The Fate and Toxicity of Fluorinated Substances used in Contact Lenses

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Report prepared on behalf of EUROMCONTACT

Summary

Fluorinated monomers are used in the preparation of rigid gas permeable (RGP) contact lens polymers due to the unique combination of beneficial properties that they confer, including oxygen permeability, deposit resistance, hardness and chemical inertness.

A recently proposed restriction on fluorine containing 'PFAS' substances put forward by five European countries could prevent the future use of fluorinated contact lens polymers within the EU.

The three fluorinated substances currently used in RGP contact lens materials, trifluoroethyl methacrylate, hexafluoroisopropyl methacrylate and bis-hexafluoroisopropyl itaconate all contain isolated -CF_3 groups (-CF_3 groups which are not adjacent to a -CF_2- group) in both monomeric and polymeric form, making them substantially different to toxic species such as PFOA and PFOS.

The available evidence, including several reports published by the Danish Environmental Protection Agency, indicates that degradation processes in the environment and *in vivo* will eventually convert any isolated -CF_3 groups which are present in a fluorinated substance to the molecule trifluoroacetic acid. Trifluoroacetic acid is a naturally occurring compound which is classified by the European Chemical Agency as 'low toxicity' and 'non PBT' (persistent, bioaccumulative and toxic). A 2023 United Nations Environment Programme report exploring the risks of trifluoroacetic acid to humans and the environment concluded that global emission levels do not pose a risk, even when extrapolated to the year 2100. Trifluoroacetic acid should not be thought of as a 'forever chemical' as it is naturally broken down by hydroxyl radicals in the lower atmosphere, albeit at a slow rate. Environmental levels would be expected to decrease by this mechanism if trifluoroacetic acid is no longer generated in large quantities from the breakdown of refrigerants and propellants.

Given the relatively small quantities of fluorinated material used in the RGP contact lens industry, the minimal environmental effects expected with these materials and the life changing benefits that RGP contact lenses bring for many patients, the detrimental societal impacts of restricting the use of fluorinated contact lens materials are considered to significantly outweigh any environmental gain.

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Introduction

In 2023, five European countries (Germany, Denmark, Netherlands, Norway and Sweden) submitted an Annex XV dossier to restrict the use of poly and per fluorinated alkyl substances (PFAS) to the European Chemicals Agency (ECHA).

The proposed restriction covers all PFAS, which are defined as “substances that contain at least one fully fluorinated methyl (-CF_3) or methylene (-CF_2-) carbon atom”.[1]

The reason given for the proposed restriction is that PFAS are persistent, toxic and bioaccumulating.

Two perfluorinated molecules in particular, perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), shown in Figure 1, were widely used by some industries in the past, but later found to be extremely harmful to humans and other animals.

Industries have since adopted numerous alternatives to PFOS and PFOA, including short-chain PFAS and fluorotelomers, substances with different molecular structures but which perform similar functions. There is concern that these alternatives (or their perfluorinated breakdown products) are also persistent, toxic and bioaccumulating.

Given that the numbers of these alternatives are in the thousands, the proposed restriction is very broad so that each does not have to be considered individually.

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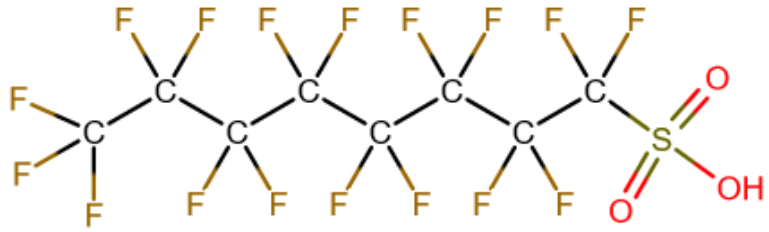

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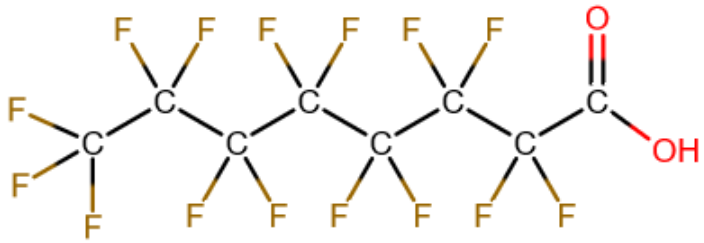

Figure 1. The molecular structures of (a) PFOS and (b) PFOA. Both molecules contain carbon atoms (labelled C), which typically form 4 covalent bonds (shown as lines between the atoms), and fluorine atoms (labelled F), which typically form 1 covalent bond. The molecules contain fully fluorinated alkyl chains, which can be defined as chains of carbon atoms which only form covalent bonds to each other or to fluorine atoms. PFOS has a fully fluorinated alkyl chain length of 8 carbon atoms. PFOA has a fully fluorinated alkyl chain length of 7 carbon atoms.

Fluorine in RGP contact lens polymers

The addition of fluorinated substances to RGP contact lens polymers facilitated the development of lathable materials with high oxygen permeability and good deposit resistance.

This advance has enabled RGP contact lenses to be worn without compromising eye health, while minimising the risk of infection and other complications such as hypoxia-related complications. Moreover, it has allowed scleral and orthokeratology modalities to become established.

The molecular structures of the three fluorinated monomers widely used in the preparation of RGP contact lens polymers, hexafluoroisopropyl methacrylate (HFPM), bis-hexafluoroisopropyl itaconate (BHI) and trifluoroethyl methacrylate (TFEM) are shown in Figure 2.

These species are best described as being polyfluorinated, but not perfluorinated, as while each contains multiple fluorine atoms, a majority of the carbon atoms in their

structures are not bonded to fluorine atoms. The fluorine atoms in each molecule are located in isolated -CF_3 groups (-CF_3 groups which do not have a -CF_2- group adjacent). The molecules could, therefore, be described as having a maximum fully fluorinated alkyl chain length of 1 carbon atom, and are categorised as ultra-short chain PFAS. This is also the case in polymerised form, where the -CF_3 groups are found in side-chains (Figure 2D).

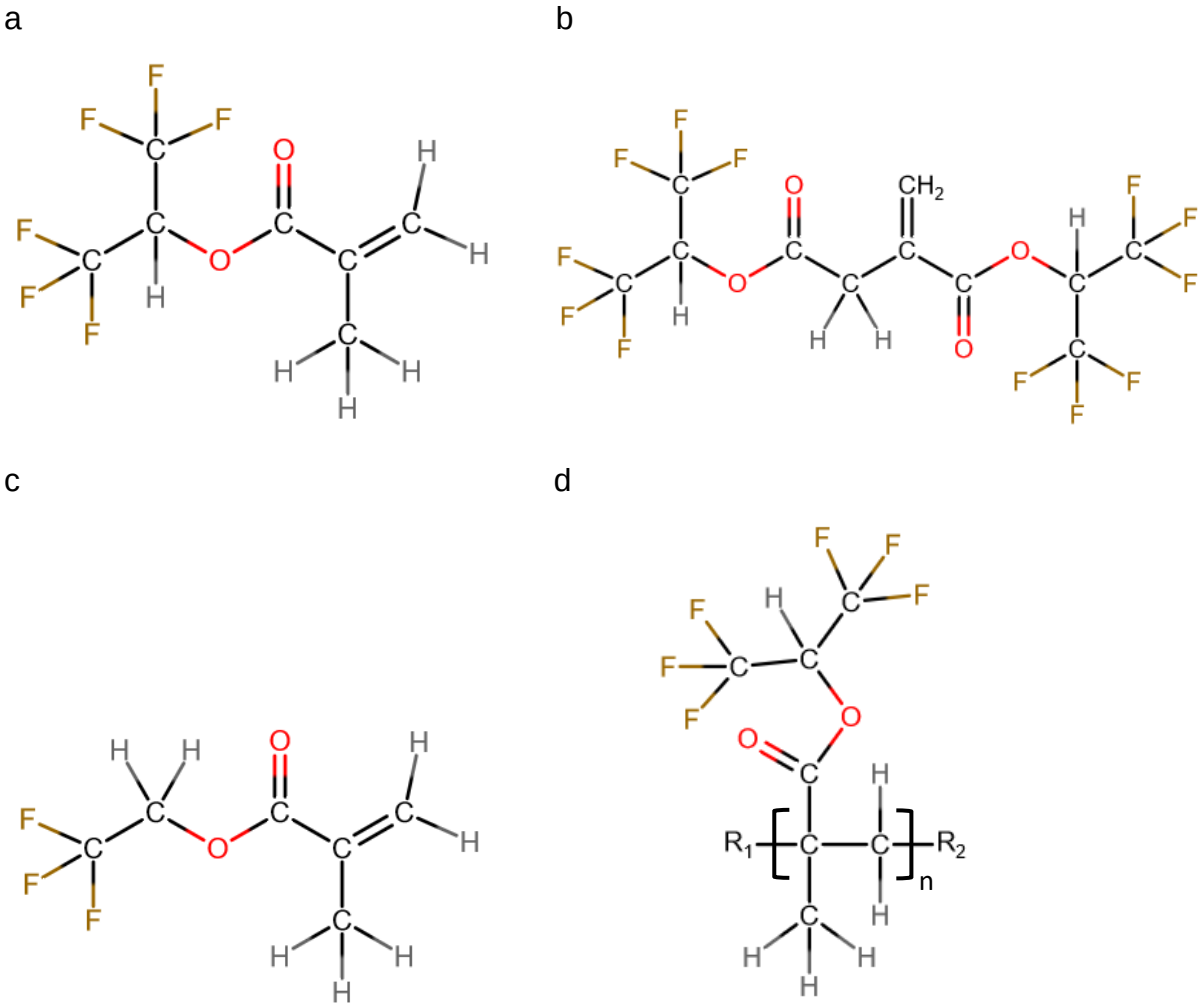

Figure 2. The molecular structures of rigid contact lens monomers (a) HFPM, (b) BHI and (c) TFEM. Oxygen atoms (labelled O) typically form 2 covalent bonds. Hydrogen atoms (labelled H) typically form 1 covalent bond. Double lines indicate a double covalent bond. (d) HFPM shown in polymerised form. Fluorine atoms are located in side-chains, not in the polymer backbone.

There are no known acute or chronic toxicity concerns over RGP lens materials which include fluorinated monomers in the formulations. Numerous different fluorinated RGP contact lens polymers have undergone safety testing as part of contact lens medical device regulatory submissions, including cytotoxicity and ocular irritation assessment, and have been widely used for over 30 years, without adverse findings. RGP contact lens polymers are considered to be inert and harmless to these CL wearers.[2]

Predictions generated using the EPI Suite and ECOSAR software programs,[3] available from the US Environmental Protection Agency, indicate that the three monomers used in the manufacture of RGP lens polymers do not meet the REACH criteria for toxicity or bioaccumulation (and so are neither PBT nor vPvB). Predicted minimum short-term aquatic toxic concentration values (algae, daphnia, fish) for TFEM, HFPM and BHI, calculated using ECOSAR v2.2, are 25.4 mg/L (green algae), 8.85 mg/L (green algae) and 0.54 mg/L (green algae) respectively, all above the toxicity criterion of < 0.1 mg/L. Predicted Log K_{ow} values for TFEM, HFPM and BHI, calculated using KOWWIN v1.69, are 2.18, 3.02 and 4.30 respectively, all below the bioaccumulation criterion of > 4.5 . Predicted bioconcentration factors (BCF) for TFEM, HFPM and BHI, calculated using BCFBAF 3.01, are 4.969, 45.33 and 317.3 respectively, all below the bioaccumulation criterion of > 2000.

These conclusions are supported by the available experimental data. TFEM has an LD50 (rat) of between 200 and 2000 mg/kg, a measured Log K_{ow} value of 2.3, has been found to be readily biodegradable in water and has an ECHA PBT Status of 'not PBT / vPvB'.[4] HFPM has an LD50 of > 2000 mg/kg and is reported to have ready biodegradability in water.[5]

Low toxicity is a feature of many molecules with a maximum fully fluorinated alkyl chain length of 1 carbon atom, which has led to widespread use as refrigerants or in medical devices. HFA134a (1,1,1,2-tetrafluoroethane, see Figure 3), for example, has a very well established safety profile and is heavily used in inhalers as a propellant.[6] Moreover, numerous studies have demonstrated that as the fluorinated chain lengths of PFAS decrease, so does toxicity and bioaccumulation.[7-11] The toxicity and bioaccumulation of harmful PFAS such as PFOA and PFOS are several orders of magnitude greater than those of equivalent ultra-short chain PFAS.[7]

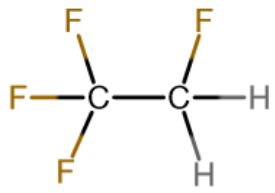

Figure 3. The molecular structure of HFA 134a.

Chemical degradation of fluorinated contact lens materials

As stated above, fluorinated contact lens materials used for RGP polymers are best described as being polyfluorinated methacrylates. The degradation products of such substances have been studied previously, with none meeting the REACH criteria for bioaccumulation or toxicity.[12,13]

Reports published by the Environmental Protection Agency of Denmark,[12,14,15] one of the EU Member States proposing the PFAS restriction, have explored in detail the fate of fluorinated materials, both in the body and in the environment, and present strong evidence that fully fluorinated alkyl chains do not readily degrade. Instead, reaction pathways eventually lead to these chains being derivatised with a carboxylic acid group to form a stable species. Where a fully fluorinated alkyl chain forms only part of a molecule, it is expected that degradation processes will break the molecule down until what remains is the carboxylic acid derivative of the fully fluorinated group, which in contact lens materials is a $-CF_3$.[16-21] This is shown schematically in Figure 4a.

For substances which incorporate one or more isolated $-CF_3$ groups (fully fluorinated alkyl chains with a length of 1 carbon atom), such as rigid contact lens monomers and polymers, the stable carboxylic acid derivative which will be formed is trifluoroacetic acid (TFA). This process is outlined in Figures 4b and 4c. A report by the US Environmental Protection Agency also concludes that molecules with an isolated $-CF_3$ group will convert to trifluoroacetic acid in the environment.[22]

Other environmental fates for RGP contact lens PFAS are conceivable, but highly unlikely. These species do not contain recalcitrant chemical groups (apart from $-CF_3$ moieties), and so won't remain intact. The fluorinated carbon chains of PFAS have not been observed to increase in length during environmental breakdown, and so this is not a realistic possibility. The only other feasible breakdown pathway involves a rare cleavage of one of the C-F bonds of the $-CF_3$ groups to yield a species with terminal $-CF_2X$ moieties. Such a species would not be classified as a PFAS and would be expected to fully degrade in the environment. The generation of TFA is, however, by far the most likely outcome of the environmental breakdown of rigid contact lens monomers and polymers and can also be considered to be the worst-case scenario.

TFA is a naturally occurring substance that is also generated in large quantities as a result of human activity, for example, through the atmospheric degradation of refrigerant gases. Despite being persistent in the environment, TFA is considered low risk. A 2016 United Nations Environment Programme report investigating the safety of TFA concluded that "risks to mammals, to plants growing in soil and to aquatic organisms is currently considered *de minimis*".[23] A message which was repeated in 2023.[7] This is because TFA is neither toxic nor bioaccumulating, as corroborated by the European Chemical Agency (ECHA).[24,25]

Perfluorinated and polyfluorinated chemicals are described as 'forever chemicals' due to the strength of the C-F chemical bond, which makes them difficult to degrade. There is, however, growing evidence that their persistence will ultimately decrease as

bacteria, which can derive energy from breaking the C-F bond, adapt to the presence of perfluorinated chemicals in the environment.[21,26-32]

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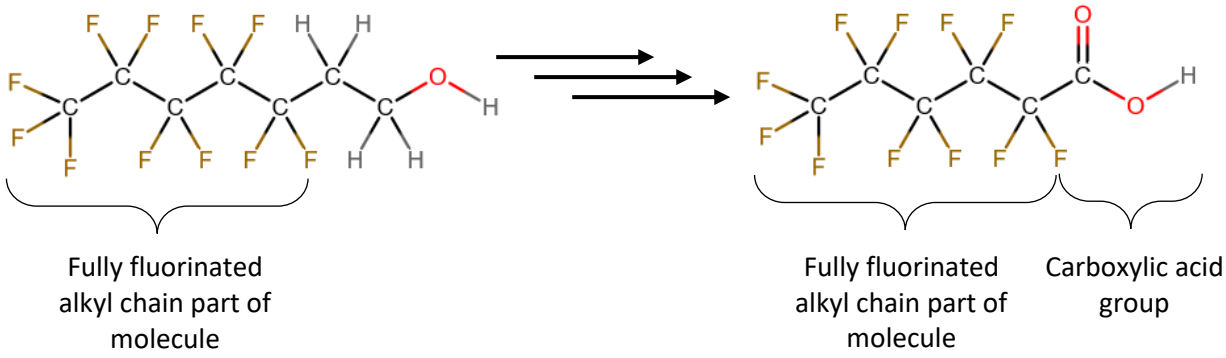

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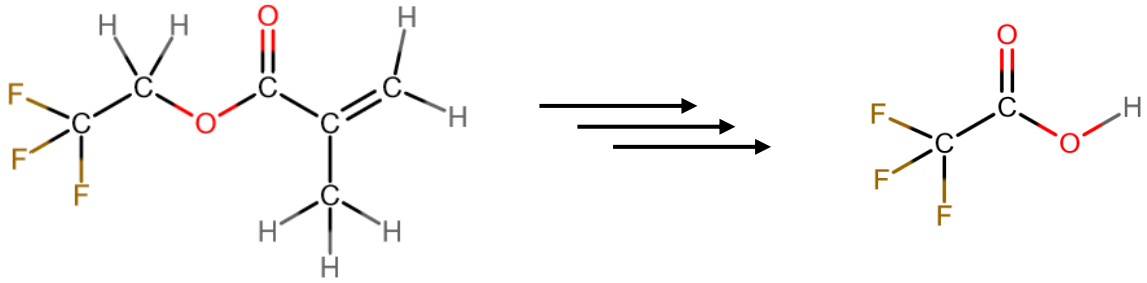

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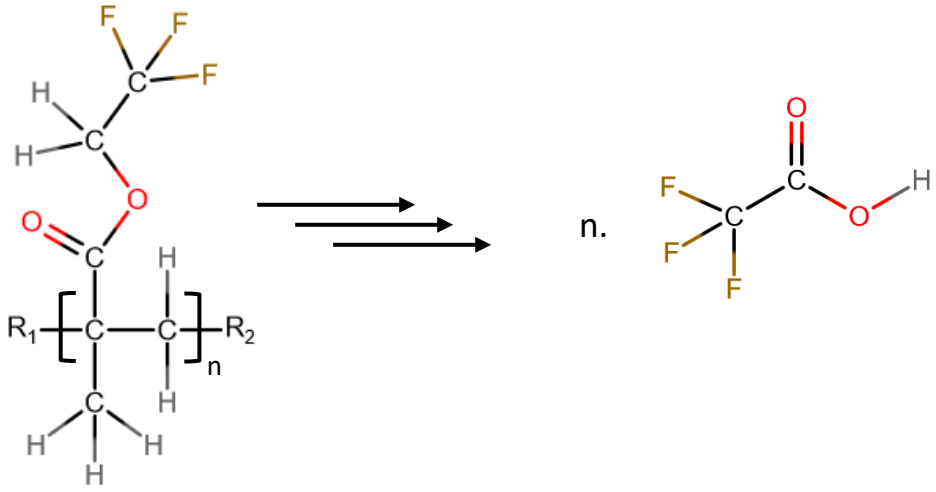

Figure 4. (a) Example of the degradation of a polyfluorinated substance. The fully fluorinated alkyl chain part of the molecule remains intact while the remainder of the molecule undergoes reactions which ultimately lead to the formation of a stable carboxylic acid. (b) Conversion of the contact lens monomer TFEM to TFA. (c) Conversion of polymeric TFEM to TFA.

In the case of TFA, for example, the label ‘forever chemical’ seems to be particularly inappropriate as it is naturally broken down by hydroxyl radicals in the troposphere into non-PFAS species.[33,34] This process limits the chemical lifetime of TFA in the troposphere to 4 months.[35] There are, however, also physical processes such as wet and dry deposition by which TFA is removed from the troposphere and transferred onto land or into bodies of water, environments where it has greater persistence. Even so, if the output of TFA were to remain constant, environmental levels would reach a steady state and cannot increase indefinitely as if often claimed with PFAS.

Any TFA entering the atmosphere is approximately 15 times more likely to be deposited to the Earth’s surface than it is to react with hydroxyl radicals,[35] so the overall environmental lifetime may be longer than 4 months. However, the conditions necessary for accumulation in terminal water sources to occur are considered to be extremely rare,[36] and a vast majority of anthropogenic TFA will end up in the oceans where it will be almost infinitely diluted and where the impact on naturally occurring, non-hazardous, TFA concentrations will be negligible.[7,37]

If, in future, regulations put a stop to the production of TFA (from anthropogenic sources at least) environmental concentrations will decrease back to pre-industrial levels. TFA in terminal water sources would now be diluted by rainwater while continuing to be removed by evaporation or aerosolization into the troposphere,[38] where it will react with hydroxyl radicals.[33,34] While a majority of the TFA entering the troposphere in this manner will be deposited back to the surface by physical processes, over successive cycles of evaporation/aerosolization and hydroxyl degradation/deposition TFA concentrations will be reduced (note that even if it is assumed that there is no natural source of TFA, and the TFA found in sea water is from anthropogenic sources, this mechanism would then act to reduce TFA levels in the oceans). This major decrease in environmental levels of TFA will still occur if small quantities of this compound continue to be generated from the manufacture of rigid contact lenses.

Conclusion and further information

Despite the relative persistence of their ultimate break-down product, TFA, there is no evidence that RGP contact lens polymers and monomers pose an environmental or health concern.

TFA itself is broken down in the troposphere, and environmental levels will naturally decrease once large-scale anthropogenic sources are eliminated.

More information on the usage of fluorinated substances in the contact lens sector, the essentiality of these substances for the performance of contact lens materials and the critical importance of rigid contact lenses to patients is given elsewhere.[39-43]

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