gas via whole-body inhalation at gestation days 6-28 for 6 hours/day at doses of 0, 1,500, 5,000, and 15,000 ppm. No maternal toxic or embryotoxic/teratogenic effects were observed. A NOAEC of 15,000 ppm was determined for maternal toxicity and embryotoxicity.

Neurotoxicity

No data.

Site of Contact Effects:

Dermal Irritation

In a skin irritation study (ECHA 2007) conducted in compliance with GLP and OECD Guideline 404, three New Zealand White rabbits were exposed to tetrafluoropropene under semi-occlusive conditions. The results indicated that the test substance did not cause irritation to rabbit skin after exposure durations of 1 minute, 3 minutes, or 4 hours.

Dermal Sensitization

No data.

Ocular Irritation

No data.

Respiratory irritation

No data.

Photo-induced toxicity

No data.

Others

None identified.

Summary of Hazard Assessment

According to the REACH dossier, tetrafluoropropene exhibits low acute toxicity via inhalation. No oral or dermal data are available for acute and repeated dose toxicity. It was not genotoxic according to *in vitro* and *in vivo* studies. A skin irritation study in rabbits showed negative results. No studies are available on skin sensitization, ocular and respiratory irritation, phototoxicity or carcinogenicity.

A 90-day repeated dose nose-only inhalation toxicity study in rats reported a NOAEC of 5,000 ppm (or 4542.9 mg/kg bw/day)[103] based on heart cell damage at 15,000 ppm. In addition, a subacute (28-day) inhalation study in rats reported effects in the heart, liver, and nasal passages at 20,000–50,000 ppm, with a NOAEC of 5,000 ppm. Another subacute rat study found inflammation in the hearts at 15,000 ppm, resulting in a NOAEC of 10,000 ppm.

Giffen, Kilgour et al. (2024) studied the toxicology of tetrafluoropropene inhalation in mice, rats, and dogs. In 14-day and 13-week mouse studies via nose-only inhalation, no exposure-related effects were observed at doses up to 29,000 mg/kg bw/day, establishing a NOEL of 29,000 mg/kg bw/day. In a 26-week rat study via nose-only inhalation, the highest dose (12,000 mg/kg bw/day) led to increased severity of rodent progressive cardiomyopathy, particularly in males, resulting in a NOAEL of 4,280 mg/kg bw/day. In dog studies lasting up to 39 weeks, no toxicological effects were found at doses up to 3,647 mg/kg bw/day, the highest dose tested for 2 hours/day, leading to a NOEL of 3,647 mg/kg bw/day. While mice and dogs showed no effects at high doses, rats exhibited heart-related toxicity at the highest exposure level.

Developmental and reproductive toxicity studies in rats via nose-only inhalation and rabbits via whole-body inhalation determined NOAECs of >15,000 ppm, as no adverse effects on maternal health, fertility, or fetal development were observed at the highest test dose of 15,000 ppm. However, in another study in rats via whole-body inhalation, a NOEC of 5,000 ppm was determined for paternal systemic toxicity based on observed mortality at the highest dose (20,000 ppm) following a 6 hours/day exposure regimen.

Inhalation and dermal exposures represent the most relevant exposure routes for the cosmetic products containing tetrafluoropropene. Based on the available information, from Giffen, Kilgour et al. (2024), we selected the lowest NOEL of 3,647 mg/kg bw/day (15,000 ppm) from dog studies to derive a POD for risk characterization purposes. This value is the smallest across all NOAELs and was chosen due to the conservative nature of the current assessment.

Given the lack of experimental inhalation absorption data for inhalation absorption, we assume 100% inhalation absorption for tetrafluoropropene. Therefore, the systemic POD (PODsys) is considered to be 3,647 mg/kg bw/day, which is used for risk characterization described after the Exposure Assessment section below.

Since no information is available on skin sensitization, a No Expected Sensitization Induction Level (NESIL) could not be identified.

Exposure Assessment

[103] This unit was converted ppm to mg/kg bw/day based on species-specific inhalation rate and body weight and adjusted for the treatment duration.

Exposure Scenario

Based on the product categories (**Table A.18.2)**, a consumer may be exposed to tetrafluoropropene via multiple exposure routes including inhalation, dermal, oral and ocular routes. Based on the use information of tetrafluoropropene, we developed three exposure scenarios for estimating systemic exposure dose (SED): 1) inhalation-only exposure from aerosol hair sprays, 2) combined exposure from inhalation and dermal contact of aerosol hair sprays, and 3) dermal-only exposure from traditional applications of makeup preparations.

Scenario 1 – Inhalation-only exposure from aerosol hair sprays

This scenario assumes 100% sprayed hair product is airborne. Rothe, Fautz et al. (2011) described a two-box model for inhalation risk assessment in cosmetic spray safety evaluations, which estimates airborne substance distribution by dividing space into a near-field and far-field. For hair sprays, Rothe, Fautz et al. (2011) assumed a 1–2 m^3 cloud around the user in the first 2 minutes, followed by distribution into a 10 m^3 volume within 18 minutes, approximating a bathroom size. Using the two-box model, the level of systemic exposure can be calculated using the following formula:

$$SED = (CRDE/V_1 \times C \times BR \times T_1 + CRDE/V_2 \times C \times BR \times T_2) \times Ip$$

Where:

CRDE represents the calculated relative daily exposure to the cosmetic product, i.e., the amount of hair spray used that is available for exposure (mg/kg bw/day)

V_1 represents the distribution volume of hair spray in a facial/body near cloud (L)

C is the concentration of tetrafluoropropene in the hair spray

BR is the breathing rate (L/min)

T_1 represents duration of exposure in the near field, min

V_2 represents the size of the whole room (L)

T_2 represents duration of exposure in the far field, min

Ip is the exchange factor for the inhaled portion

For adults, a default CRDE value of 129 mg/kg bw/day for aerosol hair spray derived from Loretz, Api et al. (2006) is used in this calculation. This CRDE value has incorporated factors including the amount of product per use, frequency of use per day, and an airborne fraction of 100% (Bremmer, Prud'homme de Lodder et al. 2006). Additionally, it has been adjusted based on body weight.

The distribution volume of hair spray in a facial/body near cloud (V_1) is assumed to be 1 m^3 (1,000 L), and the size of the whole room (V_2) is assumed for a conventional default small bathroom for hair products as 10 m^3 (10,000 L).

As the specific use concentration (C) of tetrafluoropropene is unknown, we apply a conservative approach and assume the 90% tetrafluoropropene concentration in the hair spray product based on our understanding of the limit in regulatory guidelines in China.[102]

Breathing rate (BR) is set at the conventional default value of 19 m^3/day for adults in Rothe, Fautz et al. (2011) and SCCS (2023), which converts to 13 L/min.

Exposure time in the near field (T_1) and far field (T_2) are set as 2 min and 18 min respectively as described in Rothe, Fautz et al. (2011).

Since scientists estimate that 25% of inhaled air and airborne particles are exhaled without being retained in the lungs, an exchange factor for the inhaled portion (Ip = 75%) is applied to the calculation (European Commission 1996, Rothe, Fautz et al. 2011).

Therefore, the systemic exposure to tetrafluoropropene is determined to be 4.30 mg/kg bw/day based on the calculation below:

SED = [(129 mg/kg bw/day)/1000L x 0.9 x 13 L/min x 2min + (129 mg/kg bw/day)/10000L x 0.9 x 13 L/min x 18 min] x 0.75 = 4.30 mg/kg bw/day

Scenario 2 – combined exposure from inhalation and dermal contact of aerosol hair sprays

This scenario assumes that 85% of the sprayed product stays on the hair and head, while 15% becomes airborne. Of the product retained on the hair and head, 10% is available for dermal exposure, meaning it can come into direct contact with the skin or scalp (Bremmer, Prud'homme de Lodder et al. 2006). Incorporating these assumptions, the systemic exposure resulting from dermal contact (SED_{dermal}) can be calculated as:

SED_{dermal} = CRDE x C x DAF x 0.85 x 0.1

Where:

CRDE represents the calculated relative daily exposure to the cosmetic product, i.e., the amount of hair spray used that is available for exposure (mg/kg bw/day)

C is the concentration of tetrafluoropropene in the hair spray

DAF represents the dermal absorption factor

The same values in Scenario 1 are used for calculating relative daily exposure to hair spray and the concentration of tetrafluoropropene in the hair spray. In the absence of experimentally measured dermal absorption, a default value of 50% is applied for DAF as recommended by SCCS (2023). Thus, the dermal exposure to tetrafluoropropene is determined to be 4.93 mg/kg bw/day based on the following calculation:

SED_{dermal} = 129 mg/kg bw/day x 0.9 x 0.5 x 0.85 x 0.1 = 4.93 mg/kg bw/day

While the systemic exposure resulting from inhalation ($SED_{inhalation}$) of the 15% airborne hair spray can be calculated as:

$SED_{inhalation}$ = 4.30 mg/kg bw/day (calculated from Scenario 1) x 0.15 = 0.65 mg/kg bw/day

As a result, the total exposure (SED_{total}) combined from inhalation and dermal contact of the aerosol hair spray is determined to be 5.58 mg/kg bw/day:

SED_{total} = SED_{dermal} + SED_{inh} = 4.93 mg/kg bw/day + 0.65 mg/kg bw/day = 5.58 mg/kg bw/day

Scenario 3 – dermal-only exposure from traditional applications of makeup preparations

Under the makeup product exposure scenario, the level of systemic exposure from dermal application can be calculated using the following formula:

SED = CRDE x C x DAF

Where:

CRDE represents calculated relative daily exposure, i.e., the amount of the makeup product applied that is available for dermal exposure

C represents concentration of tetrafluoropropene in the makeup

DAF represents the dermal absorption factor

For adults, a default CRDE value of 7.90 mg/kg bw/day for makeup liquid foundation, as established by the SCCS Notes of Guidance (SCCS 2023), is used in this calculation, which represents the highest amount of use under the makeup category. This CRDE value has incorporated factors including the amount of product per use, frequency of use per day, and a retention factor (RF) (RF=1 for leave-on products). Additionally, it has been adjusted based on body weight.

As the specific use concentration (C) of tetrafluoropropene is unknown, we apply a conservative approach and assume a 90% tetrafluoropropene concentration in the makeup product based on our understanding of the limit in regulatory guidelines in China.[102]

With the same default value of 50% in Scenario 2 applied for DAF, we determined the systemic exposure to tetrafluoropropene from makeup preparations to be 3.56 mg/kg bw/day based on the following calculation:

SED = 7.90 mg/kg bw/day x 0.9 x 0.5 = 3.56 mg/kg bw/day

Since Scenario 2 yields the highest SED value of 5.58 mg/kg bw/day, we selected it for the MOE calculation to ensure the most conservative analysis.

Risk Characterization

Risk characterization is the final step of a risk assessment, quantitively evaluating whether the level of exposure to a specific ingredient in a product or product type of interest poses potential health risks to the consumers. As noted in the hazard assessment section, the potential of acute inhalation toxicity for tetrafluoropropene is low. Due to a lack of data, the potential for skin sensitization and phototoxicity cannot be determined. Therefore, this current risk characterization focuses solely on the potential risk of systemic toxicity.

In risk characterization, MOE is used as a tool to assess possible health concerns. MOE is the ratio between a safety-based POD and the estimated exposure level, i.e., SED. The larger the margin, the lower the risk. Typically, a calculated MOE smaller than the target MOE (e.g. the default of 100) indicates a concern for a potential health risk, while a calculated MOE larger than the target MOE does not indicate a potential health risk.

The target MOE and the calculated MOE for tetrafluoropropene are calculated as described below.

Target MOE

Given that the POD in this assessment was derived from a 39-week repeated dose toxicity study in dogs, the target MOE for tetrafluoropropene is determined to be ≥100. Thus, a calculated MOE of ≥100 is indicative of low concern for health risks from tetrafluoropropene.

Calculated MOE

Based on the PODsys and SED values calculated in the hazard assessment and exposure assessment sections, respectively, we determined the MOE for tetrafluoropropene used in hair care products by adults (considering both inhalation and dermal exposure) to be 654, as calculated below:

MOE = PODsys/SED = 3647 mg/kg bw/day (15,000 ppm) ÷ 5.58 mg/kg bw/day = 654

In this most conservative use scenario (Scenario 2), the calculated MOE (654) is greater than the target MOE of 100, indicating a low safety concern regarding the use of tetrafluoropropene in cosmetic products under this use scenario. The result also indicates low safety concerns with the use of this ingredient under other presented scenarios with lower exposure doses.

Characterization of Uncertainty

This risk assessment for tetrafluoropropene is subject to uncertainties due to limited data availability. First, the actual concentration of tetrafluoropropene in cosmetic products on the U.S. market is unknown, and the assumed concentration of 90% may be an overestimation. Second, there is a lack of experimental data on inhalation absorption. While the toxicity effects from the repeated dose study support inhalation absorption, the actual absorption rate was not reported. The default absorption rate of 100% for inhalation absorption could be an overestimate. Finally, the mechanism or mode of action by which tetrafluoropropene induced organ damage is not known, making it impossible to evaluate whether the observed effects in animals would also occur in humans, i.e., its human relevance cannot be assessed.

By addressing these knowledge gaps, we can refine this assessment and ensure the safety of tetrafluoropropene-containing cosmetic products. However, considering the conservative nature of the assessment, the use of this ingredient in cosmetic products under the assessed scenarios is of low safety concern despite the uncertainties.

Review Summary/Conclusion

Use: According to the INCI database, tetrafluoropropene functions as a propellant in cosmetic products. As of August 30, 2024, the ingredient was used in 23 registered cosmetic products categorized into hair preparations, makeup preparations, and personal cleanliness products, based on the mandatory cosmetic product listing data submitted to the FDA. It is primarily used in hair sprays and other hair products, followed by deodorant sprays and lip care products. Historical data in the VCRP shows only 1 use by 2023, and Mintel's GNPD shows that 21 new cosmetic products containing the ingredient were launched in the past 5 years (August 2019 to July 2024), including 4 in the past year (August 2023 to July 2024). However, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend cannot be demonstrated at this time.

Safety: Based on the product types containing tetrafluoropropene, inhalation and dermal contact are expected to be the main exposure routes for its use in cosmetic products, followed by potential oral and ocular exposures.

According to the REACH dossier, tetrafluoropropene exhibits low acute toxicity via inhalation. No oral or dermal toxicity data is available. *In vitro* and *in vivo* studies showed it is not genotoxic. It's not a skin irritant. No studies are available on skin sensitization, ocular and respiratory irritation, phototoxicity or carcinogenicity. A 90-day repeated dose inhalation toxicity study and subacute inhalation studies in rats reported cell damage and inflammation in hearts at 15,000 ppm, and effects in the heart, liver, and nasal passages at 20,000–50,000 ppm. Developmental and reproductive toxicity studies in rats (nose-only inhalation) and rabbits (whole-body inhalation) established NOAECs exceeding 15,000 ppm, as no adverse effects on maternal health, fertility, or fetal development were observed at the highest tested dose. However, a separate rat study using whole-body inhalation resulted in a NOEC of 5,000 ppm for paternal systemic toxicity, based on mortality observed at the highest dose of 20,000 ppm.

Giffen, Kilgour et al. (2024) investigated the toxicological effects of tetrafluoropropene inhalation in mice (nose-only), rats (nose-only), and dogs. In 14-day and 13-week studies on mice, no exposure-related effects were detected at doses up to 29,000 mg/kg bw/day, establishing a NOEL at this level. In a 26-week study on rats, the highest dose (12,000 mg/kg bw/day) resulted in increased severity of rodent progressive cardiomyopathy, particularly in males, leading to a NOAEL of 4,280 mg/kg bw/day. In dogs, studies lasting up to 39 weeks revealed no toxicological effects at doses up to 3,647 mg/kg bw/day (15,000 ppm), establishing a NOEL at this level.

A systemic POD of 3,647 mg/kg bw/day was derived from the results of the dog inhalation study in Giffen, Kilgour et al. (2024).

We estimated systemic exposure (i.e., SED) to tetrafluoropropene from cosmetic use for three use scenarios of cosmetic products. For a conservative analysis, the highest exposure dose among these scenarios of 5.58 mg/kg bw/day was selected under our use scenario of aerosol hair sprays combining the exposure from inhalation and dermal contact.

The calculated MOE of 654 for hair spray use is greater than the target MOE of 100, which indicates a low concern for safety associated with tetrafluoropropene when used as an ingredient in cosmetic products under the exposure conditions in the assessment.

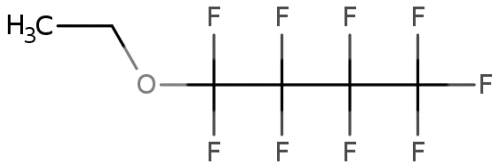
It is important to note that this assessment is preliminary and subject to significant uncertainties. Limited data on use concentration, lack of inhalation absorption studies, insufficient mechanistic understanding of toxicity for human relevance, and restricted access to full study reports contribute to these uncertainties. As more data becomes available, this assessment could be refined to provide a more accurate evaluation of the safety and potential risks of tetrafluoropropene's use in cosmetic products.

19. Ethyl Perfluorobutyl Ether

Introduction

Ethyl perfluorobutyl ether (CAS No. 163702-05-4; PubChem CID: 206000), also known as ethyl nonafluorobutyl ether, is a hydrofluoroether with the chemical formula $C_4F_9OCH_2CH_3$. **Table A.19.1** below presents the key physical and chemical properties related to ethylperfluorobutyl ether. It is a clear colorless liquid with low odor. It has a negligible water solubility but can be soluble in nonpolar organic solvents. Ethyl perfluorobutyl ether's vapor pressure indicates potential for evaporation. Ethyl perfluorobutyl ether is primarily used as a solvent and viscosity decreasing agent in various industries including cosmetic products.

Table A.19.1. Physical and chemical properties of Ethyl Perfluorobutyl Ether

Element	Description
Name	Ethyl Perfluorobutyl Ether
INCI name	Ethyl Perfluorobutyl Ether
Synonyms	1-Ethoxy-1,1,2,2,3,3,4,4,4-Nonafluorobutane Ethyl Nonafluorobutyl Ether 1-(Ethoxy)nonafluorobutane Ethoxynonafluorobutane Nonafluorobutyl Ethyl Ether NOVEC HFE 7200 3M Cosmetic Fluid CF-76
CAS#	163702-05-4
Structure	
Molecular formula	$C_4F_9OCH_2CH_3$ (or $C_6H_5F_9O$)
Molecular weight	264.09 g/mol
Particle size	Not applicable
Physical form	Clear colorless liquid; low odor
Density	1.46 g/cm^3
Solubility	3.01e-4 mol/L (or 79.5 mg/L) in water
Partition coefficient (Log K_{ow})	3.7 (predicted)
Vapor pressure	109 mmHg
Melting point	-69.3 °C
Boiling point	68.4 °C

Element	Description
Topological polar surface area	9.2 Å²
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	NA

Notes: NA, not available. Sources: PubChem; and EPA's CompTox Chemicals Dashboard for ethyl perfluorobutyl ether.

Use in Cosmetic Products

According to INCI, ethyl perfluorobutyl ether functions as solvents and viscosity decreasing agents in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, ethyl perfluorobutyl ether is used in 22 cosmetic products (**Table A.19.2)**. The 22 products are categorized in the following two main product categories: personal cleanliness (n=3, 13.6%) and skin care preparations (creams, lotions, powder, and sprays) (n=19, 86.4%). Please see **Table S2** for a full list of cosmetic product categories.

Within skin care preparations (creams, lotions, powder, and sprays), ethyl perfluorobutyl ether is used in cleansing (cold creams, cleansing lotions, liquids, and pads) (n=4, 18.2%), face and neck (excluding shaving preparations), leave-on (n=1, 4.5%), face and neck (excluding shaving preparations), rinse-off (n=1, 4.5%), moisturizing (n=6, 27.3%), paste masks (mud packs) (n=4, 18.2%), and other skin care preparations, leave-on (n=3, 13.6%) product categories as shown in **Table A.19.2**.

Table A.19.2. Frequency of Use of Ethyl Perfluorobutyl Ether in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Personal cleanliness		
Other personal cleanliness products, leave-on	2	9.1
Other personal cleanliness products, rinse-off	1	4.5
Personal cleanliness total	**3**	**13.6**
Skin care preparations (creams, lotions, powder, and sprays)		
Cleansing (cold creams, cleansing lotions, liquids, and pads)	4	18.2
Face and neck (excluding shaving preparations), leave-on	1	4.5
Face and neck (excluding shaving preparations), rinse-off	1	4.5

Product Category	Number of Products	Percentage of Total (%)
Moisturizing	6	27.3
Paste masks (mud packs)	4	18.2
Other skin care preparations, leave-on	3	13.6
Skin care total	**19**	**86.4**
Grand total	**22**	**100.0**

To assess the trend of ethyl perfluorobutyl ether's use in cosmetic products, we searched the historical data in the VCRP and the Mintel GNPD. The retrieved data from both databases do not show clear trends of the ingredient's use in cosmetic products. In the VCRP database, ethyl perfluorobutyl ether was used in 4 products in 2019, 5 products in 2021, and 5 products in 2023 (**Table S4**). The Mintel GNPD shows that the ingredient was used in 2 products launched in the U.S. market over a 5-year period (August 2019 to July 2024) and 0 products launched between August 2023 and July 2024 (**Table S4**). The use trend of ethyl perfluorobutyl ether cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for ethyl perfluorobutyl ether is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported a use concentration of 2% to 9% in various cosmetic products including facial cleanser, hair care, and lotions and moisturizers.

Based on the product types that contain ethyl perfluorobutyl ether, dermal contact is expected to be the primary route of consumer exposure to this ingredient from the use of cosmetic products, such as creams and lotions for skin care, and products for personal cleanliness.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of ethyl perfluorobutyl ether by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

We conducted a literature search on the toxicokinetics of ethyl perfluorobutyl ether in PubMed and Web of Science using the query outlined in **Table S9**. The search identified one publication in PubMed and 16 publications in Web of Science (searched on 12/10/2024). However, after abstract screening, we did not identify any publications relevant to the toxicokinetics of ethyl perfluorobutyl ether. We did not identify a REACH dossier for ethyl perfluorobutyl ether in the ECHA database (searched on 12/10/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of ethyl perfluorobutyl ether. As the FDA does not have premarket authority over cosmetic ingredients or products other than color additives which are subject to FDA approval before use, we do not have specific data to review.

Review Summary/Conclusion

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, ethyl perfluorobutyl ether, a hydrofluoroether, is currently used as an ingredient in 22 cosmetic products, primarily in skin care preparations and personal cleanliness. Data from Mintel's GNPD and the VCRP do not provide a trend for the use of ethyl perfluorobutyl ether in cosmetic products. In addition, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend cannot be demonstrated at this time.

Safety: Based on the product types containing ethyl perfluorobutyl ether, dermal contact is expected to be the primary route of consumer exposure to this ingredient. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of ethyl perfluorobutyl ether. The FDA does not have relevant information to assess the potential for skin irritation or sensitization, and whether it can be absorbed and could lead to systemic exposure and toxicity. Given the limited data and information available, the FDA cannot determine the safety of ethyl perfluorobutyl ether from its use in cosmetic products or risks associated with such use.

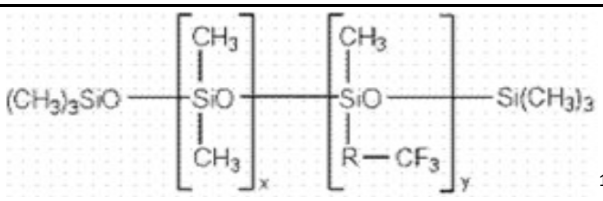
20. Trifluoromethyl C1-4 Alkyl Dimethicone

Introduction

Trifluoromethyl C1-4 alkyl dimethicone (CAS/CID numbers unavailable) is a clear fluoro silicone fluid containing trifluoroalkyl groups along the silicone backbone in its structure. **Table A.20.1** below presents the known physical and chemical properties of trifluoromethyl C1-4 alkyl dimethicone. Due to the trifluoroalkyl organic branch distribution, it exhibits excellent lubricity, conditioning, water repellency, and anti-foam characteristics and forms a protective barrier when formulated in skin and hair care products.

Trifluoromethyl C1-4 alkyl dimethicone can be used in a wide variety of cosmetic applications including protective creams, suntan creams, body lotions, shampoos, conditioners, and wherever conditioning, lubricity, and water resistance are desired.[104]

Table A.20.1. Physical and Chemical Properties of Trifluoromethyl C1-4 Alkyl Dimethicone

Element	Description
Name	Trifluoromethyl C1-4 Alkyl Dimethicone
INCI name	Trifluoromethyl C1-4 Alkyl Dimethicone
Synonym	Gransil DM-100[105]
CAS#	NA
Structure	 [106]
Molecular formula	$SiOC_3H_9(SiOC_2H_6)_x(SiOC_2H_3F_3C_nH_{2n})_ySiC_3H_9$[106]
Molecular weight	NA
Particle size	Not applicable
Physical form	Clear colorless liquid
Density	NA
Solubility	NA
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	NA
Boiling point	NA

[104] Trifluoromethyl C1-4 Alkyl Dimethicone | Ingredient | INCIGuide (accessed 12/12/2024).

[105] Gransil DM-100: Technical Datasheet (accessed 12/12/2024).

[106] Trifluoromethyl C1-4 Alkyl Dimethicone - ICID raw ingredient: EZCOS (accessed 12/12/2024).

Element	Description
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Specific gravity: 0.89-1 at 25 °C, non-volatile matter: 95-100%, refractive index: 1.395-1.405, viscosity: 90-120 cP[105]

Notes: NA, not available. Sources: See footnotes.

Use in Cosmetic Products

According to INCI, trifluoromethyl C1-4 alkyl dimethicone functions as an occlusive skin-conditioning agent in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, trifluoromethyl C1-4 alkyl dimethicone is used in 21 cosmetic products (**Table A.20.2)**. The 21 products are categorized in two main product categories: makeup preparations (not eye) (other than makeup preparations for children) (n=17, 81.0%) and skin care preparations (creams, lotions, powder, and sprays) (n=4, 19.0%). Please see **Table S2** for a full list of cosmetic product categories.

Within the two main product categories, trifluoromethyl C1-4 alkyl dimethicone is predominantly used in foundations (traditional applications), accounting for 42.9% (n=9) of the ingredient's total usage in cosmetic products as shown in **Table A.20.2**.

Table A.20.2. Frequency of Use of Trifluoromethyl C1-4 Alkyl Dimethicone in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Makeup preparations (not eye) (other than makeup preparations for children)		
Face powders	4	19.0
Foundations, traditional applications	9	42.9
Makeup bases, traditional applications	3	14.3
Makeup bases, traditional applications/Makeup bases, airbrush applications	1	4.8
Makeup (not eye) total	**17**	**81.0**
Skin care preparations (creams, lotions, powder, and sprays)		
Face and neck (excluding shaving preparations), leave-on	**4**	**19.0**

Product Category	Number of Products	Percentage of Total (%)
Grand total	**21**	**100.0**

To assess the trend of trifluoromethyl C1-4 alkyl dimethicone's use in cosmetic products, we searched historical data in the VCRP and the Mintel GNPD. VCRP data shows that trifluoromethyl C1-4 alkyl dimethicone was not used in cosmetic products in 2019 and 2021 but was used in 2 products in 2023, while Mintel's GNPD does not show any record of use in cosmetic products launched in the U.S. market over a 5-year period (August 2019 to July 2024) (**Table S4**). The use trend of trifluoromethyl C1-4 alkyl dimethicone cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for trifluoromethyl C1-4 alkyl dimethicone is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported the use concentration of 3% in various cosmetic products, including bronzer and highlighter, foundation and concealer, hair care, lotions and moisturizers, and sun care.

Given that the majority of the products containing trifluoromethyl C1-4 alkyl dimethicone are makeup and skin care products, dermal contact is expected to be the primary route of consumer exposure to this ingredient. Incidental inhalation may occur when using face powders or makeup base that is applied using an airbrush.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments for trifluoromethyl C1-4 alkyl dimethicone by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S9** did not identify any publications on the toxicokinetics of trifluoromethyl C1-4 alkyl dimethicone. We did not identify a REACH dossier for trifluoromethyl C1-4 alkyl dimethicone in the ECHA database (searched on 12/10/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publications on the toxicity of trifluoromethyl C1-4 alkyl dimethicone.

Review Summary/Conclusion

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, trifluoromethyl C1-4 alkyl dimethicone is currently used as an ingredient in 21 cosmetic products, predominantly in face foundations, face powder, and makeup bases, followed by in face and neck leave on products. Available

information from the VCRP and Mintel's GNPD indicates that trifluoromethyl C1-4 alkyl dimethicone was rarely used in cosmetic products in the past several years. Although there are significantly more registered products in the mandatory cosmetic product listing data submitted to the FDA, due to the lack of baseline or historical data, a use trend cannot be demonstrated at this time.

Safety: Based on the product types using trifluoromethyl C1-4 alkyl dimethicone, consumers may be exposed to the ingredient through multiple routes. Dermal contact is expected to be the primary route of exposure for the ingredient, as it is predominantly used in makeup and skin care preparations. Additionally, exposure may occur through incidental inhalation when face powders are applied, or when makeup base is applied using an airbrush. As the FDA does not have any relevant information to assess the potential toxicity of trifluoromethyl C1-4 alkyl dimethicone, we cannot determine the safety of trifluoromethyl C1-4 alkyl dimethicone from its use in cosmetic products or risks associated with such use.

21. Perfluorononylethyl Stearyl Dimethicone

Introduction

Perfluorononylethyl stearyl dimethicone (CAS No. 882878-48-0; PubChem CID: 121235922) is a soft paste fluorinated and alkylated silicone; the fluoro pendant gives excellent softness and slip while the alkyl pendant groups make it more compatible with many organic systems.[107] **Table A.21.1** shows the chemical structure and physicochemical properties. Perfluorononylethyl stearyl dimethicone is an off-white soft solid that is insoluble in water but soluble in mineral oil.

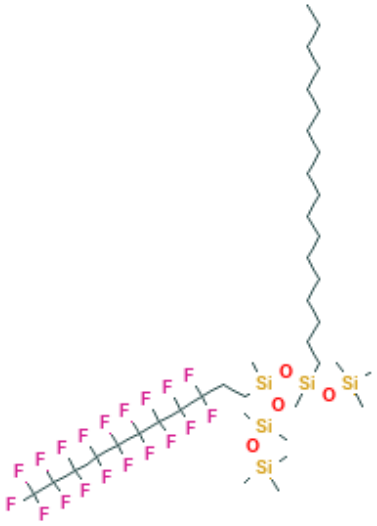
Table A.21.1. Physical and Chemical Properties of Perfluorononylethyl Stearyl Dimethicone

Element	Description
Name	Perfluorononylethyl Stearyl Dimethicone
INCI name	Perfluorononylethyl Stearyl Dimethicone
Synonyms	Perfluorononylethyl Stearyl Dimethicone (25-35% nonafluorohexylmethylsiloxane) (65-75% dimethylsiloxane) copolymer, 8-12 cSt dimethyl-[methyl-(methyl-octadecyl-trimethylsilyloxysilyl)oxy-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-nonadecafluoroundecyl)silyl]oxy-trimethylsilyloxysilane 1858250-39-1 Fluorosil L-118 (trade name)[107] SF-30W[108] Siloxanes and Silicones, di-Me, Me 3,3,4,4,5,5,6,6,6-nonafluorohexyl, Me stearyl[109]
CAS#	882878-48-0

[107] Fluorosil® L118 by Siltech Corporation - Personal Care & Cosmetics (accessed 12/10/2024)

[108] https://cosmetics.specialchem.com/product/i-basel-chemie-elkem-sf-30w (accessed 12/10/2024)

[109] Safety datasheet for Fluorosil L118, https://www.siltech.com/wp-content/uploads/2024/04/SDS-5515-Fluorosil-L118_GHS.pdf (accessed 12/10/2024)

Element	Description
Structure	
Molecular formula	$C_{39}H_{71}F_{19}O_4Si_5$
Molecular weight	1105.4 g/mol
Particle size	NA
Physical form	Liquid,[108] wax,[108,109] soft solid,[110] off-white,[109] Gardner Color Scale 4 Max[110]
Density	NA
Solubility	Insoluble in water, insoluble in IPA, soluble in mineral oil, dispersible to insoluble in cyclopentasiloxane, dispersible to insoluble in 350 viscosity silicone fluid[108]
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	30-40 °C,[108] 27 °C[110]
Boiling point	NA
Topological polar surface area	36.9 Å²
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Viscosity: 400-1000 cP,[108] flash point: 200 °C[108] odor: faint,[109] flash point (PMCC) >100 °C[107]

[110] Technical datasheet for Fluorosil L118, https://www.siltech.com/wp-content/uploads/2017/11/TP5515.pdf (accessed 12/10/2024).

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, perfluorononylethyl stearyl dimethicone functions as film formers and occlusive skin-conditioning agents in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorononylethyl stearyl dimethicone is used in 18 cosmetic products. All 18 products are in the skin care preparations (creams, lotions, powder, and sprays) or leave-on face and neck (excluding shaving preparations) product category as shown in **Table A.21.2**. Please see **Table S2** for a full list of cosmetic product categories.

Table A.21.2. Frequency of Use of Perfluorononylethyl Stearyl Dimethicone in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Skin care preparations (creams, lotions, powder, and sprays)		
Face and neck (excluding shaving preparations), leave-on	18	100.0
Total	**18**	**100.0**

To assess the trend of perfluorononylethyl stearyl dimethicone use in cosmetic products, we searched the historical data in the VCRP and the Mintel GNPD. We found no reported use of this ingredient in the VCRP or Mintel's GNPD over the past 5 years (August 2019 to July 2024) (**Table S4**). The use trend of perfluorononylethyl stearyl dimethicone cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for perfluorononylethyl stearyl dimethicone is not available to the FDA. Suppliers recommend usage at a variety of concentration ranges of 0.2% to 3.0%[109] and 0.5% to 50%[111] of the formulation. It is important to note that different suppliers of raw material may recommend varying concentrations of use, and that manufacturers or formulators ultimately determine the final concentration in their cosmetic products, which may be outside the range of suppliers' recommendations.

Given that all the 18 perfluorononylethyl stearyl dimethicone-containing cosmetic products are leave-on skin care preparation products, intended for use in face and neck areas, dermal contact is considered the primary route of consumer exposure to this ingredient. Oral and inhalation exposure are less likely.

[111] https://cosmetics.specialchem.com/product/i-basel-chemie-elkem-sf-30w (accessed 12/10/2024)

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments for perfluorononylethyl stearyl dimethicone by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S9** did not identify any publications on the toxicokinetics of perfluorononyl dimethicone. We did not identify a REACH dossier for perfluorononylethyl stearyl dimethicone in the ECHA database (searched on 12/10/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publications on the toxicity of perfluorononylethyl stearyl dimethicone. The SDS from the supplier Siltech Corp. [107] indicates that perfluorononylethyl stearyl dimethicone poses low acute toxicity under normal conditions of handling and use through ingestion and inhalation routes of exposure. The supplier does not report any classification for other toxicities such as skin irritation, eye irritation, skin sensitization, carcinogenicity or reproductive toxicity. Importantly, we note that the specific data regarding these health effects are unavailable for our independent evaluation.

Review Summary/Conclusion

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorononylethyl stearyl dimethicone, a fluorinated and alkylated silicone, is currently used as an ingredient in 18 cosmetic products, in face and neck skin care preparations (excluding shaving preparations) and leave-on products. However, due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a use trend cannot be demonstrated at this time. Suppliers recommend the use at a variety of concentration ranges of up to 50% of the formulation.

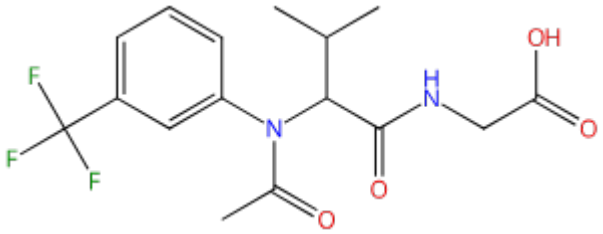
Safety: Based on the product types containing perfluorononylethyl stearyl dimethicone, consumers are expected to be primarily exposed to this ingredient via dermal contact. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of perfluorononylethyl stearyl dimethicone. The FDA does not have information to assess the potential for eye irritation, skin irritation or sensitization, and whether it can be absorbed and could lead to systemic exposure and toxicity. Given the limited data and information available, the FDA cannot determine the safety of perfluorononylethyl stearyl dimethicone from its use in cosmetic products or risks associated with such use.

22. Acetyl Trifluoromethylphenyl Valylglycine

Introduction

Information regarding acetyl trifluoromethylphenyl valylglycine (CAS No. 379685-96-8) is very limited. **Table A.22.1** shows the chemical structure and limited information on physicochemical properties. The water solubility of acetyl trifluoromethylphenyl valylglycine is generally low. Higher solubility has been reported in certain organic solvents. The predicted potential functional uses include skin conditioners, antimicrobials and antioxidants.[112]

Table A.22.1. Physical and Chemical Properties of Acetyl Trifluoromethylphenyl Valylglycine

Element	Description
Name	Acetyl Trifluoromethylphenyl Valylglycine
INCI name	Acetyl Trifluoromethylphenyl Valylglycine
Synonyms	UNII-95SP8380V9 (+/-)-Acetyl Rifluoromethylphenyl Valylglycine Acetyl Trifluoromethylphenyl Valylglycine,dl- Glycine, *N*-acetyl-*N*-(3-(trifluoromethyl)phenyl))valyl 2-[[(2S)-2-[N-acetyl-3-(trifluoromethyl)anilino]-3-methylbutanoyl]amino]acetic acid *N*-Acetyl-*N*-(3-(trifluoromethyl)phenyl)valylglycine Mexoryl SAR (trade name)
CAS#	379685-96-8
Structure	
Molecular formula	$C_{16}H_{19}F_3N_2O_4$
Molecular weight	360.33 g/mol
Physical form	NA
Density	1.311±0.06 g/cm^3
Solubility	Water: predicted range1.26e-3 to 5.10e-3 mol/L[112]
Partition coefficient (Log K_{ow})	2.5 (predicted)
Vapor pressure	2.21e-12 to 2.51e-10 mmHg

[112] 2-[[2-[N-Acetyl-3-(trifluoromethyl)anilino]-3-methylbutanoyl]amino]acetic acid - Chemical Details (accessed 12/10/2024)

Melting point	169 °C
Boiling point	537.448±50.00 °C[113]
Topological polar surface area	86.7 Å²
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	pKa: 3.297±0.10,[113] PSA: 90.2

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, acetyl trifluoromethylphenyl valylglycine functions as miscellaneous skin-conditioning agents in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, acetyl trifluoromethylphenyl valylglycine is used as an ingredient in 17 cosmetic products that are all categorized in the leave-on skin care preparations (creams, lotions, powder, and sprays) product category and used in the face and neck (excluding shaving preparations) leave-on product category, accounting for 64.7% (n= 11) of the ingredient's total usage in cosmetic products as shown in **Table A.22.2**. Please see **Table S2** for a full list of cosmetic product categories.

Table A.22.2. Frequency of Use of Acetyl Trifluoromethylphenyl Valylglycine in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Skin care preparations (creams, lotions, powder, and sprays)		
Cleansing (cold creams, cleansing lotions, liquids, and pads)	1	5.9
Face and neck (excluding shaving preparations), leave-on	11	64.7
Moisturizing	4	23.5
Other skin care preparations, leave-on	1	5.9
Total	**17**	**100.0**

[113] CAS: https://scifinder-n.cas.org/search/all/6760a63db831fb243139c79d (accessed 12/10/2024. Login is required for access).

To assess the trend of acetyl trifluoromethylphenyl valylglycine use in cosmetic products, we searched the historical data in the VCRP and the Mintel GNPD. We found no reported use of this ingredient in the VCRP (**Table S4**). Mintel's GNPD data shows that acetyl trifluoromethylphenyl valylglycine was used in 9 products launched in the U.S. market over a 5-year period (August 2019 to July 2024) but 0 products between August 2023 and July 2024 (**Table S4**). The total number was too low to determine a trend. In addition, a use trend of acetyl trifluoromethylphenyl valylglycine cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for acetyl trifluoromethylphenyl valylglycine is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported the use concentrations of 0.5-1.17% in lotion and moisturizer and sun care products. One of the manufacturers indicated usage of 1% to 25% of acetyl trifluoromethylphenyl valylglycine in their skin care products.[114] In addition, the Australian Industrial Chemicals Introduction Scheme (AICIS) assessed this chemical as a component of dermal cosmetic products at concentrations of no more than 0.5% (not intended for the eye).[115]

Given that the majority of the 17 cosmetic products that contain acetyl trifluoromethylphenyl valylglycine are leave-on skin care preparation products, dermal contact is considered the primary route of consumer exposure to this ingredient. Potential inhalation exposure could occur with products such as face powders.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of acetyl trifluoromethylphenyl valylglycine by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S9** did not identify any published data on the toxicokinetics of acetyl trifluoromethylphenyl valylglycine. We did not identify a REACH dossier for acetyl trifluoromethylphenyl valylglycine in the ECHA database (searched on 12/10/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of acetyl trifluoromethylphenyl valylglycine. In addition, a review of SDS from a raw material supplier also revealed no toxicity data.[116]

Review Summary/Conclusion

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[114] https://patentimages.storage.googleapis.com/35/bf/3e/c9e25fe3719783/US10449133.pdf (accessed 12/10/2024).

[115] https://services.industrialchemicals.gov.au/chemical-details-page/?id=53358c5d-15b0-ec11-8108-005056a07365 (accessed 12/10/2024).

[116] https://www.lookchem.com/sds379685-96-8.html (accessed 12/10/2024).

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, acetyl trifluoromethylphenyl valylglycine is used as an ingredient in 17 cosmetic products. All 17 products are categorized in the skin care preparations (creams, lotions, powder, and sprays) product category. The ingredient serves as a skin conditioning agent. It is used primarily in leave-on skin care products on the face and neck. The potential concentrations of use range from 0.5%-25%. Due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend cannot be demonstrated at this time.

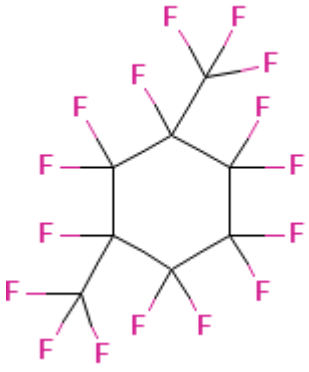
Safety: Based on the product types containing acetyl trifluoromethylphenyl valylglycine, consumers are expected to be primarily exposed to this ingredient through dermal contact. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of acetyl trifluoromethylphenyl valylglycine. The FDA does not have information to assess the potential for dermal and inhalation irritation or sensitization, and whether it can be absorbed and could lead to systemic exposure and toxicity. Given the limited data and information available, the FDA cannot determine the safety of acetyl trifluoromethylphenyl valylglycine from its use in cosmetic products or risks associated with such use.

23. Perfluorodimethylcyclohexane

Introduction

Perfluorodimethylcyclohexane, also known as perfluoro-1,3-dimethylcyclohexane (CAS No. 335-27-3; PubChem CID: 78975) is a clear, colorless liquid characterized by its chemical inertness. **Table A.23.1** shows the chemical structure and physicochemical properties. The compound has a high density and a low surface tension, making it useful in specialized applications such as coolants and lubricants. It is highly insoluble in water and organic solvents but mixes freely with other fluorocarbon liquids and freons. With a boiling point of 101.5 °C and a melting point of -70 °C, perfluorodimethylcyclohexane remains stable under normal storage conditions but it evaporates rapidly.

Table A.23.1. Physical and Chemical Properties of Perfluorodimethylcyclohexane

Element	Description
Name	Perfluorodimethylcyclohexane
INCI name	Perfluorodimethylcyclohexane
Synonyms	Perfluoro-1,3-dimethylcyclohexane 1,1,2,2,3,3,4,5,5,6-Decafluoro-4,6-bis(trifluoromethyl)cyclohexane Decafluoro-1,3-bis(trifluoromethyl)cyclohexane Cyclohexane, decafluoro-1,3-bis(trifluoromethyl) Cyclohexane, 1,1,2,2,3,3,4,5,5,6-decafluoro-4,6-bis(trifluoromethyl)- Cyclohexane, perfluoro-1,3-dimethyl- Hexadecafluoro-1,3-dimethylcyclohexane Flutec PC3 (trade name) Fiflow 100 (trade name) Carbohal (trade name)
CAS#	335-27-3
Structure	
Molecular formula	C_8F_{16}
Molecular weight	400.06 g/mol

Particle size	Not applicable
Physical form	Clear colorless liquid[117]
Density	1.8560 g/cm^3 at 20 °C, 1.829 g/cm^3 at 25 °C, 1.828 g/cm^3 (liquid) at 102 °C, 760 Torr, 0.01310 g/cm^3 (gas) at 102 °C, 760 Torr[118]
Solubility	It doesn't dissolve in water, it doesn't dissolve in organic solvents, but mixes with fluorocarbon liquids and freons unrestrictedly[119]
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	−70 °C[118]
Boiling point	101.5 °C[118]
Topological polar surface area	0 Å^2
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	Surface tension: 9.9 mN/m at Temp 375.2 K, Press 1x 10^5 Pa,[118] viscosity: 1.93 mPa.s (dynamic) at 296 K,[118] refractive index: 1.2908 at 20 °C,[118] enthalpy of vaporization: 37.4 kJ/mol[120]

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, perfluorodimethylcyclohexane functions as a solvent in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, perfluorodimethylcyclohexane is used as an ingredient in 17 cosmetic products (**Table A.23.2**). The 17 products are categorized in two main product categories: hair preparations (non-coloring) (n=3, 17.6%) and skin care preparations (creams, lotions, powder, and sprays) (n=14, 82.4%). Please see **Table S2** for a full list of cosmetic product categories.

Within the two main product categories, perfluorodimethylcyclohexane is predominantly used in leave-on hair preparations and leave-on face and neck products, respectively.

Table A.23.2. Frequency of Use of Perfluorodimethylcyclohexane in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

[117] Technical information for Perfluoro-1,3-dimethylcyclohexane, https://www.scbt.com/p/perfluoro-1-3-dimethylcyclohexane-335-27-3?srsltid=AfmBOoq2Dtk6uWN4gCdjzKUnsHE4zBQMBME3Vx4CzkPJEKKNqJp (accessed 12/12/2024)

[118] https://scifinder-n.cas.org/searchDetail/substance/67631f5d38673f014ece070d/substanceDetails (access 12/12/2024. Login is required for access)

[119] Product information for "Carbohal," https://halopolymer.com/upload/iblock/7bd/7bd0570c3471913eac7125ff63af077d.pdf (accessed 12/12/2024).

[120] https://webbook.nist.gov/cgi/cbook.cgi?ID=C335273&Mask=4#ref-1 (accessed 12/12/2024).

Product Category	Number of Products	Percentage of Total (%)
Hair preparations (non-coloring)		
Other hair preparations, leave-on	**3**	**17.6**
Skin care preparations (creams, lotions, powder, and sprays)		
Face and neck (excluding shaving preparations), leave-on	8	47.1
Face and neck (excluding shaving preparations), rinse-off	2	11.8
Body and hand (excluding shaving preparations), rinse-off	1	5.9
Other skin care preparations, leave-on	3	17.6
Skin care total	**14**	**82.4**
Grand total	**17**	**100.0**

Available data indicate a generally low use of perfluorodimethylcyclohexane in cosmetic products. The VCRP database showed its use in 7 products in 2019, 9 in 2021 and 5 in 2023 (**Table S4**). Additionally, data from Mintel's GNPD showed that 4 cosmetic products containing perfluorodimethylcyclohexane entered the U.S. market over a 5-year period (August 2019 to July 2024), with 3 of these introduced between August 2023 and July 2024 (**Table S4**). A use trend of perfluorodimethylcyclohexane cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for perfluorodimethylcyclohexane is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported a use concentration of 0.02% to 2.25% in cosmetic products.

Given its use in face and makeup products, dermal contact is considered the most significant route of consumer exposure to this ingredient, with incidental inhalation also possible when applied as a fine mist or powder.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments of perfluorodimethylcyclohexane by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S9** identified 14 publications in PubMed and 63 publications from Web of Science (searched on 12/12/2024). After abstract screening, we did not identify any published data relevant to the toxicokinetics of perfluorodimethylcyclohexane. Additionally, a search of the ECHA database for a REACH dossier on perfluorodimethylcyclohexane found no toxicokinetic studies (ECHA 2017) (searched on 12/12/2024). The REACH dossier (ECHA 2017) included a read-across study to evaluate ADME properties of perfluorodimethylcyclohexane based on a category approach using perfluorocarbons as analogs. The study authors stated that saturated perfluorocarbons are well established as a class of compounds with very similar toxicological properties. The study authors concluded that perfluorodimethylcyclohexane is not expected to be absorbed significantly and is likely to distribute to the liver and spleen. In addition, perfluorodimethylcyclohexane is not metabolized and is rapidly excreted by exhalation without bioaccumulation. However, we were unable to evaluate the quality and validity of the study due to the lack of critical details.

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no toxicity data for perfluorodimethylcyclohexane. However, a registrant's dossier on the ECHA website provides some relevant information, which is summarized below in the corresponding subsections (ECHA 2017).

It is important to note that the REACH dossier provides only limited publicly available information and the original study reports were inaccessible for review. Thus, the quality of the data cannot be independently and fully evaluated.

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

The REACH dossier (ECHA 2017) included a read-across study to evaluate the acute dermal toxicity of perfluorodimethylcyclohexane based on a category approach, using perfluoroperhydrofluorene as an analog. The study authors concluded that the ingredient does not have acute dermal toxicity because the acute lethal dermal dose to rats was >2000 mg/kg bw. However, we were unable to evaluate the quality and validity of the study due to the lack of critical details.

Oral

An acute oral toxicity study (ECHA 2017) was performed in rats at a dose of 100 ml/kg (183,000 mg/kg). No mortality or adverse effects were observed. The study authors reported a LD_{50} of >100 ml/kg bw.

Inhalation

An acute inhalation toxicity study (ECHA 2017) was performed in rats via whole-body inhalation at a concentration of 40,000 ppm v/v for 360 minutes. No adverse effects were observed. The study authors reported a LC_{50} of >40,000 ppm. No control animals were included in this study.

The REACH dossier (ECHA 2017) also included a read-across study to evaluate the acute inhalation toxicity of perfluorodimethylcyclohexane based on a category approach using octafluoropropane as an

analog. The study authors concluded that the ingredient does not have acute inhalation toxicity. However, we were unable to evaluate the quality and validity of the study due to the lack of critical details.

Repeated Dose Systemic Toxicity

We did not locate any data for repeated dose systemic toxicity via the dermal or oral routes of exposure, or for carcinogenicity, DART or neurotoxicity.

Inhalation

The REACH dossier (ECHA 2017) included a read-across study to evaluate the short-term repeated dose inhalation toxicity of perfluorodimethylcyclohexane based on a category approach, using octafluoropropane as an analog. The study authors concluded that the ingredient is not chronically toxic after inhalation exposure. However, we were unable to evaluate the quality and validity of the study due to the lack of critical details.

Genotoxicity

An Ames test was performed in 1979. Six, 4 and 2 ml of the test substances (CAS#: 335-27-3) that had vaporized in desiccator were applied with and without S9-mix. A negative response was reported. In addition, the REACH dossier (ECHA 2017) included two read-across studies to evaluate the genetic toxicity of perfluorodimethylcyclohexane based on a category approach. The REACH dossier concluded that the ingredient did not exhibit genetic toxicity in the Ames test and *in vitro* mammalian cell micronucleus test. However, the FDA is unable to evaluate the quality and validity of the studies due to the lack of critical details.

Site of Contact Effects:

We did not locate any data for dermal, ocular, or respiratory irritation, or photo-induced toxicity.

Dermal Sensitization

The REACH dossier (ECHA 2017) included a read-across study to evaluate the skin sensitization of perfluorodimethylcyclohexane based on a category approach. The study authors stated that saturated perfluorocarbons, used as analogs, are well established as a class of compounds with very similar toxicological properties. The study authors concluded that the ingredient does not cause skin sensitization. However, we were unable to evaluate the quality and validity of the study due to the lack of critical details.

Review Summary/Conclusion

Use: Perfluorodimethylcyclohexane functions as a solvent in cosmetic products, as reported by the INCI database. Based on the mandatory cosmetic product listing data submitted to the FDA, it is an ingredient in 17 cosmetic products, primarily in skin care preparations and in non-coloring hair preparations. In skin care products, it is most commonly used in face and neck leave-on products. In hair preparations, its usage is limited to leave-on products. While specific concentrations in FDA-listed cosmetic products are unavailable, literature reports show levels ranging from 0.02% to 2.25%. The VCRP and Mintel's GNPD do not show a clear trend in the use of perfluorodimethylcyclohexane in

cosmetic products. Due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend cannot be demonstrated at this time.

Safety: Based on the product types containing perfluorodimethylcyclohexane, dermal contact is expected to be the primary route of consumer exposure to this ingredient when used in cosmetic products. The REACH dossier for perfluorodimethylcyclohexane presents limited toxicological data. Acute toxicity studies found no adverse effects in rats for oral and inhalation exposure at the highest dose tested. Both experimental and read-across studies suggest this ingredient is not genotoxic. ECHA also concluded that the ingredient does not cause skin sensitization based on a read-across study. No other toxicological data is available. Overall, these data suggest minimal acute toxicity, but significant data gaps remain for certain endpoints. However, the FDA does not have access to the full study reports to assess the quality of the studies presented in the REACH dossier and therefore cannot fully evaluate and determine the safety of perfluorodimethylcyclohexane from its use in cosmetic products or risks associated with such use.

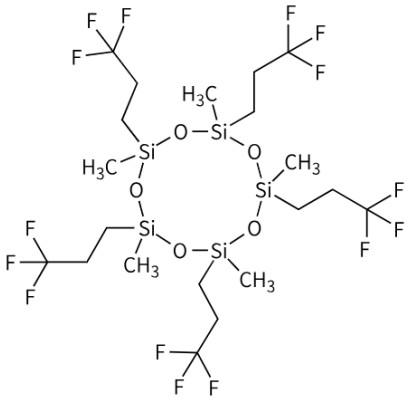
24. Trifluoropropyl Cyclopentasiloxane

Introduction

The chemical formula of trifluoropropyl cyclopentasiloxane varies depending on the exact structure but generally includes a cyclopentasiloxane ring with one or more trifluoropropyl groups attached. **Table A.24.1** shows the chemical structure and physicochemical properties of trifluoropropyl cyclopentasiloxane. As an example, the structure of "cyclopentasiloxane, 2,4,6,8,10-pentamethyl-2,4,6,8,10-pentakis(3,3,3-trifluoropropyl)-," containing five trifluoropropyl groups attached (CAS No. 2063-78-7; PubChem CID: 164923), is provided.

Trifluoropropyl cyclopentasiloxane is a liquid and is biodegradable. Due to the presence of the fluorinated group, it is highly water-repellent, making it insoluble in water but soluble in most organic solvents. It has excellent absorption, wetting, spreading, dispersing, and lubricating abilities and is used for skin and hair conditioning in cosmetic products.[121,122]

Table A.24.1. Physical and Chemical Properties of Trifluoropropyl Cyclopentasiloxane

Element	Description
Name	Trifluoropropyl Cyclopentasiloxane
INCI name	Trifluoropropyl Cyclopentasiloxane
Synonyms	Cyclopentasiloxane, 2,4,6,8,10-pentamethyl-2,4,6,8,10-pentakis(3,3,3-trifluoropropyl) DTXSID5073953
CAS#	2063-78-7
Structure	 122
Molecular formula	$C_{20}H_{35}F_{15}O_5Si_5$
Molecular weight	780.90 g/mol
Particle size	Not applicable

[121] Trifluoropropyl cyclopentasiloxane information (accessed 12/10/2024).

[122] Trifluoropropyl Cyclopentasiloxane - Surfactant - SAAPedia (accessed 12/10/2024).

Physical form	Liquid
Density	NA
Solubility	Water insoluble
Partition coefficient (Log K_{ow})	NA
Vapor pressure	NA
Melting point	NA
Boiling point	NA
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	NA
Additional properties	NA

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, trifluoropropyl cyclopentasiloxane functions as hair conditioning agents and miscellaneous skin-conditioning agents in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, trifluoropropyl cyclopentasiloxane is used as an ingredient in 11 cosmetic products as shown in **Table A.24.2**. The 11 products are categorized in the following two main product categories: makeup preparations (not eye) (other than makeup preparations for children) (n=9, 81.8%) and skin care preparations (creams, lotions, powder, and sprays) (n=2, 18.2%). Please see **Table S2** for a full list of cosmetic product categories.

Within the two main categories, trifluoropropyl cyclopentasiloxane is predominantly used in lipsticks and lip glosses, accounting for 54.5% (n=6) of the ingredient's total usage in cosmetic products as shown in **Table A.24.2**.

Table A.24.2. Frequency of Use of Trifluoropropyl Cyclopentasiloxane in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Makeup preparations (not eye) (other than makeup preparations for children)		
Blushers and rouges (all types)	1	9.1
Foundations, traditional applications	1	9.1
Lipsticks and lip glosses	6	54.5
Makeup bases, traditional applications	1	9.1

Product Category	Number of Products	Percentage of Total (%)
Makeup (not eye) total	**9**	**81.8**
Skin care preparations (creams, lotions, powder, and sprays)		
Moisturizing	**2**	**18.2**
Grand total	**11**	**100.0**

To assess the trend of trifluoropropyl cyclopentasiloxane's use in cosmetic products, we searched historical data in the VCRP and the Mintel GNPD. In the VCRP database, while there was no reported use of trifluoropropyl cyclopentasiloxane in 2019 and 2021, it was present in 31 products in 2023 (**Table S4**). However, the Mintel GNPD data shows that trifluoropropyl cyclopentasiloxane was formulated in 11 cosmetic products launched in the U.S. market over a 5-year period (August 2019 to July 2024), but no new products were launched between August 2023 and July 2024 (**Table S4**). A use trend of trifluoropropyl cyclopentasiloxane cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for trifluoropropyl cyclopentasiloxane is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) assumed a use concentration of 0.5%-5%, a similar concentration range as trifluoropropyl dimethicone, which has the same functional use. It can be used in various cosmetic products, including foundation and concealer, lip cosmetics, and lotions and moisturizers.

Given that the majority of the products containing trifluoropropyl cyclopentasiloxane are makeup and skin care products, dermal contact is expected to be the primary route of consumer exposure to this ingredient. Incidental ingestion may occur when using lipsticks and lip glosses.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments for trifluoropropyl cyclopentasiloxane by government agencies or other scientific advisory groups such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search in PubMed and Web of Science using the query outlined in **Table S9** did not identify any publications on the toxicokinetics of trifluoropropyl cyclopentasiloxane (searched on 12/10/2024). We did not identify a REACH dossier for trifluoropropyl cyclopentasiloxane in the ECHA database (searched on 12/10/2024).

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publications on the toxicity of trifluoropropyl cyclopentasiloxane. Based on limited information, the ingredient is classified as an irritant to the skin and eyes under GHS guidelines (Revision 10), but no data was provided.[121] However, as FDA does not have premarket authority over cosmetic ingredients or products, other than color additives which are subject to FDA approval before use, we do not have specific data to review or evaluate the GHS classification.

Review Summary/Conclusion

Use: Based on the mandatory cosmetic product listing data submitted to the FDA, trifluoropropyl cyclopentasiloxane is currently used as an ingredient in 11 cosmetic products, predominantly in makeup and skin care preparations, and particularly in lipsticks and lip glosses. Available information from the VCRP shows an increase in the use of trifluoropropyl cyclopentasiloxane in cosmetic products in 2023 compared to 2019 and 2021, whereas Mintel's GNPD data shows no new products introduced from August 2023-July 2024. Due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend cannot be demonstrated at this time.

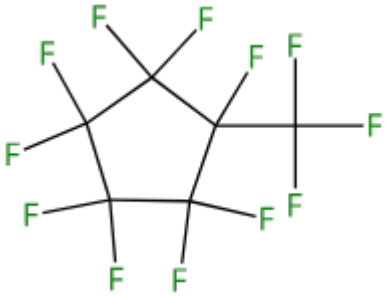
Safety: Based on the product types containing trifluoropropyl cyclopentasiloxane, consumers may be exposed to the ingredient through multiple routes. As it is predominantly used in makeup and skin care preparations, dermal contact is considered the primary route of consumer exposure to this ingredient. Additionally, use of trifluoropropyl cyclopentasiloxane in lipsticks and lip glosses may lead to incidental oral exposure. However, as the FDA does not have any relevant information to assess the potential toxicity of trifluoropropyl cyclopentasiloxane, we cannot determine the safety of trifluoropropyl cyclopentasiloxane from its use in cosmetic products or risks associated with such use.

25. Perfluoromethylcyclopentane

Introduction

Perfluoromethylcyclopentane (CAS No. 1805-22-7; PubChem CID: 74546) is a perfluorocycloalkane chemical. **Table A.25.1** shows the chemical structure and physicochemical properties. Perfluoromethylcyclopentane is a clear liquid that is insoluble in water. It is soluble in aliphatic hydrocarbons and chlorinated hydrocarbons. Perfluoromethylcyclopentane is generally stable under normal storage and handling conditions, but decomposition occurs at 400 °C.[123]

Table A.25.1. Physical and Chemical Properties of Perfluoromethylcyclopentane

Element	Description
Name	Perfluoromethylcyclopentane
INCI name	Perfluoromethylcyclopentane
Synonyms	Perfluoro(methylcyclopentane) Perfluoromethylcyclopentane Nonafluoro(trifluoromethyl)cyclopentane 1,1,2,2,3,3,4,4,5-nonafluoro-5-(trifluoromethyl)cyclopentane Cyclopentane, 1,1,2,2,3,3,4,4,5-nonafluoro-5-(trifluoromethyl)- Cyclopentane, nonafluoro(trifluoromethyl)- 8S014W4T75-UNII[124] (TRIFLUOROMETHYL)PERFLUOROCYCLOPENTANE[124] FIFLOW 50[124] FLUTEC PC-1C (trade name)[124] FLUTEC TG PMCP (trade name) FLUTEC PP1C (trade name)
CAS#	1805-22-7
Structure	
Molecular formula	C_6F_{12}

[123] Safety datasheet for FLUTEC PP1C, https://www.f2chemicals.com/pdf/sds/FLUTEC%20PP1C(1805-22-7).pdf (accessed 12/11/2024).

[124] https://gsrs.fda.gov/ginas/app/ui/substances/cd1ee042-0f2c-4f46-8fc1-7237ff105415 (accessed 12/11/2024).

Element	Description
Molecular weight	300.04 g/mol
Particle size	Not applicable
Physical form	Clear, colorless liquid[123]
Density	0.01040 g/cm³ (gas) @ Temp: 48.0 °C; Press: 760 Torr, 1.707 g/cm³ (liquid) @ Temp: 48.0 °C; Press: 760 Torr[125]
Solubility	Water solubility: 4.01e-5 mol/L (predicted avg),[124] soluble in aliphatic hydrocarbons,[123] soluble in chlorinated hydrocarbons,[123] insoluble in water,[123]
Partition coefficient (Log K_{ow})	3.67[126] (predicted)
Vapor pressure	387 mmHg (predicted average),[125] 45kPa[123]
Melting point	45 °C,[125] -50 °C[123]
Boiling point	48 °C[125]
Topological polar surface area	NA
UV light absorption spectrum	NA
Decomposes	Decomposition temp: 400 °C[123]
Additional properties	Critical temperature: 184.9 °C,[123] critical pressure: 23 bar,[123] surface tension: 12.4 mN/m @ Temp 321 K, Press 1x10^5 Pa,[125] viscosity (dynamic): 1.86 mPa·s @Temp: 321 K; Press:1x10^5 Pa,[125] thermal conductivity: 60.9 mW/(m*K),[126] index of refraction: 1.27[126]

Notes: NA, not available. Sources: PubChem; specified otherwise.

Use in Cosmetic Products

According to INCI, perfluoromethylcyclopentane functions as miscellaneous skin-conditioning agents and solvents in cosmetic products.

Based on the mandatory cosmetic product listing data submitted to the FDA, perfluoromethylcyclopentane is used as an ingredient in 10 cosmetic products as shown in **Table A.25.2**. All 10 products are categorized in the skin care preparations (creams, lotions, powder, and sprays) product category. Please see **Table S2** for a full list of cosmetic product categories.

Within the skin care preparations (creams, lotions, powder, and sprays) product category, perfluoromethylcyclopentane is predominantly used in the face and neck (excluding shaving preparations) leave-on product category, accounting for 40.0% (n= 4) of the ingredient's total usage in cosmetic products as shown in **Table A.25.2**.

[125] https://scifinder-n.cas.org/search/all/67643552fd9ec1154915f452 (accessed 12/11/2024. Login is required for access).

[126] https://comptox.epa.gov/dashboard/chemical/properties/DTXSID7061982 (accessed 12/11/2024).

Table A.25.2. Frequency of Use of Perfluoromethylcyclopentane in the Mandatory Cosmetic Product Listing Data Submitted to the FDA (as of August 30, 2024)

Product Category	Number of Products	Percentage of Total (%)
Skin care preparations (creams, lotions, powder, and sprays)		
Cleansing (cold creams, cleansing lotions, liquids, and pads)	1	10.0
Face and neck (excluding shaving preparations), leave-on	4	40.0
Paste masks (mud packs)	2	20.0
Other skin care preparations, leave-on	1	10.0
Other skin care preparations, rinse-off	2	20.0
Total	**10**	**100.0**

To assess the trend of the ingredient's use in cosmetic products, we searched the historical data in the VCRP and the Mintel GNPD. Perfluoromethylcyclopentane was used in 1 product in 2019, 3 products in 2021, and 3 products in 2023 according to the VCRP (**Table S4**). The Mintel GNPD data showed that 10 products containing perfluoromethylcycopentane were launched in the U.S. market over a 5-year period (August 2019 to July 2024) and 3 products were launched between August 2023 and July 2024 (**Table S4**). A use trend of perfluoromethylcycopentane cannot be currently determined using the mandatory cosmetic product listing data submitted to the FDA due to the lack of historical data.

Under the FD&C Act, the concentration of ingredients used in cosmetic products is not required to be submitted to the FDA as part of the product listing data. Therefore, the use concentration for perfluoromethylcyclopentane is not available to the FDA. A recent publication by Balan, Bruton et al. (2024) reported a use concentration of 0.02% to 2% in various cosmetic products including foundation and concealer, lotions and moisturizers, and shaving creams and gels.

Given that the products containing perfluoromethylcyclopentane are all skin care preparation products, dermal contact is expected to be the primary route of consumer exposure to this ingredient, occurring from its use in cosmetic products such as creams, lotions, and paste masks.

Existing Safety Assessments by Government Agencies, Scientific Advisory Groups, and Peer-Reviewed Literature

A comprehensive search of data sources as listed in **Table S5** did not identify any assessments for perfluoromethylcyclopentane by government agencies or other scientific advisory groups, such as SCCS, CIR, or IARC.

ADME/Toxicokinetics

A literature search using the query outlined in **Table S9** identified 7 publications in PubMed and 13 from Web of Science (searched on 12/11/2024). After screening abstracts of these publications, none of these were determined to be relevant to the toxicokinetics of perfluoromethylcyclopentane. In addition, we

did not find any toxicokinetics information in the REACH dossier for perfluoromethylcyclopentane (ECHA 2018) (searched on 12/11/2024). The REACH dossier (ECHA 2018) included a read-across study to evaluate ADME properties of perfluoromethylcyclopentane based on a category approach using perfluorocarbons as analogs. The study authors stated that saturated perfluorocarbons are well established as a class of compounds with very similar toxicological properties. The study authors concluded that perfluoromethylcyclopentane is not expected to be absorbed significantly and that it distributes to the liver and spleen. In addition, perfluoromethylcyclopentane is not metabolized and is rapidly excreted by exhalation without bioaccumulation. However, we were unable to evaluate the quality and validity of the study due to the lack of critical details.

Hazard Assessment

A literature search in PubMed and Web of Science using the query outlined in **Table S9** yielded no publicly available information regarding the toxicity of perfluoromethylcyclopentane. However, a registrant's dossier on the ECHA website provides some relevant information, which is summarized below in the corresponding subsections (ECHA 2018).

It is important to note that the REACH dossier provides only limited publicly available information and the original study reports were inaccessible for review. Thus, the quality of the data cannot be independently and fully evaluated.

Acute and Repeated Dose Toxicity

Acute Toxicity

Dermal

An acute dermal toxicity study (ECHA 2018) was performed in three male rabbits according to OECD Guideline 402 (Acute Dermal Toxicity) and in compliance with GLP. Perfluoromethylcyclopentane at 0.5 ml was introduced under a 2.5 cm square gauze patch and placed on the back onto shorn skin of a rabbit for 4 hours. One animal showed very slight erythema 1 hour after patch removal and at 24-, 48- and 72-hour observations. The study authors did not identify a LD_{50} (ECHA 2018).

The REACH dossier (ECHA 2018) also included a read-across study to evaluate the acute dermal toxicity of perfluoromethylcyclopentane based on a category approach using perfluoroperhydrofluorene as the analog. The study authors concluded that the ingredient does not have acute dermal toxicity because the acute lethal dermal dose to rats was >2,000 mg/kg bw. However, the FDA was unable to evaluate the quality and validity of the study due to the lack of critical details.

Oral

An acute oral toxicity study was performed in five female and five male rats at a dose of 5000mg/kg bw according to OECD Guideline 401 (Acute Oral Toxicity) and in compliance with GLP. No mortality or systemic toxicity were observed. The study authors identified a LD_{50} of >5,000 mg/kg bw (ECHA 2018).

Inhalation

The REACH dossier (ECHA 2018) included two read-across studies to evaluate the acute inhalation toxicity of perfluoromethylcyclopentane based on a category approach, using perfluorodecalin and octafluoropropane as analogs. The study authors concluded that the ingredient is not acutely toxic after

inhalation. However, the FDA was unable to evaluate the quality and validity of the study due to the lack of critical details.

Repeated Dose Systemic Toxicity

We did not locate any data for repeated dose systemic toxicity via the dermal or oral routes of exposure, or for carcinogenicity, DART or neurotoxicity.

Inhalation

The REACH dossier (ECHA 2018) included two read-across studies to evaluate the repeated dose inhalation toxicity of perfluoromethylcyclopentane based on a category approach. The study authors concluded that the ingredient is not chronically toxic after inhalation. However, the FDA was unable to evaluate the quality and validity of the study due to the lack of critical details.

Genotoxicity

An Ames test was conducted according to OECD Guideline 471 and in compliance with GLP. Perfluoromethylcyclopentane was tested at concentrations ranging from 8 to 5000 μg/plate with and without S9-mix in five *Salmonella* strains. However, it was not tested in the *E. coli* strain recommended by OECD 471. The test material was found to be non-mutagenic under the conditions of this test.

The REACH dossier (ECHA 2018) also included a read-across study to evaluate the genetic toxicity of perfluoromethylcyclopentane based on a category approach, using nonafluoro(trifluoromethyl)cyclopentane as an analog. The study authors concluded that the ingredient did not induce mutations in an Ames test. However, the FDA was unable to evaluate the quality and validity of the study due to the lack of critical details.

Another two read-across studies were included in the REACH dossier (ECHA 2018) to evaluate the genetic toxicity of perfluoromethylcyclopentane, using octafluoropropane as an analog. The study authors concluded that the ingredient did not induce genetic toxicity in an *in vitro* mammalian cell micronucleus test and an *in vivo* mouse erythrocyte micronucleus test. However, the FDA was unable to evaluate the quality and validity of the study due to the lack of critical details.

Site of Contact Effects:

Dermal Irritation

A study in the REACH dossier (ECHA 2018) evaluated perfluoromethylcyclopentane for acute skin irritation in a semi-occlusive study conducted in accordance with OECD TG 404. Three New Zealand White rabbits were exposed to 0.5 ml undiluted perfluoromethylcyclopentane for 4 hours and observed throughout a 72-hour period. The study authors found the substance to be a mild irritant to rabbit skin. However, under EEC labeling regulations, it is classified as non-irritating, requiring no symbols or risk phrases.

Dermal Sensitization

The REACH dossier (ECHA 2018) included a read-across study to evaluate the skin sensitization of perfluoromethylcyclopentane based on a category approach. The study authors stated that saturated perfluorocarbons, used as analogs, are well established as a class of compounds with very similar

toxicological properties. The study authors concluded that the ingredient does not cause skin sensitization.

Ocular Irritation

In an eye irritation study performed in compliance with OECD 405 guidelines, 0.1 ml perfluoromethylcyclopentane did not cause irritation to the eyes of three New Zealand White rabbits throughout a 72-hour observation period (ECHA 2018).

Respiratory irritation

No data.

Photo-induced toxicity

No data.

Others

No data.

Review Summary/Conclusion

Uses: Based on the mandatory cosmetic product listing data submitted to the FDA, perfluoromethylcyclopentane, a perfluorocycloalkane chemical, is currently used as an ingredient in 10 cosmetic products, all for skin care preparations, and particularly on the face and neck. The VCRP and Mintel's GNDP show consistently low use of perfluoromethylcyclopentane in cosmetic products. Due to the lack of baseline or historical data in the mandatory cosmetic product listing data submitted to the FDA, a trend cannot be demonstrated at this time.

Safety: Based on the product types containing perfluoromethylcyclopentane, consumers are primarily exposed to this ingredient via dermal contact. It is not acutely toxic and not genotoxic. It is not irritating to eyes and there is conflicting information regarding skin irritation. However, there is a lack of publicly available information regarding the toxicokinetics or toxicity of perfluoromethylcyclopentane. The FDA does not have sufficient information to assess the potential for skin sensitization, and whether it can be absorbed and could lead to systemic exposure and toxicity. Given the limited data and information available, the FDA cannot determine the safety of perfluoromethylcyclopentane from its use in cosmetic products or risks associated with such use.

Appendix 2. Supplemental Tables

Supplemental Table 1. List of INCI Names Identified as PFAS, CAS No, Reported Functions and Product Categories in wINCI (as of 2/14/24)

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
1	Acetyl sh-Decapeptide-4 SP Amide Trifluoroacetate	NA	Skin-Conditioning Agents - Miscellaneous	NA
2	Acetyl Trifluoromethylphenyl Valylglycine	379685-96-8	Skin-Conditioning Agents - Miscellaneous	Eye Lotions Face and Neck Preparations (Excluding Shaving Preparations) Moisturizing Preparations Skin Care Preparations, Misc. Eye Makeup Preparations, Misc. Foundations Night Skin Care Preparations
3	Acrylates/Methoxy PEG-23 Methacrylate/Perfluorooctyl Ethyl Acrylate Copolymer	NA	Film Formers	NA
4	Acrylates/Perfluorohexylethyl Methacrylate Copolymer	1557087-30-5	Film Formers	NA
5	Acrylates/Trifluoropropylmethacrylate/Polytrimethyl Siloxymethacrylate Copolymer	NA	Film Formers Hair Fixatives Skin-Conditioning Agents - Miscellaneous	NA
6	Acrylic Acid/Perfluorohexylethyl Acrylate Crosspolymer	1820790-78-0	Viscosity Increasing Agents - Aqueous	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
7	Adamantanylcarboxamido Trifluoromethylbenzonitrile	NA	Antimicrobial Agents Hair Conditioning Agents	NA
8	Ammonium C6-16 Perfluoroalkylethyl Phosphate	65530-70-3 65530-72-5 65530-71-4	Surfactants - Emulsifying Agents	NA
9	Ammonium C9-10 Perfluoroalkylsulfonate	NA	Surfactants - Cleansing Agents	NA
10	Ammonium Perfluorohexyl Ethylphosphates	1764-95-0	Surfactants - Emulsifying Agents	NA
11	AMP-C8-18 Perfluoroalkylethyl Phosphate	NA	Emulsion Stabilizers Slip Modifiers Surfactants - Emulsifying Agents Surfactants - Solubilizing Agents	NA
12	Behenyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer	NA	Film Formers Viscosity Increasing Agents - Nonaqueous	NA
13	Biotinoyl Histidyl D-Tryptophanyl Dipeptide-29 D-Phenylalanyl Lysinamide Trifluoroacetate	1894171-15-3	Skin-Conditioning Agents - Miscellaneous	NA
14	Biotinyl Histidyl D-Tryptophanyl Dipeptide-29 Lysinamide Trifluoroacetate	NA	Skin-Conditioning Agents - Miscellaneous	NA
15	Bis-Trifluoromethyl Phenylcaffeamide	NA	Hair Conditioning Agents	NA
16	Butyl Acrylate/C6-14 Perfluoroalkylethyl	NA	NA	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
	Acrylate/Mercaptopropyl Dimethicone Copolymer			
17	C12-16 Alkyl PEG-7 Methacrylate/Perfluorohexylethyl Methacrylate Copolymer	NA	Film Formers Hair Conditioning Agents	NA
18	C20-28 Alkyl Perfluorodecylethoxy Dimethicone	NA	Film Formers	NA
19	C4-14 Perfluoroalkylethoxy Dimethicone	NA	Skin-Conditioning Agents - Miscellaneous	NA
20	C4-18 Perfluoroalkylethyl Thiohydroxypropyltrimonium Chloride	70983-60-7	Surfactants - Cleansing Agents	NA
21	C6-12 Perfluoroalkylethanol	NA	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous Solvents	NA
22	C6-14 Perfluoroalkylethyl Acrylate	NA	NA	NA
23	C6-14 Perfluoroalkylethyl Acrylate/HEMA Copolymer	NA	Dispersing Agents - Nonsurfactant Film Formers Viscosity Increasing Agents - Nonaqueous	NA
24	C8-18 Fluoroalcohol Phosphate	NA	Bulking Agents	NA
25	C9-13 Fluoroalcohol	NA	Skin-Conditioning Agents - Miscellaneous	Face Powders Foundations

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
26	C9-15 Fluoroalcohol Phosphate	NA	Skin-Conditioning Agents - Miscellaneous	Face and Neck Preparations (Excluding Shaving Preparations) Foundations Moisturizing Preparations Face Powders Makeup Preparations (Not eye), Misc.
27	Calcium Trifluoroacetate	60884-90-4	Exfoliants	NA
28	Chlorotrifluoropropene	102687-65-0	Solvents	NA
29	Cloflucarban	369-77-7	Cosmetic Biocides Deodorant Agents	NA
30	DEA-C8-18 Perfluoroalkylethyl Phosphate	65530-63-4 65530-64-5	Surfactants - Emulsifying Agents	Foundations
31	DEA-Perfluorohexyl Ethylphosphates	NA	Surfactants - Emulsifying Agents	NA
32	DEA-Polyperfluoroethoxymethoxy PEG-2 Phosphate	NA	Surfactants - Emulsifying Agents	NA
33	Decafluoropentane	138495-42-8	Solvents	NA
34	Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer	NA	Binders Surface Modifiers	NA
35	Difluorocyclohexyloxyphenol	2001566-55-6	Antioxidants Skin Bleaching Agents	NA
36	Dimethiconol Fluoroalcohol Dilinoleic Acid	NA	Skin-Conditioning Agents - Occlusive	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
37	Dioctyldodecyl Fluoroheptyl Citrate	214334-16-4	Skin-Conditioning Agents - Miscellaneous	Hair Conditioners Lipsticks
38	Ethyl Nitrotrifluoromethylphenyl Citramalamide	1081953-87-8	Antiacne Agents	NA
39	Ethyl Perfluorobutyl Ether	163702-05-4	Solvents Viscosity Decreasing Agents	NA
40	Ethyl Perfluoroisobutyl Ether	163702-06-5	Solvents Viscosity Decreasing Agents	NA
41	Ethyl tafluprostamide	1185851-52-8	Hair Conditioning Agents Nail Conditioning Agents	NA
42	Ethyl travoprostamide	1005193-64-5	Antimicrobial Agents Antioxidants Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	NA
43	Europium Tris(Trifluorothienylbutanedione) Bis(Triphenylphosphine Oxide)	120851-64-1	Colorants	NA
44	Fluoro C2-8 Alkyldimethicone	NA	Antifoaming Agents	Foundations
45	Fluorosalan	6/1/4776	Cosmetic Biocides	NA
46	Fluridil	260980-89-0	Hair Conditioning Agents	NA
47	Galactose Difluoroethyl Aminopiperidinone	NA	Antioxidants Skin-Conditioning	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
			Agents - Humectant	
48	HC Yellow No. 13	10442-83-8	Hair Colorants	Hair Dyes and Colors
49	Heptapeptide-50 Trifluoroacetate	NA	Skin-Conditioning Agents - Miscellaneous	NA
50	Hexafluoropropylene/Tetrafluoroethylene Copolymer	25067-11-2	Film Formers Skin-Conditioning Agents - Emollient Slip Modifiers	NA
51	Hydrofluorocarbon 134a	811-97-2	Propellants	NA
52	Hydrofluorocarbon 227ea	431-89-0	Propellants	NA
53	Hydrogen Trifluoropropyl Dimethicone	766542-38-5	Antifoaming Agents Binders Emulsion Stabilizers Slip Modifiers Surface Modifiers	NA
54	Isobutylmethacrylate/Trifluoroethylmethacrylate/Bis-Hydroxypropyl Dimethicone Acrylate Copolymer	321735-42-6	Film Formers Hair Fixatives Skin-Conditioning Agents - Miscellaneous	NA
55	Isododecyl/Perfluorononylethyl Dimer Dilinoleate/Citrate	NA	Skin-Conditioning Agents - Emollient	NA
56	Isopropyl Titanium Triisostearate/Perfluorooctyl Triethoxysilane Crosspolymer	NA	Surface Modifiers	NA
57	Ketotravoprost	404830-45-1	Hair Conditioning Agents	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
58	Methyl Perfluoro Butyl/Isobutyl Ether	163702-07-6 163702-08-7	Solvents	Cleansing Products (Cold Creams, Cleansing Lotions, Liquids and Pads) Face and Neck Preparations (Excluding Shaving Preparations)
59	Methyl Perfluorobutyl Ether	163702-07-6	Solvents Viscosity Decreasing Agents	Cleansing Products (Cold Creams, Cleansing Lotions, Liquids and Pads) Skin Care Preparations, Misc. Face and Neck Preparations (Excluding Shaving Preparations)
60	Methyl Perfluoroisobutyl Ether	163702-08-7	Solvents Viscosity Decreasing Agents	Cleansing Products (Cold Creams, Cleansing Lotions, Liquids and Pads) Face and Neck Preparations (Excluding Shaving Preparations)
61	Methyl travoprost	NA	Hair Conditioning Agents	NA
62	Nortafluprost	209860-89-9	Eyelash Conditioning Agents Hair Conditioning Agents	NA
63	Octafluoropentyl Methacrylate	355-93-1	Surface Modifiers	Hair Conditioners Shampoos (Non-coloring) Hair Sprays (Aerosol Fixatives) Tonics, Dressings, and

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
				Other Hair Grooming Aids
64	Octapeptide-29 Trifluoroacetate	NA	Skin-Conditioning Agents - Miscellaneous	NA
65	Oligopeptide-177 Trifluoroacetate	NA	Skin Protectants	NA
66	PEG-10 Acrylate/Perfluorohexylethyl Acrylate Copolymer	NA	Film Formers	NA
67	PEG-10 Nonafluorohexyl Dimethicone Copolymer	NA	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	Hair Conditioners Shampoos (Non-coloring)
68	PEG-10 Trifluoropropyl Dimethicone Copolymer	NA	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	NA
69	PEG-4 Trifluoropropyl Dimethicone Copolymer	NA	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	NA
70	PEG-8 Trifluoropropyl Dimethicone Copolymer	NA	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	NA
71	Pentafluoropropane	460-73-1	Dispersing Agents - Nonsurfactant External Analgesics Fragrance	Moisturizing Preparations

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
			Ingredients Solvents	
72	Pentapeptide-34 Trifluoroacetate	NA	Skin-Conditioning Agents - Miscellaneous	NA
73	Perfluoro Dimethylethylpentane	50285-18-2	NA	NA
74	Perfluoro t-Butylcyclohexane	84808-64-0	Antistatic Agents Hair Conditioning Agents Surface Modifiers	NA
75	Perfluoroalkylsilyl Mica	NA	NA	NA
76	Perfluorobutoxydiglycol Difluoroethoxy Propyl Trimethoxysilane	NA	Skin-Conditioning Agents - Miscellaneous	NA
77	Perfluorobutylcyclohexane	374-60-7	Antistatic Agents Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous Surface Modifiers	NA
78	Perfluorobutylethyl Dimethicone	NA	Hair Conditioning Agents Skin-Conditioning Agents - Humectant Surfactants - Foam Boosters	NA
79	Perfluorobutylethyl Stearyl Dimethicone	915223-67-5	Antifoaming Agents Dispersing Agents - Nonsurfactant Hair Conditioning Agents Skin-Conditioning	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
			Agents - Emollient Slip Modifiers Surface Modifiers	
80	Perfluorocaprylyl Bromide	423-55-2	Solvents	NA
81	Perfluorocaprylyl Triethoxysilylethyl Methicone	NA	Binders Skin-Conditioning Agents - Emollient	NA
82	Perfluorocyclohexylmethanol	28788-68-3	Emulsion Stabilizers Skin-Conditioning Agents - Miscellaneous Slip Modifiers Surface Modifiers	NA
83	Perfluorodecalin	306-94-5	Skin-Conditioning Agents - Miscellaneous Solvents	Eye Makeup Preparations, Misc. Moisturizing Preparations Skin Care Preparations, Misc. Face and Neck Preparations (Excluding Shaving Preparations) Nail Polish and Enamels
84	Perfluorodimethylcyclohexane	26637-68-3 335-27-3	Solvents	Eye Makeup Preparations, Misc.
85	Perfluoroheptane	335-57-9	Absorbents Anticaking Agents Emulsion Stabilizers Skin-Conditioning Agents - Miscellaneous	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
			Slip Modifiers Surface Modifiers	
86	Perfluorohexane	355-42-0	Solvents	Eye Makeup Preparations, Misc. Moisturizing Preparations Face and Neck Preparations (Excluding Shaving Preparations) Skin Care Preparations, Misc.
87	Perfluorohexyl Ethylphosphonic Acid	252237-40-4	Surface Modifiers	NA
88	Perfluorohexylethoxy Dimethicone	NA	Skin-Conditioning Agents - Miscellaneous	NA
89	Perfluorohexylethyl alcohol	647-42-7	Dispersing Agents - Nonsurfactant Emulsion Stabilizers Plasticizers	NA
90	Perfluorohexylethyl Dimethylbutyl Ether	210896-25-6	Skin-Conditioning Agents - Miscellaneous	NA
91	Perfluorohexylethyl Triethoxysilane	51851-37-7	Binders Skin-Conditioning Agents - Miscellaneous	Eye Shadows Lipsticks Foundations Makeup Preparations (Not eye), Misc.
92	Perfluoroisohexane	355-04-4	Anticaking Agents Skin-Conditioning Agents - Emollient	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
93	Perfluoromethylcyclohexane	355-02-2	Absorbents Anticaking Agents Binders Emulsion Stabilizers Skin-Conditioning Agents - Miscellaneous Slip Modifiers Surface Modifiers	NA
94	Perfluoromethylcyclopentane	1805-22-7	Skin-Conditioning Agents - Miscellaneous Solvents	NA
95	Perfluoromethyldecalin	51294-16-7	Absorbents Anticaking Agents Binders Emulsion Stabilizers Skin-Conditioning Agents - Miscellaneous Slip Modifiers Surface Modifiers	NA
96	Perfluorononyl Dimethicone	259725-95-6	Skin-Conditioning Agents - Miscellaneous Skin-Conditioning Agents - Occlusive Slip Modifiers	Eye Shadows Lipsticks Eyeliners Makeup Preparations (Not eye), Misc.
97	Perfluorononyl Dimethicone/Methicone/Amodimethicone Crosspolymer	NA	Surface Modifiers	Skin Care Preparations, Misc.
98	Perfluorononyl Octyldodecyl Glycol Grapeseedate	NA	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	Face Powders

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
99	Perfluorononyl Octyldodecyl Glycol Meadowfoamate	NA	Dispersing Agents - Nonsurfactant Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	NA
100	Perfluorononylethyl Carboxy PEG-7 Dimethicone Phosphate	NA	Hair Conditioning Agents	NA
101	Perfluorononylethyl Carboxydecyl Behenyl Dimethicone	NA	Skin-Conditioning Agents - Emollient Skin-Conditioning Agents - Occlusive	NA
102	Perfluorononylethyl Carboxydecyl Hexacosyl Dimethicone	NA	Skin-Conditioning Agents - Emollient Skin-Conditioning Agents - Occlusive	NA
103	Perfluorononylethyl Carboxydecyl Lauryl Dimethicone	NA	Skin-Conditioning Agents - Emollient Skin-Conditioning Agents - Occlusive	NA
104	Perfluorononylethyl Carboxydecyl Lauryl/Behenyl Dimethicone	NA	Skin-Conditioning Agents - Emollient Skin-Conditioning Agents - Occlusive	NA
105	Perfluorononylethyl Carboxydecyl PEG-10 Dimethicone	NA	Skin-Conditioning Agents - Emollient Surface Modifiers Surfactants - Emulsifying Agents	NA
106	Perfluorononylethyl Carboxydecyl PEG-8 Dimethicone	NA	Skin-Conditioning Agents - Emollient	NA
107	Perfluorononylethyl Dimethicone/Methicone Copolymer	NA	Slip Modifiers Surface Modifiers	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
108	Perfluorononylethyl PEG-8 Dimethicone	NA	NA	NA
109	Perfluorononylethyl PEG-8 Phenylisopropyl Dimethicone	NA	Skin-Conditioning Agents - Emollient	NA
110	Perfluorononylethyl Stearyl Dimethicone	NA	Film Formers Skin-Conditioning Agents - Occlusive	NA
111	Perfluorooctylethyl Triethoxysilane	101947-16-4	Anticaking Agents	NA
112	Perfluorooctylethyl Trimethoxysilane	83048-65-1	Bulking Agents	NA
113	Perfluorooctylethyl Trisiloxane	163921-85-5	Binders	NA
114	Perfluorooctylethyl/Diphenyl Dimethicone Copolymer	NA	Skin-Conditioning Agents - Emollient	Lipsticks
115	Perfluoroperhydrobenzyl Tetralin	116265-66-8	Skin-Conditioning Agents - Miscellaneous Solvents	NA
116	Perfluoroperhydrofluorene	307-08-4	Solvents	NA
117	Perfluoroperhydrophenanthrene	306-91-2	Skin-Conditioning Agents - Miscellaneous Solvents	Eye Makeup Preparations, Misc. Skin Care Preparations, Misc. Moisturizing Preparations
118	Perfluoropropane	76-19-7	NA	NA
119	Perfluoropropoxy (Perfluoro PPG)-9 Dimethylaminopropylamide	NA	Surface Modifiers	NA
120	Perfluoropropylene	116-15-4	NA	NA
121	Perfluoropropylene/Vinylidene Difluoride Copolymer	9011-17-0	Film Formers	NA
122	Perfluorotetralin	2342-07-6	Skin-Conditioning Agents -	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
			Miscellaneous Solvents	
123	Polyacrylate-37	NA	Binders Surface Modifiers	NA
124	Polyacrylate-48	NA	Skin Protectants	NA
125	Polychlorotrifluoroethylene	9002-83-9	Film Formers Skin-Conditioning Agents - Occlusive	NA
126	Polyperfluoroethoxymethoxy Difluoroethyl PEG Diisostearate	NA	Skin Protectants Skin-Conditioning Agents - Emollient Slip Modifiers Viscosity Increasing Agents - Nonaqueous	NA
127	Polyperfluoroethoxymethoxy Difluoroethyl PEG Ether	162492-15-1	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous Skin-Conditioning Agents - Occlusive	NA
128	Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate	NA	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	Face Powders Moisturizing Preparations Lipsticks
129	Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether	88645-29-8	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	NA
130	Polyperfluoroethoxymethoxy Difluoromethyl Distearamide	NA	Skin-Conditioning Agents - Miscellaneous Viscosity	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
			Increasing Agents - Nonaqueous	
131	Polyperfluoroethoxymethoxy Difluoromethyl Ether	161075-02-1	Solvents	NA
132	Polyperfluoroethoxymethoxy PEG-2 Phosphate	162567-74-0	Dispersing Agents - Nonsurfactant	NA
133	Polyperfluoroisopropyl Ether	NA	Skin-Conditioning Agents - Miscellaneous Skin-Conditioning Agents - Occlusive	Eye Makeup Preparations, Misc. Face Powders
134	Polyperfluoromethylisopropyl Ether	69991-67-9	Skin-Conditioning Agents - Miscellaneous Skin-Conditioning Agents - Occlusive	Blushers (All types) Eye Lotions Eye Shadows Face Powders Indoor Tanning Preparations Makeup Bases Manicuring Preparations, Misc. Skin Care Preparations, Misc. Body and Hand Preparations (Excluding Shaving Preparations) Eye Makeup Preparations, Misc. Face and Neck Preparations (Excluding Shaving Preparations) Foundations Lipsticks Makeup Preparations (Not eye), Misc. Moisturizing Preparations Suntan Gels, Creams, and Liquids

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
135	Polyperfluoroperhydrophenanthrene	NA	Film Formers Hair Fixatives Skin-Conditioning Agents - Miscellaneous	NA
136	Polysilicone-10	NA	Antifoaming Agents Hair Conditioning Agents	NA
137	Polysilicone-7	146632-08-8	Antifoaming Agents Hair Conditioning Agents	NA
138	Polytetrafluoroethylene Acetoxypropyl Betaine	NA	NA	NA
139	Polyurethane-26	NA	Film Formers Hair Conditioning Agents Skin Protectants	NA
140	Polyurethane-27	328389-91-9	Film Formers Hair Conditioning Agents Skin Protectants	NA
141	Polyvinylidene difluoride	24937-79-9	Binders Skin-Conditioning Agents - Miscellaneous Slip Modifiers	NA
142	Potassium Perfluorohexyl Ethylphosphate	1224952-82-2	Surface Modifiers	NA
143	Polytetrafluoroethylene (PTFE)	9002-84-0	Bulking Agents, Slip Modifiers	Blushers and rouges (All types) Eye Lotions Eye Shadows Eyeliners Face Powders Lipsticks

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
				Makeup Preparations (Not eye), Misc. Moisturizing Preparations Shaving Preparations, Misc. Body and Hand Preparations (Excluding Shaving Preparations) Eye Makeup Preparations, Misc. Eyebrow Pencils Face and Neck Preparations (Excluding Shaving Preparations) Foundations Makeup Bases Mascara Night Skin Care Preparations Shaving Cream (Aerosol, Brushless and Lather)
144	s-Enterobacteria Phage T4 Decapeptide-1 SP Trifluoroacetate	NA	Skin-Conditioning Agents - Miscellaneous	NA
145	sh-Heptapeptide-4 SP Trifluoroacetate	NA	Skin-Conditioning Agents - Humectant	NA
146	sh-Oligopeptide-73 Amide Trifluoroacetate	NA	Antioxidants Skin Protectants Skin-Conditioning Agents - Humectant	NA
147	sh-Pentapeptide-6 Trifluoroacetate	NA	Skin-Conditioning Agents - Miscellaneous	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
148	sh-Tetrapeptide-38 Trifluoroacetate	NA	Skin-Conditioning Agents - Miscellaneous	NA
149	Sodium Formylhippurate Trifluoroacetylisobutyl Dipeptide-42 Amide	144055-55-0	Skin-Conditioning Agents - Miscellaneous	NA
150	Sodium Perfluorohexyl Ethylphosphonate	1189052-95-6	Surface Modifiers	NA
151	Sorbitan Hexa-Guanidinohexanoate Trifluoroacetate	NA	Skin-Conditioning Agents - Miscellaneous	NA
152	Stearyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer	NA	Film Formers Viscosity Increasing Agents - Nonaqueous	NA
153	Tafluprost	209860-87-7	Hair Conditioning Agents	NA
154	TEA-C8-18 Perfluoroalkylethyl Phosphate	NA	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous Surface Modifiers Surfactants - Solubilizing Agents	NA
155	TEA-Perfluorohexyl Ethylphosphates	NA	Surfactants - Emulsifying Agents	NA
156	Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate	934368-60-2	Skin-Conditioning Agents - Miscellaneous	Face and Neck Preparations (Excluding Shaving Preparations) Moisturizing Preparations
157	Tetrafluoropropene	29118-24-9	Propellants	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
158	Trifluoroacetic Acid	76-05-1	pH Adjusters	NA
159	Trifluoroacetyl Tripeptide-2	64577-63-5	Skin Protectants Skin-Conditioning Agents - Miscellaneous	Face and Neck Preparations (Excluding Shaving Preparations)
160	Trifluoroethyl Methacrylate	352-87-4	Artificial Nail Builders	Nail Extenders
161	Trifluoromethyl C1-4 Alkyl Dimethicone	NA	Skin-Conditioning Agents - Occlusive	Face and Neck Preparations (Excluding Shaving Preparations) Moisturizing Preparations Foundations Skin Care Preparations, Misc.
162	Trifluoromethyl Dehydrolatanoprost	NA	Eyelash Conditioning Agents	NA
163	Trifluoromethylbipyridyl Bromobenzimidazole	NA	Skin-Conditioning Agents - Miscellaneous	NA
164	Trifluoromethylphenethyl Mesalazine	NA	Skin Protectants Skin-Conditioning Agents - Miscellaneous	NA
165	Trifluoropropyl Cyclopentasiloxane	NA	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	Makeup Preparations (Not eye), Misc. Moisturizing Preparations
166	Trifluoropropyl Cyclotetrasiloxane	429-67-4	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	Makeup Preparations (Not eye), Misc. Moisturizing Preparations

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
167	Trifluoropropyl Cyclotrisiloxane	2374-14-3	Plasticizers Slip Modifiers Surface Modifiers	NA
168	Trifluoropropyl Dimethicone	115361-68-7	Hair Conditioning Agents Skin-Conditioning Agents - Miscellaneous	NA
169	Trifluoropropyl Dimethicone/PEG-10 Crosspolymer	NA	Skin-Conditioning Agents - Miscellaneous Surfactants - Emulsifying Agents Viscosity Increasing Agents - Nonaqueous	NA
170	Trifluoropropyl Dimethicone/Trifluoropropyl Divinyldimethicone Crosspolymer	NA	Skin-Conditioning Agents - Miscellaneous Viscosity Increasing Agents - Nonaqueous	Makeup Preparations (Not eye), Misc.
171	Trifluoropropyl Dimethicone/Vinyl Trifluoropropyl Dimethicone/Silsesquioxane Crosspolymer	NA	Viscosity Increasing Agents - Nonaqueous	NA
172	Trifluoropropyl Dimethiconol	NA	Anticaking Agents Skin-Conditioning Agents - Miscellaneous	NA
173	Trifluoropropyl Methicone	63148-56-1	Anticaking Agents Skin-Conditioning Agents - Miscellaneous	NA

No.	INCI Names of PFAS	CAS No.	Reported Functions	Reported Product Categories
174	Trifluoropropyldimethyl/trimethylsiloxysilicate	NA	Binders Skin-Conditioning Agents - Emollient	NA
175	Trifluoropropyldimethylsiloxy/Trimethylsiloxy Silsesquioxane	NA	Film Formers	NA
176	Trimethyl Trifluoromethylindolino Piperidinylspironaphthooxazine	172208-34-3	Antioxidants Colorants	NA
177	Vinylidene difluoride	75-38-7	NA	NA

NA = not available.

Supplemental Table 2. Cosmetic Product Categories and Codes

(01) Baby products.
(a) Baby shampoos.
(b) Lotions, oils, powders, and creams.
(c) Baby wipes.
(d) Other baby products.
1. Leave-on.
2. Rinse-off.
(02) Bath preparations.
(a) Bath oils, tablets, and salts.
(b) Bubble baths.
(c) Bath capsules.
(d) Other bath preparations.
(03) Eye makeup preparations (other than children's eye makeup preparations).
(a) Eyebrow pencils.
(b) Eyeliners.
(c) Eye shadows.
(d) Eye lotions.
(e) Eye makeup removers.
(f) False eyelashes.
(g) Mascaras.
(h) Eyelash and eyebrow adhesives, glues, and sealants.
(i) Eyelash and eyebrow preparations (primers, conditioners, serums, fortifiers).
(j) Eyelash cleansers.
(k) Other eye makeup preparations.
(04) Children's eye makeup preparations.
(a) Children's eyeshadows.
(b) Other children's eye makeup.
(05) Fragrance preparations.
(a) Colognes and toilet waters.
(b) Perfumes.
(c) Powders (dusting and talcum) (excluding aftershave talc).

(d) Other fragrance preparations.
(06) Hair preparations (non-coloring).
(a) Hair conditioners.
1. Leave-on.
2. Rinse-off.
(b) Hair sprays (aerosol fixatives).
(c) Hair straighteners.
(d) Permanent waves.
(e) Rinses (non-coloring).
(f) Shampoos (non-coloring).
1. Leave-on.
2. Rinse-off.
(g) Tonics, dressings, and other hair grooming aids.
(h) Wave sets.
(i) Other hair preparations.
1. Leave-on.
2. Rinse-off.
(07) Hair coloring preparations.
(a) Hair dyes and colors (all types requiring caution statement and patch test).
(b) Hair tints.
(c) Hair rinses (coloring).
1. Leave-on.
2. Rinse-off.
(d) Hair shampoos (coloring).
1. Leave-on.
2. Rinse-off.
(e) Hair color sprays (aerosol).
(f) Hair lighteners with color.
(g) Hair bleaches.
(h) Eyelash and eyebrow dyes.
(i) Other hair coloring preparations.
1. Leave-on.

2. Rinse-off.
(08) Makeup preparations (not eye) (other than makeup preparations for children).
(a) Blushers and rouges (all types).
(b) Face powders.
(c) Foundations.
1. Traditional applications.
2. Airbrush applications.
(d) Leg and body paints.
1. Traditional applications.
2. Airbrush applications.
(e) Lipsticks and lip glosses.
(f) Makeup bases.
1. Traditional applications.
2. Airbrush applications.
(g) Makeup fixatives.
(h) Other makeup preparations.
1. Traditional applications.
2. Airbrush applications.
(09) Makeup preparations for children (not eye).
(a) Children’s blushers and rouges (all types).
(b) Children’s face paints.
(c) Children’s face powders.
(d) Children’s foundations.
(e) Children’s lipsticks and lip glosses.
(f) Children’s color hairsprays.
(g) Other children’s makeup.
(10) Manicuring preparations.
(a) Basecoats and undercoats.
(b) Cuticle softeners.
(c) Nail creams and lotions.
(d) Nail extenders.
(e) Nail polishes and enamels.

(f) Nail polish and enamel removers.
(g) Other manicuring preparations.
(11) Oral products.
(a) Dentifrices (aerosols, liquids, pastes, and powders).
(b) Mouthwashes and breath fresheners (liquids and sprays).
(c) Other oral products.
(12) Personal cleanliness.
(a) Bath soaps and body washes.
(b) Deodorants (underarm).
1. Sticks, roll-ons, gels, creams, and wipes.
2. Sprays.
(c) Douches.
(d) Feminine deodorants.
1. Leave-on.
2. Rinse-off.
(e) Disposable wipes.
(f) Other personal cleanliness products.
1. Leave-on.
2. Rinse-off.
(13) Shaving preparations.
(a) Aftershave lotions.
(b) Beard softeners.
(c) Men's talcum.
(d) Pre-shave lotions (all types).
(e) Shaving creams (aerosol, brushless, and lather).
(f) Shaving soaps (cakes, sticks, etc.).
(g) Other shaving preparation products.
(14) Skin care preparations, (creams, lotions, powder, and sprays).
(a) Cleansing (cold creams, cleansing lotions, liquids, and pads).
(b) Depilatories.
(c) Face and neck (excluding shaving preparations).
1. Leave-on.

2. Rinse-off.
(d) Body and hand (excluding shaving preparations).
1. Leave-on.
2. Rinse-off.
(e) Foot powders and sprays.
(f) Moisturizing.
(g) Night.
(h) Paste masks (mud packs).
(i) Skin fresheners.
(j) Other skin care preparations.
1. Leave-on.
2. Rinse-off.
(15) Suntan preparations.
(a) Suntan gels, creams, and liquids.
(b) Indoor tanning preparations.
1. Traditional applications (creams, lotions, etc.).
2. Airbrush applications.
3. Spray applications.
4. Professional airbrush tanning applications.
5. Professional spray tanning applications.
(c) Other suntan preparations.
(16) Tattoo preparations.
(a) Permanent tattoo inks.
(b) Temporary tattoo inks.
(c) Other tattoo preparations.
(17) Other preparations (i.e., those preparations that do not fit another category)

Note: the product categories are also available at FDA webpage: https://www.fda.gov/cosmetics/registration-listing-cosmetic-product-facilities-and-products/cosmetic-product-categories-and-codes.

Supplemental Table 3. Categories of PFAS-Containing Cosmetic Products in FDA's Mandatory Cosmetic Product Listing Data

Product category	Product number	% of Total
(03) Eye makeup preparations (other than children's eye makeup preparations) (03C) Eye shadows	348	20.5
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on	270	15.9
(03) Eye makeup preparations (other than children's eye makeup preparations) (03B) Eyeliners	143	8.4
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08B) Face powders	112	6.6
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08C1) Foundations, traditional applications	76	4.5
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08H1) Other makeup preparations, traditional applications	68	4.0
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08E) Lipsticks and lip glosses	62	3.6
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08A) Blushers and rouges (all types)	59	3.5
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (14F) Moisturizing	59	3.5
(14) Skin care preparations (creams, lotions, powder, and sprays) (14F) Moisturizing	51	3.0
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C2) Face and neck (excluding shaving preparations), rinse-off	40	2.4
(14) Skin care preparations (creams, lotions, powder, and sprays) (14J1) Other skin care preparations, leave-on	38	2.2
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads)	36	2.1
(07) Hair coloring preparations (07A) Hair dyes and colors (all types requiring caution statement and patch test)	29	1.7
(10) Manicuring preparations (10E) Nail polishes and enamels	29	1.7
(14) Skin care preparations (creams, lotions, powder, and sprays) (14H) Paste masks (mud packs)	20	1.2
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C2) Face and neck (excluding shaving preparations), rinse-off	15	0.9

Product category	Product number	% of Total
(17) Other preparations (i.e., those preparations that do not fit another category)	15	0.9
(06) Hair preparations (non-coloring) (06I1) Other hair preparations, leave-on	14	0.8
(14) Skin care preparations (creams, lotions, powder, and sprays) (14J2) Other skin care preparations, rinse-off	14	0.8
(06) Hair preparations (non-coloring) (06G) Tonics, dressings, and other hair grooming aids	11	0.6
(03) Eye makeup preparations (other than children's eye makeup preparations) (03D) Eye lotions	10	0.6
(03) Eye makeup preparations (other than children's eye makeup preparations) (03G) Mascaras	9	0.5
(03) Eye makeup preparations (other than children's eye makeup preparations) (03K) Other eye makeup preparations	9	0.5
(06) Hair preparations (non-coloring) (06B) Hair sprays (aerosol fixatives)	9	0.5
(06) Hair preparations (non-coloring) (06F2) Shampoos (non-coloring), rinse-off	9	0.5
(03) Eye makeup preparations (other than children's eye makeup preparations) (03A) Eyebrow pencils	8	0.5
(14) Skin care preparations (creams, lotions, powder, and sprays) (14D1) Body and hand (excluding shaving preparations), leave-on	8	0.5
(07) Hair coloring preparations (07G) Hair bleaches	7	0.4
(14) Skin care preparations (creams, lotions, powder, and sprays) (14G) Night	7	0.4
(03) Eye makeup preparations (other than children's eye makeup preparations) (03I) Eyelash and eyebrow preparations (primers, conditioners, serums, fortifiers)	6	0.4
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08F1) Makeup bases, traditional applications	6	0.4
(03) Eye makeup preparations (other than children's eye makeup preparations) (03H) Eyelash and eyebrow adhesives, glues, and sealants	5	0.3
(06) Hair preparations (non-coloring) (06E) Rinses (non-coloring)	5	0.3
(06) Hair preparations (non-coloring) (06I2) Other hair preparations, rinse-off	5	0.3
(10) Manicuring preparations (10G) Other manicuring preparations	5	0.3
(12) Personal cleanliness (12F2) Other personal cleanliness products, rinse-off	4	0.2
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C1) Face and neck (excluding shaving preparations), leave-on	4	0.2

Product category	Product number	% of Total
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C1) Face and neck (excluding shaving preparations), leave-on (14D1) Body and hand (excluding shaving preparations), leave-on (14I) Skin fresheners	4	0.2
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (14F) Moisturizing (14G) Night	4	0.2
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (14J1) Other skin care preparations, leave-on	4	0.2
(03) Eye makeup preparations (other than children's eye makeup preparations) (03C) Eye shadows (08) Makeup preparations (not eye) (other than makeup preparations for children) (08B) Face powders	3	0.2
(06) Hair preparations (non-coloring) (06A1) Hair conditioners, leave-on	3	0.2
(06) Hair preparations (non-coloring) (06A2) Hair conditioners, rinse-off	3	0.2
(06) Hair preparations (non-coloring) (06C) Hair straighteners	3	0.2
(06) Hair preparations (non-coloring) (06F1) Shampoos (non-coloring), leave-on	3	0.2
(12) Personal cleanliness (12B2) Deodorants (underarm), sprays	3	0.2
(12) Personal cleanliness (12F1) Other personal cleanliness products, leave-on	3	0.2
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C2) Face and neck (excluding shaving preparations), rinse-off (14F) Moisturizing	3	0.2
(15) Suntan preparations (15A) Suntan gels, creams, and liquids	3	0.2
(15) Suntan preparations (15B1) Indoor tanning preparations	3	0.2
(03) Eye makeup preparations (other than children's eye makeup preparations) (03A) Eyebrow pencils (03K) Other eye makeup preparations	2	0.1
(03) Eye makeup preparations (other than children's eye makeup preparations) (03K) Other eye makeup preparations (08) Makeup preparations (not eye) (other than makeup preparations for children) (08H1) Other makeup preparations, traditional applications	2	0.1
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08A) Blushers and rouges (all types) (08B) Face powders	2	0.1
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08C2) Foundations, airbrush applications	2	0.1
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08G) Makeup fixatives	2	0.1

Product category	Product number	% of Total
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08G) Makeup fixatives (08H1) Other makeup preparations, traditional applications	2	0.1
(10) Manicuring preparations (10A) Basecoats and undercoats	2	0.1
(10) Manicuring preparations (10D) Nail extenders	2	0.1
(12) Personal cleanliness (12A) Bath soaps and body washes (14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C1) Face and neck (excluding shaving preparations), leave-on (14F) Moisturizing (14G) Night (14H) Paste masks (mud packs) (14I) Skin fresheners (14J1) Other skin care preparations, leave-on	2	0.1
(13) Shaving preparations (13A) Aftershave lotions	2	0.1
(13) Shaving preparations (13E) Shaving creams (aerosol, brushless, and lather)	2	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C1) Face and neck (excluding shaving preparations), leave-on (14F) Moisturizing	2	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14J2) Other skin care preparations, rinse-off	2	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (14D1) Body and hand (excluding shaving preparations), leave-on (14F) Moisturizing (14I) Skin fresheners	2	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (14G) Night	2	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14F) Moisturizing (14J1) Other skin care preparations, leave-on	2	0.1
(01) Baby products (01B) Lotions, oils, powders, and creams (14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on	1	0.1
(03) Eye makeup preparations (other than children's eye makeup preparations) (03B) Eyeliners (03K) Other eye makeup preparations	1	0.1
(03) Eye makeup preparations (other than children's eye makeup preparations) (03C) Eye shadows (03K) Other eye makeup preparations (08) Makeup preparations (not eye) (other than makeup preparations for children) (08H1) Other makeup preparations, traditional applications	1	0.1

Product category	Product number	% of Total
(03) Eye makeup preparations (other than children's eye makeup preparations) (03D) Eye lotions (14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on	1	0.1
(03) Eye makeup preparations (other than children's eye makeup preparations) (03D) Eye lotions (14) Skin care preparations (creams, lotions, powder, and sprays) (14J1) Other skin care preparations, leave-on	1	0.1
(03) Eye makeup preparations (other than children's eye makeup preparations) (03H) Eyelash and eyebrow adhesives, glues, and sealants (03K) Other eye makeup preparations	1	0.1
(05) Fragrance preparations (05D) Other fragrance preparations (06) Hair preparations (non-coloring) (06G) Tonics, dressings, and other hair grooming aids (14) Skin care preparations (creams, lotions, powder, and sprays) (14J1) Other skin care preparations, leave-on	1	0.1
(06) Hair preparations (non-coloring) (06A1) Hair conditioners, leave-on (06G) Tonics, dressings, and other hair grooming aids	1	0.1
(06) Hair preparations (non-coloring) (06E) Rinses (non-coloring) (06G) Tonics, dressings, and other hair grooming aids (06I2) Other hair preparations, rinse-off (08) Makeup preparations (not eye) (other than makeup preparations for children) (08E) Lipsticks and lip glosses (12) Personal cleanliness (12C) Douches (14) Skin care preparations (creams, lotions, powder, and sprays) (14F) Moisturizing (14I) Skin fresheners	1	0.1
(06) Hair preparations (non-coloring) (06G) Tonics, dressings, and other hair grooming aids (06I2) Other hair preparations, rinse-off (08) Makeup preparations (not eye) (other than makeup preparations for children) (08C1) Foundations, traditional applications (08E) Lipsticks and lip glosses (10) Manicuring preparations (10C) Nail creams and lotions (10G) Other manicuring preparations (12) Personal cleanliness (12C) Douches (14) Skin care preparations (creams, lotions, powder, and sprays) (14F) Moisturizing (14I) Skin fresheners	1	0.1
(07) Hair coloring preparations (07A) Hair dyes and colors (all types requiring caution statement and patch test) (07F) Hair lighteners with color	1	0.1
(07) Hair coloring preparations (07B) Hair tints	1	0.1
(07) Hair coloring preparations (07B) Hair tints (07I2) Other hair coloring preparations, rinse-off	1	0.1
(07) Hair coloring preparations (07C2) Hair rinses (coloring), rinse-off	1	0.1
(07) Hair coloring preparations (07I1) Other hair coloring preparations, leave-on	1	0.1
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08B) Face powders (08H1) Other makeup preparations, traditional applications	1	0.1

Product category	Product number	% of Total
(08) Makeup preparations (not eye) (other than makeup preparations for children) (08F1) Makeup bases, traditional applications (08F2) Makeup bases, airbrush applications	1	0.1
(10) Manicuring preparations (10A) Basecoats and undercoats (10E) Nail polishes and enamels	1	0.1
(10) Manicuring preparations (10C) Nail creams and lotions	1	0.1
(12) Personal cleanliness (12A) Bath soaps and body washes	1	0.1
(12) Personal cleanliness (12A) Bath soaps and body washes (14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C1) Face and neck (excluding shaving preparations), leave-on (14F) Moisturizing (14G) Night (14J1) Other skin care preparations, leave-on	1	0.1
(12) Personal cleanliness (12A) Bath soaps and body washes (14) Skin care preparations (creams, lotions, powder, and sprays) (14F) Moisturizing (14I) Skin fresheners	1	0.1
(12) Personal cleanliness (12B1) Deodorants (underarm), sticks, roll-ons, gels, creams, and wipes	1	0.1
(12) Personal cleanliness (12F2) Other personal cleanliness products, rinse-off (14) Skin care preparations (creams, lotions, powder, and sprays) (14F) Moisturizing	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14B) Depilatories (14C1) Face and neck (excluding shaving preparations), leave-on (14D1) Body and hand (excluding shaving preparations), leave-on (14I) Skin fresheners	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C1) Face and neck (excluding shaving preparations), leave-on (14F) Moisturizing (14G) Night	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C1) Face and neck (excluding shaving preparations), leave-on (14F) Moisturizing (14G) Night (14I) Skin fresheners	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C1) Face and neck (excluding shaving preparations), leave-on (14G) Night	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14C2) Face and neck (excluding shaving preparations), rinse-off (14J2) Other skin care preparations, rinse-off	1	0.1

Product category	Product number	% of Total
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14F) Moisturizing	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14F) Moisturizing (14J2) Other skin care preparations, rinse-off	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14A) Cleansing (cold creams, cleansing lotions, liquids, and pads) (14J1) Other skin care preparations, leave-on	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (14D1) Body and hand (excluding shaving preparations), leave-on (14F) Moisturizing	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (14F) Moisturizing (14G) Night (14J1) Other skin care preparations, leave-on	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (14F) Moisturizing (14J1) Other skin care preparations, leave-on	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (14H) Paste masks (mud packs)	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C1) Face and neck (excluding shaving preparations), leave-on (17) Other preparations (i.e., those preparations that do not fit another category)	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14C2) Face and neck (excluding shaving preparations), rinse-off (14F) Moisturizing (14H) Paste masks (mud packs) (14J2) Other skin care preparations, rinse-off	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14D1) Body and hand (excluding shaving preparations), leave-on (14F) Moisturizing	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14D2) Body and hand (excluding shaving preparations), rinse-off	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14H) Paste masks (mud packs) (14J1) Other skin care preparations, leave-on	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14H) Paste masks (mud packs) (14J2) Other skin care preparations, rinse-off	1	0.1
(14) Skin care preparations (creams, lotions, powder, and sprays) (14I) Skin fresheners	1	0.1
(15) Suntan preparations (15C) Other suntan preparations	1	0.1

Product category	Product number	% of Total
(14) Skin care preparations (creams, lotions, powder, and sprays) (14D2) Body and hand (excluding shaving preparations), rinse-off (14F) Moisturizing	1	0.1
Grand Total	**1744**	**100.0**

Supplemental Table 4. Market Trend of Top Used PFAS in Cosmetic Products in the U.S. Market

CAS No.	INCI Names of PFAS	FDA's mandatory cosmetic product listing data	VCRP	VCRP	VCRP	Mintel's GNPD* US_5 year	Mintel's GNPD US_1 year
		As of 8/30/2024	8/22/2019	8/18/2021	3/27/2023	7/27/2024	7/27/2024
9002-84-0	PTFE	490	249	102	79	222	4
259725-95-6	Perfluorononyl Dimethicone	232	65	33	29	61	6
64577-63-5	Trifluoroacetyl Tripeptide-2	164	NA	NA	21	66	14
934368-60-2	Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate	156	NA	NA	39	69	11
163702-07-6	Methyl Perfluorobutyl Ether	114	13	17	23	28	5
163702-08-7	Methyl Perfluoroisobutyl Ether	108	11	16	22	20	4
306-94-5	Perfluorodecalin	71	36	35	28	29	6
51851-37-7	Perfluorohexylethyl Triethoxysilane	124	19	105	172	33	1
69991-67-9	Polyperfluoromethylisopropyl Ether	54	79	NA	12	11	3
10442-83-8	HC Yellow No. 13	40	NA	NA	6	0	0
355-42-0	Perfluorohexane	40	18	23	18	21	3
NA	Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer	35	NA	NA	NA	0	0
NA	Pentapeptide-34 Trifluoroacetate	33	NA	NA	NA	9	4
NA	Trifluoropropyldimethyl/trimethylsiloxysilicate	28	NA	NA	4	6	0
NA	Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate	27	29	2	1	9	0
306-91-2	Perfluoroperhydrophenanthrene	25	20	13	7	10	3

CAS No.	INCI Names of PFAS	FDA's mandatory cosmetic product listing data	VCRP	VCRP	VCRP	Mintel's GNPD* US_5 year	Mintel's GNPD US_1 year
		As of 8/30/2024	8/22/2019	8/18/2021	3/27/2023	7/27/2024	7/27/2024
NA	Dimethiconol Fluoroalcohol Dilinoleic Acid	24	NA	NA	NA	0	0
29118-24-9	Tetrafluoropropene	23	NA	NA	1	21	4
163702-05-4	Ethyl Perfluorobutyl Ether	22	4	5	5	2	0
NA	Trifluoromethyl C1-4 Alkyl Dimethicone	21	NA	NA	2	0	0
NA	Perfluorononylethyl Stearyl Dimethicone	18	NA	NA	NA	0	0
379685-96-8	Acetyl Trifluoromethylphenyl Valylglycine	17	NA	NA	NA	9	0
26637-68-3 335-27-3	Perfluorodimethylcyclohexane	17	7	9	5	4	3
NA	Trifluoropropyl Cyclopentasiloxane	11	NA	NA	31	7	0
1805-22-7	Perfluoromethylcyclopentane	10	1	3	3	10	3

* Mintel's GNPD tracks new product launches, so the data presented in the table reflect new cosmetic products introduced during the timeframe, not the total products available on the market in the U.S.

NA: not available.

Supplemental Table 5. Template for Searching Existing Assessments

Data Source
Tier 1
US FDA Data (use as food, drug, cosmetic, or color additive)
Scientific Committee on Consumer Safety (SCCS) Opinion
Cosmetic Ingredient Review (CIR) Assessment
Research Institute of Fragrance Materials (RIFM) Assessment
Tier 2
Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile
US EPA Reviews
National Toxicology Program (NTP)
Consumer Product Safety Commission (CPSC)
Health Canada
Joint FAO/WHO Expert Committee on Food Additives (JECFA)
World Health Organization (WHO)/International Programme on Chemical Safety (IPCS)
European Food Safety Authority (EFSA) Opinion
German Federal Institute for Risk Assessment (BfR)
International Agency for Research on Cancer (IARC)
European Chemicals Agency Committee for Risk Assessment (ECHA RAC)
Other sources as needed
(e.g., regulatory status details)

Supplemental Table 6. Search Syntax for PTFE Using PubMed and Web of Science

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
Toxicity in general	(("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) NOT ("graft*"[tw] OR "reconstruction"[tw] OR "stent*"[tw] OR “filter*”[tw] OR “membrane*”[tw] OR “ePTFE”[tw] OR “mesh”[tw] OR “tube*”[tw] OR “ring*”[tw] OR “catheter*”[tw] OR “contact*”[tw])) AND (“toxicity”[tw] OR "toxicological effect*"[tw] OR “adverse effect*”[tw] OR "acute exposure"[tw] OR LD50[tw])	TS=(("polytetrafluoroethylene" OR "PTFE" OR "Teflon") NOT ("graft*" OR "reconstruction" OR "stent*" OR “filter*” OR “membrane*” OR “ePTFE” OR “mesh” OR “tube*” OR “ring*” OR “catheter*” OR “contact*”)) AND TS=(“toxicity” OR "toxicological effect*" OR “adverse effect*” OR "acute exposure" OR LD50)
ADME	(("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) NOT ("graft*"[tw] OR "reconstruction"[tw] OR "stent*"[tw] OR “filter*”[tw] OR “membrane*”[tw] OR “ePTFE”[tw] OR “mesh”[tw] OR “tube*”[tw] OR “ring*”[tw] OR “catheter*”[tw] OR “contact*”[tw])) AND ("ADME"[tw] OR "absorption"[tw] OR "distribution"[tw] OR "metabolism"[tw] OR "excretion"[tw] OR "elimination"[tw] OR "toxicokinetic*"[tw] OR "pharmacokinetic*"[tw] OR "bioavailability"[tw])	TS=(("polytetrafluoroethylene" OR "PTFE" OR "Teflon") NOT ("graft*" OR "reconstruction" OR "stent*" OR “filter*” OR “membrane*” OR “ePTFE” OR “mesh” OR “tube*” OR “ring*” OR “catheter*” OR “contact*”)) AND TS=("ADME" OR "absorption" OR "distribution" OR "metabolism" OR "excretion" OR "elimination" OR "toxicokinetic*" OR "pharmacokinetic*" OR "bioavailability")
Genotoxicity	("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) AND ("genotox*"[tw] OR "DNA damage"[tw] OR "DNA adduct*"[tw] OR "DNA fragmentation"[tw] OR "mutagen*"[tw])	TS= ("polytetrafluoroethylene" OR "PTFE" OR "Teflon") AND TS=("genotox*" OR "DNA damage" OR "DNA adduct*" OR "DNA fragmentation" OR "mutagen*")
Carcinogenicity	(("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) NOT ("graft*"[tw] OR "reconstruction"[tw] OR "stent*"[tw] OR “filter*”[tw] OR “membrane*”[tw] OR “ePTFE”[tw] OR “mesh”[tw] OR “tube*”[tw] OR “ring*”[tw] OR “catheter*”[tw] OR “contact*”[tw])) AND	TS=(("polytetrafluoroethylene" OR "PTFE" OR "Teflon") NOT ("graft*" OR "reconstruction" OR "stent*" OR “filter*” OR “membrane*” OR “ePTFE” OR “mesh” OR “tube*” OR “ring*” OR “catheter*” OR “contact*”)) AND

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
	("carcinogen*"[tw] OR "cancer*"[tw] OR "tumor*" [tw] OR "neoplas*"[tw])	TS=("carcinogen*" OR "cancer*" OR "tumor*" OR "neoplas*")
DART	("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) AND ((("toxicity"[tw] OR "hazard"[tw]) AND ("DART"[tw] OR "developmental"[tw] OR "reproductive"[tw] OR "matern*"[tw] OR "pregnan*"[tw] OR "prenatal"[tw] OR "antenatal"[tw] OR "perinatal"[tw] OR "postnatal"[tw] OR "postpartum"[tw] OR "offspring*"[tw] OR "infant*"[tw] OR "newborn"[tw] OR "neonat*"[tw] OR "fetal"[tw] OR "fetus"[tw] OR "feotal"[tw] OR "feotus"[tw] OR "testes"[tw] OR "testicular"[tw] OR "ovar*"[tw] OR "uter*"[tw])) OR "reprotoxicity"[tw] OR "*fertility"[tw] OR "teratogenicity"[tw] OR "embryotoxicity"[tw] OR "birth defects"[tw])	TS= ("polytetrafluoroethylene" OR "PTFE" OR "Teflon") AND TS=((("toxicity" OR "hazard") AND ("DART" OR "developmental" OR "reproductive" OR "matern*" OR "pregnan*" OR "prenatal" OR "antenatal" OR "perinatal" OR "postnatal" OR "postpartum" OR "offspring*" OR "infant*" OR "newborn*" OR "neonat*" OR "fetal" OR "fetus" OR "foetal" OR "foetus" OR "testes" OR "testicular" OR "ovar*" OR "uter*")) OR "reprotoxicity" OR "teratogenicity" OR "embryotoxicity" OR "birth defects")
Skin Sensitization	("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) AND ("allerg*"[tw] OR "sensitiz*"[tw] OR "sensitis*"[tw] OR "allergic contact dermatitis"[tw] OR “hypersensitivity” [tw] OR "HRIPT"[tw] OR "human maximization test*"[tw] OR "patch test*"[tw] OR "LLNA"[tw] OR "local lymph node assay"[tw])	TS= ("polytetrafluoroethylene" OR "PTFE" OR "Teflon") AND TS=("allerg*" OR "sensitiz*" OR "sensitis*" OR "allergic contact dermatitis" OR “hypersensitivity” OR "HRIPT" OR "human maximization test*" OR "patch test*" OR "LLNA" OR "local lymph node assay")
Skin Irritation	("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) AND (("irrita*"[tw] AND ("skin"[tw] OR "dermal" [tw])) OR "erythema"[tw] OR "dermatitis"[tw] OR “Pruritus”[tw])	TS= ("polytetrafluoroethylene" OR "PTFE" OR "Teflon") AND TS=("skin irrita*" OR "dermal irrita*" OR "erythema" OR "dermatitis" OR “pruritus”)
Eye Irritation	("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) AND (("eye"[tw] OR "ocular"[tw]) AND ("irrita*"[tw] OR “discomfort”[tw] OR “redness”[tw] OR burning [tw] OR	TS= ("polytetrafluoroethylene" OR "PTFE" OR "Teflon") AND TS=((“eye" OR "ocular") AND ("corrosion" OR “discomfort” OR “redness” OR

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
	stinging [tw] OR "corrosion") OR "conjunctivitis"[tw])	“burning” OR “stinging”) OR "conjunctivitis")
Respiratory Irritation	("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) AND (("irrita*"[tw] AND ("inhalation"[tw] OR "upper airway"[tw] OR "upper respiratory"[tw] OR “respiratory tract”[tw] OR "lung"[tw] OR "lungs"[tw] OR "nose"[tw] OR "nasal"[tw] OR “tracke*”[tw] OR "nasopharyngeal"[tw])) OR "asthma"[tw])	TS= ("polytetrafluoroethylene" OR "PTFE" OR "Teflon") AND TS=("irrita*" AND ("inhalation" OR "upper airway" OR "upper respiratory" OR “respiratory tract” OR "lung" OR "lungs" OR "nose" OR "nasal" OR “tracke*” OR "nasopharyngeal") OR ("asthma"))
Photo-induced Toxicity	("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) AND ("phototoxicity"[tw] OR "photo-toxicity"[tw] OR "photosensitiz*"[tw] OR "photo-sensitiz*"[tw] OR "photosensitis*"[tw] OR "photo-sensitis*"[tw] OR "photoirrita*"[tw] OR "photo-irrita*"[tw] OR "photogenotoxicity"[tw] OR "photo-genotoxicity"[tw])	TS= ("polytetrafluoroethylene" OR "PTFE" OR "Teflon") AND TS=("phototoxicity" OR "photo-toxicity" OR "photosensitiz*" OR "photo-sensitiz*" OR "photosensitis*" OR "photo-sensitis*" OR "photoirrita*" OR "photo-irrita*" OR "photogenotoxicity" OR "photo-genotoxicity")
Other endpoints		
Neurotoxicity	("polytetrafluoroethylene"[tw] OR "PTFE"[tw] OR "Teflon"[tw]) AND ("neurotox*"[tw] OR "neural"[tw] OR "neuron*"[tw] OR "nervous system"[tw] OR "neurologic*"[tw] OR "neurodegenerati*"[tw] OR "cogniti*"[tw] OR "learning impairment"[tw] OR "Parkinson's"[tw] OR "Alzheimer's"[tw] OR "dementia"[tw])	TS=(("polytetrafluoroethylene" OR "PTFE" OR "Teflon") NOT ("graft*" OR "reconstruction" OR "stent*" OR “filter*” OR “membrane*” OR “ePTFE” OR “mesh” OR “tube*” OR “ring*” OR “catheter*” OR “contact*”)) AND TS=("neurotox*" OR "neural" OR "neuron*" OR "nervous system" OR "neurologic*" OR "neurodegenerat*" OR "cogniti*" OR "learning impairment" OR "Parkinson's" OR "Alzheimer's" OR "dementia")

Supplemental Table 7. Search Syntax for Perfluorodecalin using PubMed and Web of Science

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
Toxicity in general	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND (“toxicity”[tw] OR "toxicological effect*"[tw] OR “adverse effect*”[tw] OR "acute exposure"[tw] OR “LD50”[tw])	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR "Perfluorodecahydronaphthalene") AND TS=(“toxicity” OR "toxicological effect*" OR “adverse effect*” OR "acute exposure" OR “LD50”)
ADME	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND ("ADME"[tw] OR "absorption"[tw] OR "distribution"[tw] OR "metabolism"[tw] OR "excretion"[tw] OR "elimination"[tw] OR "toxicokinetic*"[tw] OR "pharmacokinetic*"[tw] OR "bioavailability"[tw])	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR "Perfluorodecahydronaphthalene") AND TS=("ADME" OR "absorption" OR "distribution" OR "metabolism" OR "excretion" OR "elimination" OR "toxicokinetic*" OR "pharmacokinetic*" OR "bioavailability")
Genotoxicity	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND ("genotox*"[tw] OR "DNA damage"[tw] OR "DNA adduct*"[tw] OR "DNA fragmentation"[tw] OR "mutagen*"[tw])	TS= ("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR "Perfluorodecahydronaphthalene") AND TS=("genotox*" OR "DNA damage" OR "DNA adduct*" OR "DNA fragmentation" OR "mutagen*")
Carcinogenicity	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND ("carcinogen*"[tw] OR "cancer*"[tw] OR "tumor*" [tw] OR "neoplas*"[tw])	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR "Perfluorodecahydronaphthalene") AND TS=("carcinogen*" OR "cancer*" OR "tumor*" OR "neoplas*")
DART	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND ((("toxicity"[tw] OR "hazard"[tw]) AND ("DART"[tw] OR "developmental"[tw] OR "reproductive"[tw] OR "matern*"[tw] OR "pregnan*"[tw] OR "prenatal"[tw]	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR "Perfluorodecahydronaphthalene") AND TS=((("toxicity" OR "hazard") AND ("DART" OR "developmental" OR "reproductive" OR "matern*" OR "pregnan*" OR "prenatal" OR "antenatal" OR "perinatal" OR

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
	OR "antenatal"[tw] OR "perinatal"[tw] OR "postnatal"[tw] OR "postpartum"[tw] OR "offspring*"[tw] OR "infant*"[tw] OR "newborn"[tw] OR "neonat*"[tw] OR "fetal"[tw] OR "fetus"[tw] OR "feotal"[tw] OR "feotus"[tw] OR "testes"[tw] OR "testicular"[tw] OR "ovar*"[tw] OR "uter*"[tw])) OR "reprotoxicity"[tw] OR "*fertility"[tw] OR "teratogenicity"[tw] OR "embryotoxicity"[tw] OR "birth defects"[tw])	"postnatal" OR "postpartum" OR "offspring*" OR "infant*" OR "newborn*" OR "neonat*" OR "fetal" OR "fetus" OR "foetal" OR "foetus" OR "testes" OR "testicular" OR "ovar*" OR "uter*")) OR "reprotoxicity" OR "teratogenicity" OR "embryotoxicity" OR "birth defects")
Skin Sensitization	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND ("allerg*"[tw] OR "sensitiz*"[tw] OR "sensitis*"[tw] OR "allergic contact dermatitis"[tw] OR “hypersensitivity” [tw] OR "HRIPT"[tw] OR "human maximization test*"[tw] OR "patch test*"[tw] OR "LLNA"[tw] OR "local lymph node assay"[tw])	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR " Perfluorodecahydronaphthalene") AND TS=("allerg*" OR "sensitiz*" OR "sensitis*" OR "allergic contact dermatitis" OR “hypersensitivity” OR "HRIPT" OR "human maximization test*" OR "patch test*" OR "LLNA" OR "local lymph node assay")
Skin Irritation	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND (("irrita*"[tw] AND ("skin"[tw] OR "dermal" [tw])) OR "erythema"[tw] OR "dermatitis"[tw] OR “Pruritus”[tw])	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR " Perfluorodecahydronaphthalene") AND TS=("skin irrita*" OR "dermal irrita*" OR "erythema" OR "dermatitis" OR “pruritus”)
Eye Irritation	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND (("eye"[tw] OR "ocular"[tw]) AND ("irrita*"[tw] OR “discomfort”[tw] OR “redness”[tw] OR burning [tw] OR stinging [tw] OR "corrosion") OR "conjunctivitis"[tw])	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR " Perfluorodecahydronaphthalene") AND TS=((“eye" OR "ocular") AND ("corrosion" OR “discomfort” OR “redness” OR “burning” OR “stinging”) OR "conjunctivitis")
Respiratory Irritation	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw])	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR " Perfluorodecahydronaphthalene") AND

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
	AND (("irrita*"[tw] AND ("inhalation"[tw] OR "upper airway"[tw] OR "upper respiratory"[tw] OR “respiratory tract”[tw] OR "lung"[tw] OR "lungs"[tw] OR "nose"[tw] OR "nasal"[tw] OR “tracke*”[tw] OR "nasopharyngeal"[tw])) OR "asthma"[tw])	TS=("irrita*" AND ("inhalation" OR "upper airway" OR "upper respiratory" OR “respiratory tract” OR "lung" OR "lungs" OR "nose" OR "nasal" OR “tracke*” OR "nasopharyngeal") OR ("asthma"))
Photo-induced Toxicity	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND ("phototoxicity"[tw] OR "photo-toxicity"[tw] OR "photosensitiz*"[tw] OR "photo-sensitiz*"[tw] OR "photosensitis*"[tw] OR "photo-sensitis*"[tw] OR "photoirrita*"[tw] OR "photo-irrita*"[tw] OR "photogenotoxicity"[tw] OR "photo-genotoxicity"[tw])	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR " Perfluorodecahydronaphthalene") AND TS=("phototoxicity" OR "photo-toxicity" OR "photosensitiz*" OR "photo-sensitiz*" OR "photosensitis*" OR "photo-sensitis*" OR "photoirrita*" OR "photo-irrita*" OR "photogenotoxicity" OR "photo-genotoxicity")
Other endpoints		
Neurotoxicity	("Perfluorodecalin"[tw] OR "306-94-5"[rn] OR "Perflunafene"[tw] OR "Perfluorodecahydronaphthalene"[tw]) AND ("neurotox*"[tw] OR "neural"[tw] OR "neuron*"[tw] OR "nervous system"[tw] OR "neurologic*"[tw] OR "neurodegenerati*"[tw] OR "cogniti*"[tw] OR "learning impairment"[tw] OR "Parkinson's"[tw] OR "Alzheimer's"[tw] OR "dementia"[tw])	TS=("Perfluorodecalin" OR "306-94-5" OR "Perflunafene" OR " Perfluorodecahydronaphthalene") AND TS=("neurotox*" OR "neural" OR "neuron*" OR "nervous system" OR "neurologic*" OR "neurodegenerat*" OR "cogniti*" OR "learning impairment" OR "Parkinson's" OR "Alzheimer's" OR "dementia")

Supplemental Table 8. Search Syntax for Perfluorohexane Using PubMed and Web of Science

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
Toxicity in general	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND (“toxicity”[tw] OR "toxicological effect*"[tw] OR “adverse effect*”[tw] OR "acute exposure"[tw] OR “LD50”[tw])	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=(“toxicity” OR "toxicological effect*" OR “adverse effect*” OR "acute exposure" OR “LD50”)
ADME	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND ("ADME"[tw] OR "absorption"[tw] OR "distribution"[tw] OR "metabolism"[tw] OR "excretion"[tw] OR "elimination"[tw] OR "toxicokinetic*"[tw] OR "pharmacokinetic*"[tw] OR "bioavailability"[tw])	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=("ADME" OR "absorption" OR "distribution" OR "metabolism" OR "excretion" OR "elimination" OR "toxicokinetic*" OR "pharmacokinetic*" OR "bioavailability")
Genotoxicity	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND ("genotox*"[tw] OR "DNA damage"[tw] OR "DNA adduct*"[tw] OR "DNA fragmentation"[tw] OR "mutagen*"[tw])	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=("genotox*" OR "DNA damage" OR "DNA adduct*" OR "DNA fragmentation" OR "mutagen*")
Carcinogenicity	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND ("carcinogen*"[tw]	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=("carcinogen*" OR "cancer*" OR "tumor*" OR "neoplas*")

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
	OR "cancer*"[tw] OR "tumor*" [tw] OR "neoplas*"[tw])	
DART	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND ((("toxicity"[tw] OR "hazard"[tw]) AND ("DART"[tw] OR "developmental"[tw] OR "reproductive"[tw] OR "matern*"[tw] OR "pregnan*"[tw] OR "prenatal"[tw] OR "antenatal"[tw] OR "perinatal"[tw] OR "postnatal"[tw] OR "postpartum"[tw] OR "offspring*"[tw] OR "infant*"[tw] OR "newborn"[tw] OR "neonat*"[tw] OR "fetal"[tw] OR "fetus"[tw] OR "feotal"[tw] OR "feotus"[tw] OR "testes"[tw] OR "testicular"[tw] OR "ovar*"[tw] OR "uter*"[tw])) OR "reprotoxicity"[tw] OR "*fertility"[tw] OR "teratogenicity"[tw] OR "embryotoxicity"[tw] OR "birth defects"[tw])	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=((("toxicity" OR "hazard") AND ("DART" OR "developmental" OR "reproductive" OR "matern*" OR "pregnan*" OR "prenatal" OR "antenatal" OR "perinatal" OR "postnatal" OR "postpartum" OR "offspring*" OR "infant*" OR "newborn*" OR "neonat*" OR "fetal" OR "fetus" OR "foetal" OR "foetus" OR "testes" OR "testicular" OR "ovar*" OR "uter*")) OR "reprotoxicity" OR "teratogenicity" OR "embryotoxicity" OR "birth defects")
Skin Sensitization	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND ("allerg*"[tw] OR "sensitiz*"[tw] OR "sensitis*"[tw] OR "allergic contact dermatitis"[tw] OR “hypersensitivity” [tw] OR "HRIPT"[tw] OR "human maximization test*"[tw] OR "patch test*"[tw] OR "LLNA"[tw] OR "local lymph node assay"[tw])	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=("allerg*" OR "sensitiz*" OR "sensitis*" OR "allergic contact dermatitis" OR “hypersensitivity” OR "HRIPT" OR "human maximization test*" OR "patch test*" OR "LLNA" OR "local lymph node assay")
Skin Irritation	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
	“Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND (("irrita*"[tw] AND ("skin"[tw] OR "dermal" [tw])) OR "erythema"[tw] OR "dermatitis"[tw] OR “Pruritus”[tw])	“Perfluorohexanesulfon*” OR "PFHxS")) AND TS=("skin irrita*" OR "dermal irrita*" OR "erythema" OR "dermatitis" OR “pruritus”)
Eye Irritation	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND (("eye"[tw] OR "ocular"[tw]) AND ("irrita*"[tw] OR “discomfort”[tw] OR “redness”[tw] OR burning [tw] OR stinging [tw] OR "corrosion") OR "conjunctivitis"[tw])	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=((“eye" OR "ocular") AND ("corrosion" OR “discomfort” OR “redness” OR “burning” OR “stinging”) OR "conjunctivitis")
Respiratory Irritation	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND (("irrita*"[tw] AND ("inhalation"[tw] OR "upper airway"[tw] OR "upper respiratory"[tw] OR “respiratory tract”[tw] OR "lung"[tw] OR "lungs"[tw] OR "nose"[tw] OR "nasal"[tw] OR “tracke*”[tw] OR "nasopharyngeal"[tw])) OR "asthma"[tw])	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=("irrita*" AND ("inhalation" OR "upper airway" OR "upper respiratory" OR “respiratory tract” OR "lung" OR "lungs" OR "nose" OR "nasal" OR “tracke*” OR "nasopharyngeal") OR ("asthma"))
Photo-induced Toxicity	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND ("phototoxicity"[tw] OR "photo-toxicity"[tw] OR "photosensitiz*"[tw] OR "photo-sensitiz*"[tw] OR "photosensitis*"[tw] OR "photo-sensitis*"[tw] OR "photoirrita*"[tw] OR "photo-	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=("phototoxicity" OR "photo-toxicity" OR "photosensitiz*" OR "photo-sensitiz*" OR "photosensitis*" OR "photo-sensitis*" OR "photoirrita*" OR "photo-irrita*" OR "photogenotoxicity" OR "photo-genotoxicity")

Endpoints	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
	irrita*"[tw] OR "photogenotoxicity"[tw] OR "photo-genotoxicity"[tw])	
Other endpoints		
Neurotoxicity	(("Perfluorohexane"[tw] OR "355-42-0"[rn] OR "Perflexane"[tw] OR "Tetradecafluorohexane"[tw]) NOT (“Perfluorohexane sulfon*”[tw] OR “Perfluorohexanesulfon*”[tw] OR "PFHxS"[tw])) AND ("neurotox*"[tw] OR "neural"[tw] OR "neuron*"[tw] OR "nervous system"[tw] OR "neurologic*"[tw] OR "neurodegenerati*"[tw] OR "cogniti*"[tw] OR "learning impairment"[tw] OR "Parkinson's"[tw] OR "Alzheimer's"[tw] OR "dementia"[tw])	TS=(("Perfluorohexane" OR "355-42-0" OR "Perflexane" OR "Tetradecafluorohexane") NOT (“Perfluorohexane sulfon*” OR “Perfluorohexanesulfon*” OR "PFHxS")) AND TS=("neurotox*" OR "neural" OR "neuron*" OR "nervous system" OR "neurologic*" OR "neurodegenerat*" OR "cogniti*" OR "learning impairment" OR "Parkinson's" OR "Alzheimer's" OR "dementia")

Supplemental Table 9. Search Syntax for Other PFAS Using PubMed and Web of Science

PFAS	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
Perfluorononyl Dimethicone	"Perfluorononyl Dimethicone"[tw] OR "259725-95-6"[tw] OR "siloxanes and silicones, di-Me, Me 3,3,4,4,5,5,6,6,6-nonafluorohexyl"[tw]	TS=("Perfluorononyl Dimethicone" OR "259725-95-6" OR "siloxanes and silicones, di-Me, Me 3,3,4,4,5,5,6,6,6-nonafluorohexyl")
Trifluoroacetyl Tripeptide-2	"Trifluoroacetyl Tripeptide-2"[tw] OR "64577-63-5"[tw]	TS=("Trifluoroacetyl Tripeptide-2" OR "64577-63-5")
Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate	"Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate"[tw] OR "934368-60-2"[tw]	TS=("Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate" OR "934368-60-2")
Perfluorohexylethyl Triethoxysilane	"Perfluorohexylethyl Triethoxysilane"[tw] OR "perfluorooctyl triethoxysilane"[tw] OR "51851-37-7"[tw]	TS=("Perfluorohexylethyl Triethoxysilane" OR "perfluorooctyl triethoxysilane" OR "51851-37-7")
Methyl Perfluorobutyl Ether	"Methyl Perfluorobutyl Ether"[tw] OR "163702-07-6" [tw] OR "Methyl Nonafluorobutyl Ether"[tw]	TS=("Methyl Perfluorobutyl Ether" OR "163702-07-6" OR "Methyl Nonafluorobutyl Ether")
Methyl Perfluoroisobutyl Ether	"Methyl Perfluoroisobutyl Ether"[tw] OR "163702-08-7"[tw] OR "Methyl Nonafluoroisobutyl Ether"[tw]	TS=("Methyl Perfluoroisobutyl Ether" OR "163702-08-7" OR "Methyl Nonafluoroisobutyl Ether")
Polyperfluoromethylisopropyl Ether	"Polyperfluoromethylisopropyl Ether"[tw] OR "69991-67-9"[tw] OR “Fomblin HC”[tw]	TS=("Polyperfluoromethylisopropyl Ether" OR "69991-67-9" OR "Fomblin HC")
HC Yellow No. 13	"HC Yellow No. 13"[tw] OR "10442-83-8"[tw] OR "2-(2-Nitro-4-trifluoromethylphenylamino)ethanol"[tw]	TS=("HC Yellow No. 13" OR "10442-83-8" OR "2-(2-Nitro-4-trifluoromethylphenylamino)ethanol")
Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer	"Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer"[tw]	TS=("Diethylaminoethyl Methacrylate/HEMA/Perfluorohexylethyl Methacrylate Crosspolymer")
Pentapeptide-34 Trifluoroacetate	"Pentapeptide-34 Trifluoroacetate"[tw]	TS=("Pentapeptide-34 Trifluoroacetate")

PFAS	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
Trifluoropropyldimethyl/trimethylsiloxysilicate	"Trifluoropropyldimethyl/trimethylsiloxysilicate"[tw]	TS=("Trifluoropropyldimethyl/trimethylsiloxysilicate")
Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate	"Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate"[tw] OR "200013-65-6"[tw]	TS=("Polyperfluoroethoxymethoxy Difluoroethyl PEG Phosphate" OR "200013-65-6")
Perfluoroperhydrophenanthrene	"Perfluoroperhydrophenanthrene"[tw] OR "306-91-2"[tw] OR "Perfluorophenanthrene"[tw] OR "tetracosafluorophenanthrene"[tw] OR "perfluorotetradecahydrophenanthrene"[tw] OR "tetracosafluorotetradecahydrophenanthrene"[tw]	TS=("Perfluoroperhydrophenanthrene" OR "306-91-2" OR "Perfluorophenanthrene" OR "tetracosafluorophenanthrene" OR "perfluorotetradecahydrophenanthrene" OR "tetracosafluorotetradecahydrophenanthrene")
Dimethiconol Fluoroalcohol Dilinoleic Acid	"Dimethiconol Fluoroalcohol Dilinoleic Acid"[tw] OR "Silwax F"[tw]	TS=("Dimethiconol Fluoroalcohol Dilinoleic Acid" OR "Silwax F")
Tetrafluoropropene	"Tetrafluoropropene"[tw] OR "29118-24-9"[tw] OR "(1E)-1,3,3,3-tetrafluoroprop-1-ene"[tw]	TS=("Tetrafluoropropene" OR "29118-24-9" OR "(1E)-1,3,3,3-tetrafluoroprop-1-ene")
Ethyl Perfluorobutyl Ether	"Ethyl Perfluorobutyl Ether"[tw] OR "163702-05-4"[tw] OR "Ethyl Nonafluorobutyl Ether"[tw] OR "1-ethoxy-1,1,2,2,3,3,4,4,4-nonafluorobutane"[tw]	TS=("Ethyl Perfluorobutyl Ether" OR "163702-05-4" OR "Ethyl Nonafluorobutyl Ether" OR "1-ethoxy-1,1,2,2,3,3,4,4,4-nonafluorobutane")
Trifluoromethyl C1-4 Alkyl Dimethicone	"Trifluoromethyl C1-4 Alkyl Dimethicone"[tw]	TS=("Trifluoromethyl C1-4 Alkyl Dimethicone")
Perfluorononylethyl Stearyl Dimethicone	"Perfluorononylethyl Stearyl Dimethicone"[tw] OR "882878-48-0"[tw]	TS=("Perfluorononylethyl Stearyl Dimethicone" OR "882878-48-0")
Acetyl Trifluoromethylphenyl Valylglycine	"Acetyl Trifluoromethylphenyl Valylglycine"[tw] OR "379685-96-8"[tw] OR "2-[[2-[N-acetyl-3-(trifluoromethyl)anilino]-3-methylbutanoyl]amino]acetic acid"[tw]	TS=("Acetyl Trifluoromethylphenyl Valylglycine" OR "379685-96-8" OR "2-[[2-[N-acetyl-3-(trifluoromethyl)anilino]-3-methylbutanoyl]amino]acetic acid")

PFAS	PubMed: https://www.PubMed.gov	Web of Science: https://www.webofscience.com/wos/woscc/advanced-search
Perfluorodimethylcyclohexane	"Perfluorodimethylcyclohexane"[tw] OR "26637-68-3"[tw] OR "335-27-3"[tw] OR "Perfluoro-1,3-dimethylcyclohexane"[tw] OR "1,1,2,2,3,3,4,5,5,6-decafluoro-4,6-bis(trifluoromethyl)cyclohexane"[tw]	TS=("Perfluorodimethylcyclohexane" OR "26637-68-3" OR "335-27-3" OR "Perfluoro-1,3-dimethylcyclohexane" OR "1,1,2,2,3,3,4,5,5,6-decafluoro-4,6-bis(trifluoromethyl)cyclohexane")
Trifluoropropyl Cyclopentasiloxane	"Trifluoropropyl Cyclopentasiloxane"[tw]	TS=("Trifluoropropyl Cyclopentasiloxane")
Perfluoromethylcyclopentane	"Perfluoromethylcyclopentane"[tw] OR "1805-22-7"[tw] OR "Nonafluoro(trifluoromethyl)cyclopentane"[tw] OR "1,1,2,2,3,3,4,4,5-nonafluoro-5-(trifluoromethyl)cyclopentane"[tw]	TS=("Perfluoromethylcyclopentane" OR "1805-22-7" OR "Nonafluoro(trifluoromethyl)cyclopentane" OR "1,1,2,2,3,3,4,4,5-nonafluoro-5-(trifluoromethyl)cyclopentane")