SUPPLEMENTAL DATA

A Critical Review of the Application of Polymer of Low Concern and Regulatory Criteria to Fluoropolymers

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Contents

Glossary of Terms

TERM	DEFINITION
Biocompatible	the ability of a material to perform with an appropriate host response in a specific application. *(*Williams, 1987*).*
e-PTFE	expanded polytetrafluoroethylene
ETFE	ethylene-tetrafluoroethylene co-polymer
FEP	fluorinated ethylene-propylene; a co-polymer of tetrafluoroethylene (TFE) and hexafluoropropylene (HFP)
Fluoropolymer	a distinct subset of fluorinated polymers, namely, those made by (co)polymerization of olefinic monomers, at least one of which contains F bound to one or both of the olefinic C atoms, to form a carbon-only polymer backbone with F atoms directly attached to it, e.g., polytetrafluoroethylene (Buck et al., 2011)
Fluorinated Polymer	the broad generic term to encompass all polymers for which one or more of the monomer units contains the element F, in the backbone and/or in side chains. Fluorinated polymers may or may not be PFAS, depending on whether they contain perfluoroalkyl moieties (Buck et al., 2011)
Fluoroelastomer	An elastic rubber-like polymer to which fluorine is bound. Fluoroelastomers are highly durable and resistant to heat, oils, solvents, fuels, and ozone.
Fluorochemical	a general, nonspecific name that describes a universe of organic and inorganic substances that contain at least 1 F atom, with vastly different physical, chemical, and biological properties. Synonyms include “fluorinated substance” and “fluorinated chemicals.” (Buck et al., 2011)
Fluorosurfactant	A substance used to lower aqueous surface tension in which the hydrophobic portion contains F bound to C, often as a perfluoroalkyl moiety, often referred to as ‘‘fluorinated surfactants’’, ‘‘fluorosurfactants,’’ ‘‘fluorinated tensides,’’ or ‘‘fluorotensides’’ (Buck et al., 2011)
Food Contact Material (FCM)	is made with the FCS (any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use of the substance is not intended to have any technical effect in such food) and (usually) other substances. It is often (but not necessarily) a mixture, such as an antioxidant in a polymer. The composition may be variable. (https://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm)
Functional Group Equivalent Weight (FGEW)	the ratio of the molecular weight to the number of occurrences of that functional group in the molecule. It is the weight of substance that contains one formula-weight of the functional group. (40 CFR 723.250(b))
HFP	hexafluoropropylene: $CF_3CF=CF_2$
Homopolymer	a polymer made with one monomer only
Modified Homopolymer	polymers containing not more than 1 % by weight of other fluoromonomers. (ASTM D4895 Standard Specification for Polytetrafluoroethylene (PTFE) Resin Produced From Dispersion section 1.1)
Oligomer	a polymer molecule consisting of only a few monomer units (dimer, trimer, tetramer) (40 CFR 723.250(b))
PAVE	perfluoroalkyl vinyl ether (generic name) in which the alkyl group is methyl, ethyl or propyl
PPVE	perfluoropropyl vinyl ether $CF_3CF_2CF_2$-O-$CF=CF_2$
PFA	perfluoroalkoxy polymer (generic name)
PTFE	Polytetrafluoroethylene
PVDF	polyvinylidene fluoride $–(CF_2CH_2)_n$-
PVF	polyvinyl fluoride $–(CFH-CH_2)_n$-
PFPE	A perfluoropolyether is a polymer in whose backbone -CF_2-, -CF_2CF_2-, and possibly -$CF(CF_3)CF_2$- units are separated by O atoms (Buck et al., 2011)
Perfluoroalkyl acid (PFAA)	long-chain perfluoroalkyl acids, include perfluoroalkyl carboxylic, sulfonic, sulfinic, phosphonic, and phosphinic acids which are highly persistent

	substances, such as PFOA or PFOS. They are released into the environment directly or are formed indirectly from the environmental degradation or metabolism of precursor substances (Buck et al., 2011)
PFAS	a very diverse group of per- and poly-fluoroalkyl substances including the class of polymers (fluoropolymers, perfluoropolyethers, side chain fluorinated polymers) and non-polymers (perfluoroalkyl substances for which all hydrogens on all carbon not associated with functional groups have been replaced by fluorines, and polyfluoroalkyl substances for which all hydrogens on at least one, but not all, carbon have been replaced by fluorines). (Buck et al., 2011)
PFECA	Per- and poly-fluoroether carboxylate
PFSA	perfluoroalkyl sulfonic acid: $F(CF_2)_nSO_3H$
PFCA	perfluorocarboxylic acid: $F(CF_2)_nCOOH$
Polymerization processing aid (PPA)	A substance (e.g., catalyst, stabilizer, surfactant) added to the reactor vessel from 0.01% to 0.5% of the weight of water, depending on the rate and degree of reaction (Ebnesajjad, 2000)
Polymer of Low Concern (PLC)	a polymer deemed to have insignificant environmental and human health impacts (OECD, 2009).
Reactive Functional Group (RFG)	A reactive functional group (RFG) is defined as an atom or associated group of atoms in a chemical substance that is intended or can be reasonably anticipated to undergo facile chemical reaction.
Specific Migration Limit (SML) Migration Limits	is the maximum permitted amount of substance (e.g., monomer) in food that has been determined to not pose a risk to human health
TFE	tetrafluoroethylene: CF2=CF2

PFAS & Fluoropolymers

The very broad term PFAS, per- and poly-fluoroalkyl substances, describes a very large universe of substances with very different properties. (See Buck et al., 2011.) The term "PFAS" was created in the context of focus on long-chain perfluoroalkyl acids (PFAAs, such as PFOS) and their precursors as a way to talk about substances that were relevant including alternatives, all of which have the requisite perfluoroalkyl moiety and are aliphatic. The environmental concern focus was (and is) on PFAAs and things that can turn in to them (aka precursors). The term PFC or PFCs has been erroneously used somewhat synonymously with the term PFAS. The term PFC was defined in the 1980's and codified by industry, regulators (including the U.S. EPA) and NGOs (including Greenpeace) to mean perfluorocarbons in the context of global warming and the Kyoto Protocol.

The long-chain perfluoroalkyl acids (PFAAs, such as perfluorooctanoic acid and perfluorooctane sulfonate) are highly fluorinated, small enough to be bioavailable, mobile and persistent. As such, these PFAAs and precursor substances (that may degrade to form PFAAs under normal foreseeable use and environmental conditions) are PFCs of environmental concern. Although not all PFAS are of environmental concern (e.g., PTFE fluoropolymer is highly stable, too large to be bioavailable, practically insoluble in water, and does not degrade in the environment) some PFAS are hazardous (e.g., PFOA), that is, some are highly persistent and have the potential to become widely dispersed in water, where they will remain for multiple generations.

PFAS definition (See Buck et al., 2011.):

"PFASs are aliphatic substances containing one or more carbon atoms on which all the hydrogen substituents present in the non-fluorinated analogs from which they are notionally derived have been replaced by fluorine atoms, in such a manner that PFASs contain the perfluoroalkyl moiety C_nF_{2n+1}—."

- Two essential functional attributes of a PFAS substance are that it is aliphatic and has a perfluoroalkyl moiety C_nF_{2n+1}—.
    - This means that a PFAS substance contains, at minimum, a CF_3- functional group
    - Also, PFASs are defined as aliphatic. This means that substances with a C_nF_{2n+1}—moiety bound to an aromatic ring such as is present in many drug and pesticide actives are not PFASs.

Perfluoroalkyl Substances (See Buck et al., 2011.):

"defined as aliphatic substances for which all of the hydrogen atoms attached to carbon atoms in the non-fluorinated substance from which they are notionally derived have been replaced by fluorine atoms, except those hydrogen atoms whose substitution would modify the nature of any functional groups present."

Polyfluoroalkyl Substances (See Buck et al., 2011.):

"defined here as aliphatic substances for which all hydrogen atoms attached to at least one (but not all) carbons have been replaced by fluorine atoms, in such a manner that they contain the perfluoroalkyl moiety C_nF_{2n+1}— (e.g., $C_8F_{17}CH_2CH_2OH$). Thus, while the general chemical concept of "polyfluorination" embraces compounds containing "scattered" multiple fluorine atoms (such as in $CH_2FCHFCHFCH_2OH$), as well as "grouped" ones (such as in $CF_3CF_2CH_2COOH$), we consider that only those polyfluorinated substances having at least one perfluoroalkyl moiety C_nF_{2n+1}—belong to the PFAS family."
The key functional attribute of a PFAS substance is the perfluoroalkyl moiety C_nF_{2n+1}-. This functional group is THE critical structural element that defines a PFAS substance.

Fluoropolymers (See Buck et al., 2011.):

Fluoropolymers are a distinct class of polymeric PFAS based on their common chemical structure as well as exhibiting similar thermal, physical, chemical and biological characteristics.

"In compliance with time-honored usage within the industry, we recommend further that the term "fluoropolymers" be applied only to a distinct subset of fluorinated polymers, namely, those made by (co)polymerization of olefinic monomers, at least one of which contains F bound to one

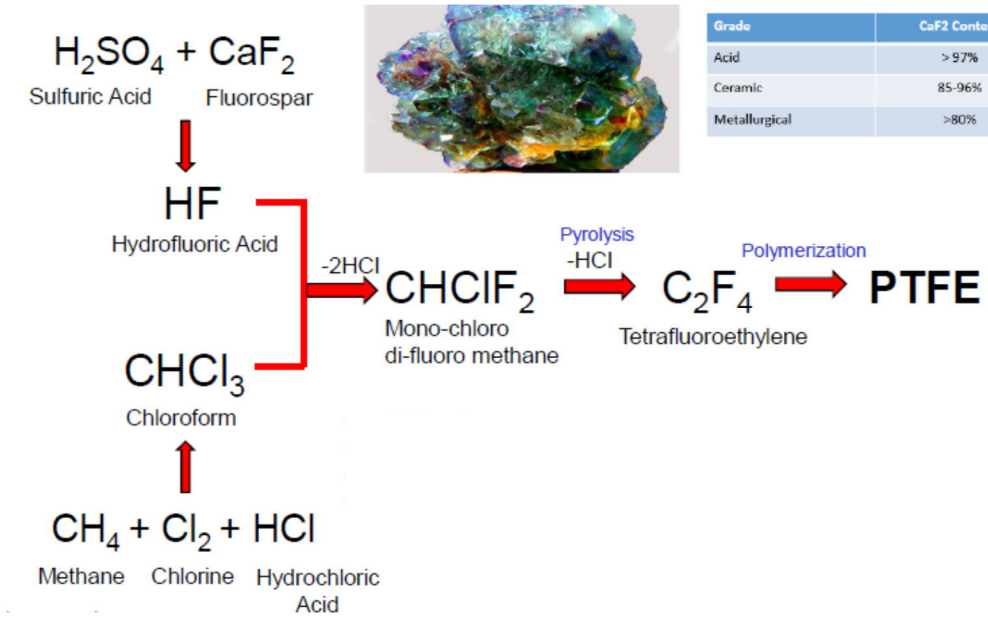
or both of the olefinic C atoms, to form a carbon-only polymer backbone with F atoms directly attached to it, e.g., polytetrafluoroethylene"

Fluoropolymer Primer

Fluoropolymers have been the subject of many prior reviews, books and articles (Gangal and Brothers, 2015; Ebnesajjad, 2011a; Ameduri, 2010; Drobny, 2008; Schiers, 1997). Fluoropolymers are typically synthesized via free radical polymerization methods. These fluoropolymer resins can be homopolymers like PTFE, or, copolymers like FEP, ETFE and PFA. Fluoropolymers are linear, semi-crystalline, high molecular weight polymers. Copolymers may have a monomer sequence that is either random (FEP, PFA) or alternating (ETFE).

Fluoromonomers are produced from minerals (e.g., fluorospar, calcium fluoride, CaF_2, also known as fluorite) and their manufacture involves the use of ozone depleting chemicals, whose use is strictly regulated by the Montreal Protocol and best available control technology is employed during their use.

Figure S1. Where Does PTFE Come From?



Grade	CaF2 Content	Percent of Total
Acid	> 97%	49%
Ceramic	85-96%	4%
Metallurgical	>80%	47%

Note: Mono-chloro di-fluoro methane (aka $CHClF_2$ or R22) is regulated under the Montreal Protocol as an ozone depleting substance with high global warming potential.

Fluoromonomer purity is essential to achieve high molecular weight fluoropolymers. For example, one of the routes in which, the high molecular weight PTFE (for expanded PTFE) is produced requires 99.999% pure tetrafluoroethylene (TFE) monomer (gas) for polymerization.

Very pure/deionized water is required for polymerization. Polymerization aids, ranging from 0.01% to 0.5% of the weight of water in the reactor, are used depending on the rate and degree of polymerization (Ebnesajjad, 2000). See Table S1 showing PTFE polymerization and post polymerization aids, which was assembled from patents, literature, publications and the authors' experience. Note that no PTFE manufacturer uses all of these in a PTFE polymer.

Low MW Leachables: Ingredients used in the Manufacture of Fluoropolymers

Note: Table S1 is a survey list. Not all are used in all manufacturing processes. These ingredients were disclosed in patents and publicly available literature.

Table S1: PTFE Polymerization and Post Polymerization Aids

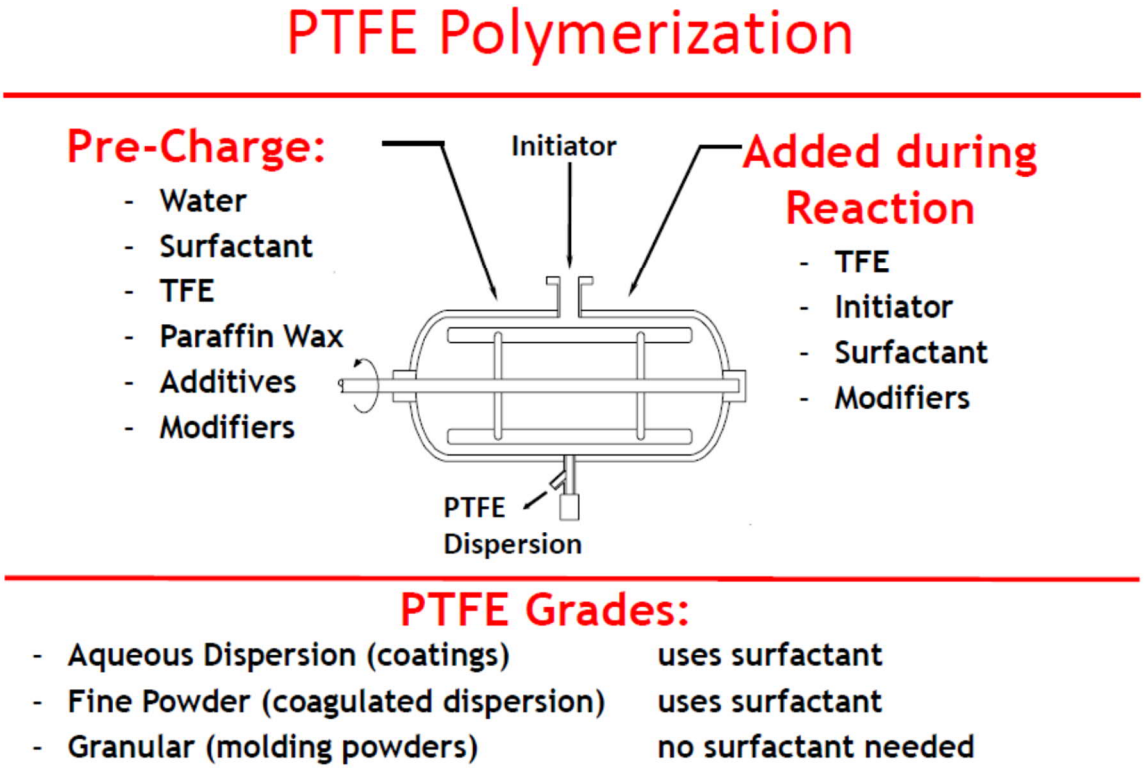
PTFE polymerization / post polymerization aids based on PTFE patents and publicly available information (no single PTFE uses all of these) (Note: Initiator concentration depends on rate and degree of polymerization, from 0.01 wt% to 0.5 wt% of the water.)	
Function	Name
coagulating agent	Acetone
Surfactant	4,9-dioxa-3H-perfluorononanoate
Initiator	Ammonium carbonate
pH adjuster	Ammonium hydroxide
Initiator	Ammonium persulfate
Initiator	Ammonium sulfite
Initiator	Barium peroxide
Initiator	Borax
Initiator	Disuccinic peroxide
Surfactant	Ammonium, 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy-) propionate
pH adjuster	Hydrochloric acid
Initiator	Hydrogen peroxide
Initiator	Lithium persulfate
Modifier, coagulating agent	methanol
pH adjuster	Nitric acid
Stabilizer	Nitrogen
Anticoagulant stabilizer	Parrafin wax
Surfactant	Perfluoro, 2-2-(methoxypropoxy)propanoic acid ammonium
Coagulation aid	Potassium nitrate
Initiator	Potassium permanganate

Dispersant	Purified deionized water
Surfactant	Ammonium, difluoro[1,1,2,2-tetrafluoro-2(pentafluoroethoxy)ethoxy] acetate
Removes monomer inhibitor	Silica gel
Initiator	Sodium bisulfite
Initiator	Sodium hydrosulfite
pH adjuster	Sodium hydroxide
Initiator	Succinic acid
Initiator	Zinc peroxide

Concentration of leachables from fluoropolymers, particularly PTFE “fine powder” (ASTM4895-16 Type I fine powder definition) are typically very low (<1ppm). (See the analytical report starting on page 32 of this Supplemental Data). This finding can be explained by the sensitivity of the PTFE polymerization reaction to contamination, and, is due to the post polymerization processing steps aggressively exercised to wash out residuals and drive off volatiles. In order to achieve high molecular weight polymerization of TFE, all traces of telogenic hydrogen or chlorine-bearing impurities must be removed (Ebnesajjad, 2011b). Therefore, despite the use of one or more of the aids on Table S1, after the PTFE resin is washed and dried to a fine powder, the final fluoropolymer has the inherent hazard of the polymer alone, as the data presented in this article and Supplemental section verify.

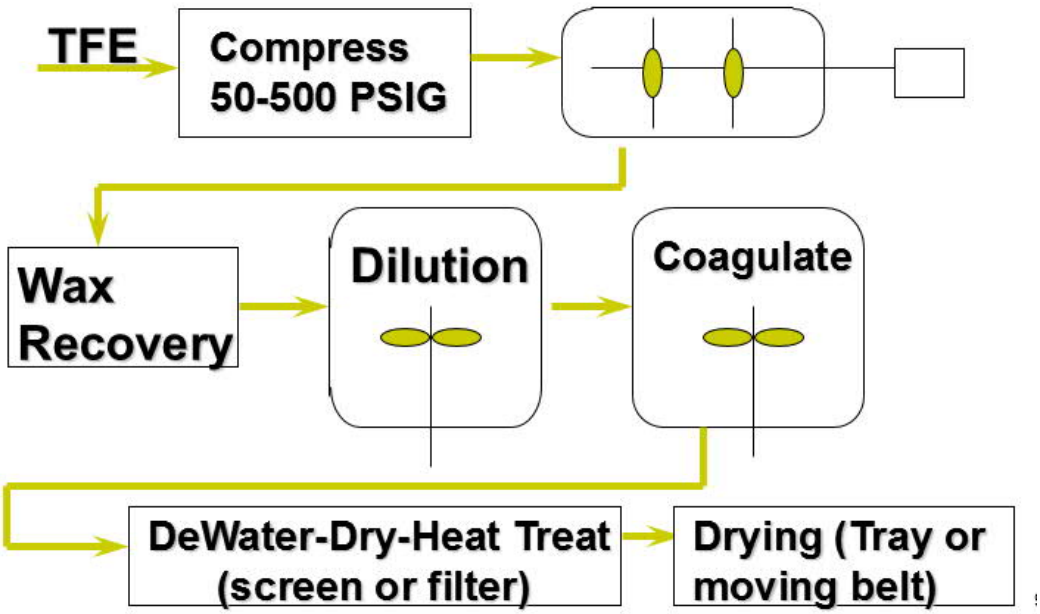
To further illustrate the low concentration of leachables, some details of the responsible manufacture of fluoropolymers are provided here. Fluoropolymers, such as PTFE, may be produced from aqueous dispersions by free-radical polymerization via addition polymerization (Ebnesajjad, 2011b): the PTFE fine powder polymerization starts with 99.999% pure TFE monomer and purified/deionized water in reactor vessel. (See Figure S2.) Other polymerization aids, (e.g., initiator, catalyst, stabilizer, surfactant) are added to the reactor vessel from 0.01% to 0.5% of the weight of water, depending on the rate and degree of reaction (Ebnesajjad, 2000).

Figure S2. Fluoropolymer Primer – PTFE Polymerization Scheme



Removal of residuals in a "finishing" step is performed on equipment with strict environmental control technology, such as thermal oxidizers, which have been demonstrated to be effective on TFE monomer (ECETOC, 2003). The result of the polymerization is an aqueous dispersion (with ~30% by weight PTFE polymer) which exits the reactor, is further diluted, pH adjusted, coagulated and dried in an oven to evaporate water and volatile residuals, leaving the pure PTFE polymer behind. (See Figure S3.)

Figure S3. Fluoropolymer Primer – PTFE Finishing Scheme



The ASTM4895-16 standard pertains to polytetrafluoroethylene (PTFE) prepared by coagulation of a dispersion, such as described above (ASTM4895-16). To adhere to this standard, PTFE resins must be homopolymers of TFE, or, be modified homopolymers containing not more than 1 % by weight of other fluoromonomers. In addition, PTFE resins meeting this specification do not include mixtures of PTFE with additives such as colors, fillers, or plasticizers, nor do they include reprocessed or reground resin or any fabricated articles. Therefore, none of these additives are available within the PTFE polymer to leach out of the polymer and potentially affect health or the environment. Other fluoropolymer standards include: ASTM D2116-16, Standard Specification for FEP Resin Molding and Extrusion Materials and ASTM D3307, Standard Specification for Perfluoroalkoxy (PFA) Resin Molding and Extrusion Materials.

Monomers, by nature, are reactive. Unreacted monomer left in a polymer may migrate out of the polymer to react with biomolecules to cause potential adverse effects. Regulatory authorities (BIO by Deloitte, 2014) and the OECD Expert Group on Polymers (OECD, 2009) agree that the residual monomer content of a polymer is critical to determining if it qualifies to be a PLC. TFE, for example, is a highly volatile gas monomer (boiling point of −76.3 °C) used in the making of PTFE. TFE is listed on the National Toxicology Program's Annual Report on Carcinogens (U.S.

Dept. of Health and Human Services, 1997). The fluoropolymer industry is well aware of TFE health and safety risks. TFE polymerization facility explosions have been documented (Reza and Christiansen, 2007). Fluoropolymer manufacturers follow documented industry best practices to ensure the safety of workers, manufacturing processes and products (Society of the Plastics Industry, 2005; Plastics Europe, 2012). These include increasing process automation, such as automatic cleaning and automation at the autoclaves, and use of localized ventilation and vacuum extraction at the end of the polymerization process (IARC, 2017). In the EU, for example, TFE must be used in a closed process with no likelihood of exposure (ECHA, 2014). Residual TFE monomer is not detected in PTFE resin by headspace GC-MS with a limit of detection of 1 ppm. (See the analytical report starting on page 32 of this Supplemental Data.) In addition, publicly available analytical data from independent industry authorities demonstrates that TFE is not detected in finished articles made from fluoropolymers at detection limits down to about 0.01ppm wt/wt (Society of the Plastics Industry, 2005).

Table S2: Alterative Fluoropolymer Processing Aids – Sources of Data

NOTE to the READER: please be aware that there are additional fluorinated alternative processing aids (see Table S1 above) commercially manufactured and used in fluoropolymer manufacturing for which there is no publicly available, citable data, such as is provided below.

Sources of Additional Details on Surfactants Used in Fluoropolymer Manufacturing		
Author	Source	Surfactant Addressed
European Chemicals Agency	ANNEX XV PROPOSAL FOR A RESTRICTION – Perfluorooctanoic acid (PFOA), PFOA salts and PFOA-related substances. The German and Norwegian competent authorities, VERSION NUMBER: 1.0, DATE: 17 October 2014	ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) –propanoate; ammonium 4,8-dioxa-3,4-perfluorononanoate; ammonium difluoro[1,1,2,2-tetrafluoro-2-(pentafluoroethoxy) ethoxy]acetate
Gordon, Steven C.	Toxicological evaluation of ammonium 4,8-dioxa-3,4-perfluorononanoate, a new emulsifier to replace ammoniumm perfluorooctanoate in fluoropolymer manufacturing, Regulatory Toxicology and Pharmacology 59(2011) 64-80.	ammonium 4,8-dioxa-3,4-perfluorononanoate
European Chemicals Agency	https://echa.europa.eu/registration-dossier/-/registered-dossier/6858	ammonium 4,8-dioxa-3,4-perfluorononanoate
European Chemicals Agency	https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/4729/1	ammonium difluoro[1,1,2,2-tetrafluoro-2-(pentafluoroethoxy)ethoxy]acetate
J.M. Caverly Rae, et al.	Evaluation of chronic toxicity and carcinogenicity of ammonium2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate in Sprague–Dawley rats. Toxicology Reports 2 (2015) 939–949.	ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) –propanoate
Robert A. Hoke, et al.	Aquatic hazard, bioaccumulation and screening risk assessment for ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) –propanoate. Chemosphere 149 (2016) 336-342.	ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) –propanoate

Shawn A. Gannon, et al.	Absorption, distribution, metabolism, excretion, and kinetics of 2,3,3,3- tetrafluoro-2-(heptafluoropropoxy)propanoic acid ammonium salt following a single dose in rat, mouse, and cynomolgus monkey. Toxicology 340 (2016) 1–9.	ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) –propanoate
European Chemicals Agency	https://echa.europa.eu/hr/registration-dossier/-/registered-dossier/2679/1	ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) –propanoate
Yoshinori Nanba	Patent #US20150299342, Production Method for Polytetrafluoroethylene Aqueous Dispersion, Daikin Industries, LTD, October 22, 2015.	perfluoro[2-(2-methoxypropoxy)propanoic acid] ammonium
Yoshinori Nanba	Patent #US 201503222.37A1, POLYTETRAFLUOROETHYLENE AQUEOUS DISPERSION, AND POLYTETRAFLUOROETHYLENE FINE POWDER, DAIKIN INDUSTRIES, LTD., Osaka, November 12, 2015.	perfluoro[2-(2-methoxypropoxy)propanoic acid] ammonium

U.S. EPA – Hazard Determination for a Polymer

The following example is provided to show how an EPA polymer hazard determination (based on molecular weight and physicochemical properties) in combination with a low exposure potential (based on the same characteristics) leads to a "no unreasonable risk" determination for the polymer in question. For additional examples like this one, the reader is directed to U.S. EPA's web page on PMN decisions (https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/chemicals-determined-not-likely).

Example text from a PMN Determination Letter published on the website above:

> **TSCA Section 5(a)(3)(C) Determination for Premanufacture Notice (PMN)**
> **TSCA Section 5(a)(3) Determination:** Chemical substance not likely to present an unreasonable risk (5(a)(3)(C))
>
> **Assessed Conditions of Use (intended, known, or reasonably foreseen)[1]:**
> Intended use(s) (generic): Additive for plastics. Known and reasonably foreseen use(s): Adhesive and sealant chemical.
>
> **Summary:** The chemical substance is not likely to present an unreasonable risk based on low human health hazard and low environmental hazard. Although EPA estimated that the new chemical substance would be very persistent, this did not indicate a likelihood that the chemical substance would present an unreasonable risk, given that the chemical substance has low potential for bioaccumulation, low human health hazard, and low environmental hazard.
>
> **Fate:** Environmental fate is the determination of which environmental compartment(s) a chemical moves to, the expected residence time in the environmental compartment(s) and removal and degradation processes. Environmental fate is an important factor in determining exposure and thus in determining whether a chemical may present an unreasonable risk. EPA estimated a number of physical-chemical and

fate properties of this new chemical substance using EPI (Estimation Programs Interface) Suite, a suite of physical/chemical property and environmental fate estimation programs (https://www.epa.gov/tsca-screening-tools/epi- uitetmestimation-program-interface). Overall, these estimates are indicative of low potential for this chemical substance to volatilize into the air and a low potential for this chemical to migrate into ground water. Removal of the substance in wastewater treatment is likely due to sorption.

Persistence: Persistence is relevant to whether a new chemical substance is likely to present an unreasonable risk because chemicals that are not degraded in the environment at rates that prevent substantial buildup in the environment, and thus increase potential for exposure, may present a risk if the substance presents a hazard to human health or the environment. EPA estimated biodegradation half-lives of this new chemical substance using EPI (Estimation Programs Interface) Suite, a suite of physical/chemical property and environmental fate estimation programs (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-programinterface). These estimates indicate that the chemical substance is very persistent.

Bioaccumulation[3]: Bioaccumulation is relevant to whether a new chemical substance is likely to present an unreasonable risk because substances that bioaccumulate in aquatic and/or terrestrial species pose the potential for elevated exposures to humans and other organisms via food chains. EPA estimated the potential for this new chemical substance to bioaccumulate using EPI Suite (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface).
These estimates indicate that this new chemical substance has low bioaccumulation potential.

Human Health Hazard[4]: Human health hazard is relevant to whether a new chemical substance is likely to present an unreasonable risk because the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and the extent of exposure to the substance. EPA estimated the human health hazard of this chemical substance based on its estimated physical/chemical properties (which indicate that it will not be absorbed if inhaled, ingested or by dermal contact) and by comparing it to structurally analogous chemical substances for which there is information on human health hazard. There is low concern for human health hazard for the chemical substance based on physical/chemical properties of the chemical, as well as estimates of potential hazard based on analogous chemical substances/structure-activity relationships.

Environmental Hazard[5]: Environmental hazard is relevant to whether a new chemical substance is likely to present unreasonable risks because the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and the extent of exposure to the substance. EPA estimated environmental hazard of this new chemical substance using the Ecological Structure Activity Relationships (ECOSAR) Predictive Model (https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictivemodel).

Based on these estimated hazard values from ECOSAR, EPA concludes that this chemical substance has low environmental hazard.

Potential Exposures: The exposure to a new chemical substance is potentially relevant to whether a new chemical substance is likely to present unreasonable risks because the significance of the risk is dependent upon both the hazard (or toxicity) of the chemical substance and the extent of exposure to the substance. In this case, EPA did not estimate the exposure because EPA determined that the chemical substance presents both low human health hazard and low environmental hazard. Due to low hazard, EPA believes that this chemical substance would be unlikely to present an unreasonable risk even if exposures were high.

Potentially Exposed or Susceptible Subpopulation(s): Workers are potentially exposed. Given the low hazard of this chemical substance, EPA finds that this chemical substance is not likely to present unreasonable risk to workers.

Polymers are too large to penetrate cell membranes

Molecular weight is an important predictor of biological effect because very large molecules (>1,000 – 10,000 Da) are too large to penetrate cell membranes. References that describe this:

- Alberts B, Bray D, Lewis J et al., Molecular Biology of the Cell, 3rd Ed., Garland Science, NY, 1994, pp. 958, 963.

- Beyer EC, Gap Junctions. Inter. Rev. Cytol. 137, p2, in Molecular Biology of Receptors and Transporters: Pumps, Transporters and Channels, Friedlander M and Mueckler M, Editors, Academic Press, Inc., San Diego, 1993.

- Walmor C. De Mello, Ed., Cell-to-Cell Communication, Plenum Press, NY, 1987, p34.

Water Solubility

Table S3 Solubility Table from USP 34 NF29 General Notices, Section 5.3.0, p6

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble or insoluble	Greater than or equal to 10,000

Representative SMLs for Fluoropolymers

Table S4. EU Specific Migration Limits (SMLs) for Monomers in Representative Fluoropolymers (in mg monomer/kg food)

PTFE	FEP	ETFE	PFA
0.05 mg/kg TFE	0.05 mg/kg TFE, 0.01 mg/kg HFP	None for Ethylene, 0.05 mg/kg for TFE	0.05 mg/kg for PMVE and PPVE, None for PEVE

ISO 10993 Biocompatibility Tests

Website for ISO 10993: http://www.iso.org/iso/catalogue_detail.htm?csnumber=44908

- Cytotoxicity
- Irritation or Intracutaneous Reactivity
- Acute Systemic Toxicity
- Implantation
- *In Vitro* Genotoxicity
- *In Vivo* Genotoxicity
- Material Mediated Pyrogenicity
- Sensitization
- Subchronic Systemic Toxicity
- Hemocompatibility – Hemolysis
- Hemocompatibility - Complement Activation
- Hemocompatibility – Thrombogenicity
- Chronic Systemic Toxicity
- Carcinogenicity
- Reproductive/Developmental Toxicity
- Degradation

Additional text describing the 10993 Biocompatibility Tests.

- Irritation and intracutaneous reactivity tests are performed whereby pieces of the device are extracted in polar and nonpolar solvents at 50°C for 72 hours followed by subcutaneous injection of the extracts into rabbits. Signs of localized irritation or reactivity are noted in the animals after 72 hours of observation indicating the device readily leaches irritating substances.
- Acute systemic toxicity is also performed where similar extractions are intravenously and/or intraperitoneally administered to mice. Signs of toxicity are observed after 72 hours post-injection, indicating if acute toxicity results from systemic administration of the device extracts. Mortality and body weight are also collected in the acute systemic toxicity test.

- The implantation study involves intramuscular placement of solid strips of the device into rabbits for 3 and 7 days. The implantation sites are then examined for any adverse reactions aside from slight inflammation and fibrosis surrounding the strips, reactions that are ubiquitously observed after short implantation durations.
- To determine the compatibility of a device with circulating blood, hemocompatibility is examined with both *in vitro* and *in vivo* hemolysis (breakage of red blood cells) protocols to determine if potentially deleterious interactions with red blood cells may occur. Other hemocompatibility studies include complement activation and thrombogenicity.
- To examine whether the device is a mutagen (capable of altering DNA structure), three standardized genotoxicity studies (an Ames bacterial mutagenesis assay, a mouse lymphoma assay and an *in vivo* micronucleus study) are performed according to OECD guidelines with extracts of the device.

Evaluation of PTFE in Medical Devices

PTFE, a representative fluoropolymer, in three physical forms (sheet, fiber, tube) was subjected to the BS EN ISO 10993-1 (Biological evaluation of medical devices – Part 1: Evaluation and testing) testing in compliance with Good Laboratory Practices (GLPs, 21 CFR, Part 58) at an accredited contract laboratory, NAMSA (Northwood, OH) in accordance with current ISO 10993 guidelines. All three physical forms of PTFE were manufactured, sterilized and packaged using methods intended for commercial product. Traceability of samples is maintained by reference numbers supplied in the associated study reports. Extraction conditions were established in each study protocol as indicated in the following data tables and were based upon the surface area of the test sample (ISO 10993-12:2009). The results of these tests are summarized in the following table.

This PTFE data was generated under Good Laboratory Practices in compliance with ISO 10993, ASTM and OECD standards.

ISO 10993-3: Bacterial Mutagenicity (Ames test)	OECD 471
ISO 10993-3: Mouse Lymphoma Assay	OECD 476
ISO 10993-3: Peripheral Mouse Micronucleus Test	OECD 474
ISO 10993-4: Hemolysis	ASTM F756
ISO 10993-4: Partial Thromboplastin Time (PTT)	ASTM F2382
ISO 10993-10: Irritation and Skin Sensitization	OECD 406
ISO 10993-11: Systemic Toxicity	OECD 408

Table S5. Biocompatibility Tests, Conditions and Acceptance Criteria Results for ePTFE patch

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
In Vitro* Cytotoxicity** ***MEM Elution Test (12T_2724_03) (April/2012) ISO 10993-5 ISO 10993-12	Extraction: Minimum Essential Medium with 5% fetal bovine serum, 2% antibiotics, 1% L-glutamine. Conditions: 37°C, 24 hours. Extraction Ratio: 6 cm^2/mL Test system: Mouse fibroblast L-929 cells.	ePTFE patch, Code: SMR108314 Neg. Control = High density polyethylene (HDPE) Pos. Control = Powder-Free Latex Gloves	No signs of cellular morphologic change or death (ie, Grade ≤ 2 [mild]) should be seen for the test article extracts at 48 hours.	**PASS** – non cytotoxic Test article was not cytotoxic.
Delayed-Type Hypersensitivity ***Kligman Maximization Test in Guinea Pigs*** (12T_2724_13, 12T_2724_14) (June/2012) ISO 10993-10	Extraction: 0.9% NaCl; sesame oil. Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE patch, Code: SMR108314 Neg. Control = 0.9% NaCl, sesame oil Pos. Control = 1-chloro-2,4-dinitrobenzene (DNCB)	Clinical Observations: No treatment-related signs of toxicity. Sensitization: None of the treated or Neg. Control animals elicit any reaction at challenge.	**PASS** - non-sensitizing All animals increased in weight, no signs of systemic toxicity, no reaction to challenge. One (sesame oil, Test group) animal (#6256) was euthanized on day 26. Necropsy revealed a broken left rear leg. No evidence of sensitization was observed in the sesame oil group; therefore the loss of this animal did not impact the conclusion.

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
Irritation				
Intracutaneous Irritation Study in Rabbits (12T_2724_06, 12T_2724_07) (May/2012) ISO 10993-2 ISO 10993-10 ISO 10993-12	Extraction: 0.9% NaCl; sesame oil. Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE patch, Code: SMR108314 Neg. Control = 0.9% NaCl, sesame oil Pos. Control: N/A.	Clinical Observations: No treatment-related signs of toxicity. None of the extracts elicit a greater reaction than the controls (ie, the mean difference in scores ≤ 1).	**PASS** – non-irritating No treatment-related signs of toxicity. The difference in the mean score for both test and control was ≤ 1 for both the NaCl and sesame oil test.
Systemic Toxicity				
Acute Systemic Toxicity Study in Mice (12T_2724_04, 12T_2724_05) (May/2012) ISO 10993-2 ISO 10993-11 ISO 10993-12	Extraction: 0.9% NaCl; sesame oil. Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE patch, Code: SMR108314 Neg. Control = 0.9% NaCl, sesame oil Pos. Control: N/A	Clinical Observations: No treatment-related signs of toxicity or loss of body weight. Pass if < 2 animals exhibit marked signs of toxicity.	**PASS** – not systemically toxic No treatment-related signs of toxicity or loss of body weight in any group.
Rabbit Pyrogen Study (Material Mediated) (12T_2724_12) (May/2012) ISO 10993-11 USP 151	Extraction: 0.9% NaCl. Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE patch, Code: SMR108314 Neg. Control = 0.9% NaCl. Pos. Control: N/A	Body temperature increases for individual treated animals are < 0.5°C and < 3.3°C for all treated animals.	**PASS** – non-pyrogenic Body temperature increases were < 0.5°C for individual test animals and < 3.3°C for all treated animals.

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
Genotoxicity				
Bacterial Reverse Mutation Assay (12T_30255_03, 12T_30255_04) (May/2012) OECD Test No. 471 ISO 10993-3 ISO 10993-12	Extraction: 0.9% NaCl, dimethyl sulfoxide Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537; *Escherichia coli* strain WP2uvrA.	ePTFE patch, Code: SMR108314 Neg. Control = vehicle only Pos. Control = Sodium azide, Methyl Methanesulfonate, Benzo[a]pyrene, 2-aminoanthracene, 2-Nitrofluorene, ICR-191	Non-mutagenic: normal background lawn and < 2-fold increase in number of mean revertants over the Neg. Control for strains TA98, TA100, WP2*uvrA*, and < 3-fold increase in number of mean revertants for strains TA1535 and TA1537 in both the presence and absence of metabolic activation.	**PASS** – non mutagenic The test article extracts were not considered to be mutagenic.
Mouse Lymphoma Assay (12T_30255_05, 12T_30255_06) (June/2012) OECD Test No. 476 ASTM E1280 ISO 10993-3 ISO 10993-12	Extraction: RPMI culture medium, dimethyl sulfoxide Conditions: RPMI: 37°C, 72 hours dimethyl sulfoxide: 50°C, 72 hours Extraction Ratio: 6 cm^2/mL Test system: Mouse Lymphoma L5178Y/TK$^{+/-}$ cells	ePTFE patch, Code: SMR108314 Neg. Control = vehicle only Pos. Control = 3-Methylchol-anthrene, Methyl Methanesulfonate	Mutagenic: a ≥ 2-fold increase in mean mutation frequency over the vehicle control. Non-mutagenic: < 2-fold increase. Results from cell cultures with < 10% Rel. Total Growth (RTG) are not biologically relevant due to high cytotoxicity.	**PASS** – non mutagenic The test article extracts did not induce gene mutations or chromosomal damage.
Mouse Peripheral Blood Micronucleus Study (12T_30255_07, 12T_30255_08) (June/2012) OECD Test No. 474 ISO 10993-3 ISO 10993-12	Extraction: 0.9% NaCl, Sesame Oil Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE patch, Code: SMR108314 Neg. Control = 0.9% NaCl, Sesame Oil Pos. Control = Methyl methanesulfonate, 50 mg/kg	Statistical analyses (p values < 0.05) will be used to determine whether test extract administration induces multi-nucleated reticulocytes. Biological relevance of results will be considered in the final determination of genotoxicity.	**PASS** – non mutagenic The test article extracts did not induce micronuclei formation.

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
Local Effects after Implantation				
Muscle Implantation Study in Rabbits (4 weeks) (12T_2724_15) (June/2012) ISO 10993-6	N/A	ePTFE patch, Code: SMR108314 Four 1×1×10 mm sections were implanted/rabbit. Neg. Control = HDPE. Four 1×1×10 mm sections were implanted/rabbit. Pos. Control: N/A	Tissue response (eg, width of inflammation) to the test article in all animals is NOT significantly stronger than that of the Neg. Control.	**PASS** - Non adverse No adverse effects were observed micro- or macroscopically. The test article was a non-irritant.
Hemocompatibility				
Hemolysis Study Direct Contact and Indirect Contact (12T_2724_11) (April/2012) ISO 10993-4 ISO 10993-12 ASTM F756	Direct contact: The test article was introduced directly to test system at 6 cm^2/mL Indirect contact: Extraction: PBS Conditions: 50 °C for 72 hours. Test Article: extracted at 6 cm^2/mL	ePTFE patch, Code: SMR108314 Negative Control = HDPE Positive control = sterile water for injection	Percentage hemolysis must be ≤ 2 % to be non-hemolytic.	**PASS** – Non-hemolytic. Direct contact: ≤ 2 % hemolysis. Indirect contact: ≤ 2 % hemolysis.
Partial Thromboplastin Time, Direct Contact (12T_2724_08) (May/2012) ASTM F2382 ISO 10993-12	No extraction. The test article was introduced directly to human plasma at 4 cm^2/mL	ePTFE patch, Code: SMR108314 Negative Control = Polypropylene tube Positive Control = soda lime glass beads	A test result >50% of the negative control is passing.	**PASS** – No effect on coagulation. The average Partial Thromboplastin Time (PTT) was 75% of the negative control.

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
Complement Activation **C3a Complement Activation Assay (Direct Contact)** (12T_2724_09) (May/2012) ISO 10993-4	No extraction. Test article was directly exposed to test system at a ratio of 6 cm^2/mL at 37°C for 60 minutes.	ePTFE patch, Code: SMR108314 Negative Control = HDPE, LDPE Positive Controls = latex gloves, Cobra Venom Factor (CVF)	The test article is considered to have no effect on complement activation if the C3a concentration is not statistically higher than activated normal human serum (NHS) and negative control concentrations.	**PASS** – No activation of complement. The test article sample was not statistically higher ($p<0.05$) than both the activated human serum and negative controls.
SC5b-9 Complement Activation Assay (Direct Contact) (12T_2724_10) (May/2012) ISO 10993-4	No extraction. Test article was directly exposed to test system at a ratio of 6 cm^2/mL at 37°C for 60 minutes.	ePTFE patch, Code: SMR108314 Negative Control = HDPE, LDPE Positive Controls = latex gloves, CVF	The test article is considered to have no effect on complement activation if the SC5b-9 concentration is not statistically higher than activated NHS and negative control concentrations.	**PASS** – No activation of complement. The test article sample was not statistically higher ($p<0.05$) than both the activated human serum and negative controls.
Subchronic toxicity ***13-Week Systemic Toxicity Study in Rats*** (12T_2724_16) (October/2012) ISO 10993-6 ISO 10993-11	N/A	ePTFE patch, Code: SMR108314 Test Article Dose: 6, 1 mm x 1 cm x 2cm pieces per animal was the maximum implant in this subcutaneous rat model. Neg. Control = HDPE Pos. Control = N/A	N/A. Information from these studies is used to inform clinicians of potential target organs and associated toxicities at multiples of the intended clinical exposure.	**PASS** – There were no clinical or systemic signs of toxicity (including gross-, microscopic-, and clinical-pathology evaluations). The test article was considered a non-irritant.

[a] Note: ePTFE patch is referred to as "*ePTFE patch, 1mm*" in the study reports.

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
<u>*In Vitro* Cytotoxicity</u> ***MEM Elution Test*** (12T_29147_03) (5/2012) ISO 10993-5 ISO 10993-12	Extraction: Minimum Essential Medium with 5% fetal bovine serum, 2% antibiotics, 1% L-glutamine. Conditions: 37°C, 24 hours. Extraction Ratio: 6 cm^2/mL Test system: Mouse fibroblast L-929 cells.	ePTFE fiber, Code: SMR108316 Neg. Control = High density polyethylene (HDPE) Pos. Control = Powder-Free Latex Gloves	No signs of cellular morphologic change or death (ie, Grade ≤ 2 [mild]) should be seen for the test article extracts at 48 hours.	**PASS** – non cytotoxic Test article was not cytotoxic.
<u>Delayed-Type Hypersensitivity</u> ***Kligman Maximization Test in Guinea Pigs*** (12T_29147_06, 12T_29147_07) (6/2012) ISO 10993-10	Extraction: 0.9% NaCl; sesame oil. Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE fiber, Code: SMR108316 Neg. Control = 0.9% NaCl, sesame oil Periodic Pos. Control = 1-chloro-2,4-dinitrobenzene (DNCB)	Clinical Observations: No treatment-related signs of toxicity. Sensitization: None of the treated or Neg. Control animals elicit any reaction at challenge.	**PASS** - non-sensitizing All animals increased in weight, no signs of systemic toxicity, no reaction to challenge.
<u>Irritation</u> ***Intracutaneous Irritation Study in Rabbits*** (12T_29147_04, 12T_29147_05) (5/2012) ISO 10993-10	Extraction: 0.9% NaCl; sesame oil. Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE fiber, Code: SMR108316 Neg. Control = 0.9% NaCl, sesame oil Pos. Control: N/A.	Clinical Observations: No treatment-related signs of toxicity. None of the extracts elicit a greater reaction than the controls (ie, the mean difference in scores ≤ 1).	**PASS** – non-irritating No treatment-related signs of toxicity. The difference in the mean score for both test and control was ≤ 1 for both the NaCl and sesame oil test.

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
<u>Systemic Toxicity</u> ***Acute Systemic Toxicity Study in Mice*** (12T_29147_08, 12T_29147_09) (5/2012) ISO 10993-11	Extraction: 0.9% NaCl; sesame oil. Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE fiber, Code: SMR108316 Neg. Control = 0.9% NaCl, sesame oil Pos. Control: N/A	Clinical Observations: No treatment-related signs of toxicity or loss of body weight. Pass if < 2 animals exhibit marked signs of toxicity.	**PASS** – not systemically toxic No treatment-related signs of toxicity or loss of body weight in any group.
Rabbit Pyrogen Study (Material Mediated) (12T_29147_10) (5/2012) ISO 10993-11 USP 151	Extraction: 0.9% NaCl. Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE fiber, Code: SMR108316 Neg. Control = 0.9% NaCl. Pos. Control: N/A	Body temperature increases for individual treated animals are < 0.5°C and < 3.3°C for all treated animals.	**PASS** – non-pyrogenic Body temperature increases were < 0.5°C for individual test animals and < 3.3°C for all treated animals.
<u>Genotoxicity</u> ***Bacterial Reverse Mutation Assay*** (12T_31264_03, 12T_31264_04) (5/2012) OECD Test No. 471 ISO 10993-3 ISO 10993-12	Extraction: 0.9% NaCl, dimethyl sulfoxide Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537; *Escherichia coli* strain WP2uvrA.	ePTFE fiber, Code: SMR108316 Neg. Control = vehicle only Pos. Control = Sodium azide, Methyl Methanesulfonate, Benzo[a]pyrene, 2-aminoanthracene, 2-Nitrofluorene, ICR-191	Non-mutagenic: normal background lawn and < 2-fold increase in number of mean revertants over the Neg. Control for strains TA98, TA100, WP2*uvrA*, and < 3-fold increase in number of mean revertants for strains TA1535 and TA1537 in both the presence and absence of metabolic activation.	**PASS** – non mutagenic The test article extracts were not considered to be mutagenic.

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
Mouse Lymphoma Assay (12T_31264_05, 12T_31264_06) (7/2012) OECD Test No. 476 ISO 10993-3 ISO 10993-12	Extraction: RPMI culture medium, dimethyl sulfoxide Conditions: RPMI: 37°C, 72 hours dimethyl sulfoxide: 50°C, 72 hours Extraction Ratio: 6 cm^2/mL Test system: Mouse Lymphoma L5178Y/TK$^{+/-}$ cells	ePTFE fiber, Code: SMR108316 Neg. Control = vehicle only Pos. Control = 3-Methylchol-anthrene, Methyl Methanesulfonate	Mutagenic: a ≥ 2-fold increase in mean mutation frequency over the vehicle control. Non-mutagenic: < 2-fold increase. Results from cell cultures with < 10% Rel. Total Growth (RTG) are not biologically relevant due to high cytotoxicity.	**PASS** – non mutagenic The test article extracts did not induce gene mutations or chromosomal damage.
Mouse Peripheral Blood Micronucleus Study (12T_31264_07, 12T_31264_08) (6/2012) OECD Test No. 474 ISO 10993-3 ISO 10993-12	Extraction: 0.9% NaCl, Sesame Oil Conditions: 50°C, 72 hours. Extraction Ratio: 6 cm^2/mL	ePTFE fiber, Code: SMR108316 Neg. Control = 0.9% NaCl, Sesame Oil Pos. Control = Methyl methanesulfonate, 50 mg/kg	Statistical analyses (p values < 0.05) will be used to determine whether test extract administration induces multi-nucleated reticulocytes. Biological relevance of results will be considered in the final determination of genotoxicity.	**PASS** – non mutagenic The test article extracts did not induce micronuclei formation.
<u>Local Effects after Implantation</u> ***Muscle Implantation Study in Rabbits (4 weeks)*** (12T_29147_11) (6/2012) ISO 10993-6	N/A	ePTFE fiber, Code: SMR108316 Four 1×1×10 mm sections were implanted/rabbit. Neg. Control = HDPE. Four 1×1×10 mm sections were implanted/rabbit.	Tissue response (eg, width of inflammation) to the test article in all animals is significantly stronger than that of the Neg. Control.	**PASS** - Non adverse No adverse effects were observed micro- or macroscopically. The test article was a non-irritant.

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
<u>Hemocompatibility</u> **Hemolysis Study Direct Contact and Indirect Contact** (12T_29147_13) (5/2012) ISO 10993-4 ISO 10993-12 ASTM F756	Direct contact: The test article was introduced directly to test system at 6 cm^2/mL Indirect contact: Extraction: PBS Conditions: 50 °C for 72 hours. Test Article: extracted at 6 cm^2/mL	ePTFE fiber, Code: SMR108316 Negative Control = HDPE Positive control = sterile water for injection	Percentage hemolysis must be ≤ 2 % to be non-hemolytic.	**PASS** – Non-hemolytic. Direct contact: ≤ 2 % hemolysis. Indirect contact: ≤ 2 % hemolysis.
Partial Thromboplastin Time, Direct Contact (12T_29147_14) (5/2012) ASTM F2382 ISO 10993-12	No extraction. The test article was introduced directly to human plasma at 4 cm^2/mL	ePTFE fiber, Code: SMR108316 Negative Control = Polypropylene tube Positive Control = soda lime glass beads	ASTM F2382 defines the test result >50% of the negative control as a passing result.	**PASS** – No effect on coagulation. The average Partial Thromboplastin Time was 94% of the negative control.
<u>Complement Activation</u> **C3a Complement Activation Assay (Direct Contact)** (12T_29147_15) (5/2012) ISO 10993-4	No extraction. Test article was directly exposed to test system at a ratio of 6 cm^2/mL at 37°C for 60 minutes.	ePTFE fiber, Code: SMR108316 Negative Control = HDPE Negative Control = LDPE; Positive Controls = latex gloves, Cobra Venom Factor (CVF)	The test article is considered to have no effect on complement activation if the C3a concentration is not statistically higher than activated normal human serum (NHS) and negative control concentrations.	**PASS** – No activation of complement. The test article sample was not statistically higher ($p<0.05$) than both the activated human serum and negative controls.

Test Performed (Lab Report No.) (Date Completed) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article[a] and Control(s)	Acceptance Criteria	Conclusions
SC5b-9 Complement Activation Assay (Direct Contact) (12T_29147_16) (5/2012) ISO 10993-4	No extraction. Test article was directly exposed to test system at a ratio of 6 cm^2/mL at 37°C for 60 minutes.	ePTFE fiber, Code: SMR108316 Negative Control = HDPE Negative Control = LDPE; Positive Controls = latex gloves, CVF	The test article is considered to have no effect on complement activation if the SC5b-9 concentration is not statistically higher than activated NHS and negative control concentrations.	**PASS** – No activation of complement. The test article sample was not statistically higher ($p<0.05$) than both the activated human serum and negative controls.
Subchronic toxicity ***13-Week Systemic Toxicity Study in Rats*** (12T_29147_12) (9/2012) OECD Test No. 408 ISO 10993-11	N/A	ePTFE fiber, Code: SMR108316 Test Article Dose: 90 linear cm/rat. Based upon an average male 250 g rat (ie, 360 cm/kg), which is equivalent to a 70 kg patient receiving 25,200 linear cm. Neg. Control = HDPE	N/A. Information from these studies is used to inform clinicians of potential target organs and associated toxicities at multiples of the intended clinical exposure.	**PASS** – There were no clinical or systemic signs of toxicity (including gross-, microscopic-, and clinical-pathology evaluations). The test article was considered a non-irritant.

[a] Note: ePTFE fiber is referred to as "*Large diameter ePTFE fiber*" in the study reports.

Test Performed (Lab Report #) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article and Control(s)	Acceptance Criteria	Conclusions
***In Vitro* Cytotoxicity** **L929 MEM Elution Test** Completed 4/2012 12T_28380_03 ISO 10993-5 ISO 10993-12	Test article was extracted at a ratio of 6cm²/ml in 1X MEM media + 5% FBS + 2% antibiotics at 37°C for 24 hours. Test system: Mouse fibroblast L-929 cells	Test article name: VT6[1] Lot: SMR108669 Negative Controls = HDPE, 1X MEM Positive Control = Powder-free latex gloves	No signs of cellular morphologic change or death (ie, Grade ≤ 2 [mild]) should be seen for the test article extracts at 48 hours.	**PASS** – non cytotoxic Test article was not cytotoxic.
Delayed-Type Hypersensitivity **Kligman Maximization Test in Guinea Pigs** Completed 6/2012 12T_28380_06 12T_28380_07 ISO 10993-10	Test article was extracted at a ratio of 6cm²/ml in 0.9% USP NaCl and sesame oil at 50°C for 72 hours.	Test article name: VT6 Lot: SMR108669 Negative Controls = 0.9% USP NaCl, sesame oil; Positive Control = Dinitrochlorobenzene.	Clinical Observations: No treatment-related signs of toxicity. Sensitization: None of the treated or Neg. Control animals elicit any reaction at challenge.	**PASS** - non-sensitizing All animals increased in weight, no signs of systemic toxicity, no reaction to challenge.
Irritation **ISO Intracutaneous Study in Rabbits** Completed 5/2012 12T_28380_04 12T_28380_05 ISO 10993-10 MHLW, Part 5	Test article was extracted at a ratio of 6cm²/ml in 0.9% USP NaCl and sesame oil at 50°C for 72 hours.	Test article name: VT6 Lot: SMR108669 Negative Controls = 0.9% USP NaCl, sesame oil; Positive Control: N/A.	Clinical Observations: No treatment-related signs of toxicity. None of the extracts elicit a greater reaction than the controls (ie, the mean difference in scores ≤ 1).	**PASS** – non-irritating No treatment-related signs of toxicity. The difference in the mean score for both test and control was ≤ 1 for both the NaCl and sesame oil test.

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Test Performed (Lab Report #) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article and Control(s)	Acceptance Criteria	Conclusions
Systemic Toxicity **Acute Systemic Toxicity Study in Mice** Completed 5/2012 12T_28380_08 12T_28380_09 ISO 10993-11	Test article was extracted at a ratio of 6cm²/ml in 0.9% USP NaCl and sesame oil at 50°C for 72 hours.	Test article name: VT6 Lot: SMR108669 Negative Control = 0.9% USP NaCl, sesame oil; Positive Control: N/A	Clinical Observations: No treatment-related signs of toxicity or loss of body weight. Pass if < 2 animals exhibit marked signs of toxicity.	**PASS** – not systemically toxic No treatment-related signs of toxicity or loss of body weight in any group.
Rabbit Pyrogen Study (Material-Mediated) Completed 4/2012 12T_28380_10 ISO 10993-11 USP 151	Test article was extracted at a ratio of 6cm²/ml in 0.9% USP NaCl at 50°C for 72 hours.	Test article name: VT6 Lot: SMR108669 Negative Control = 0.9% USP NaCl; Positive Control: N/A.	Body temperature increases for individual treated animals are < 0.5°C and < 3.3°C for all treated animals.	**PASS** – non-pyrogenic Body temperature increases were < 0.5°C for individual test animals and < 3.3°C for all treated animals.

Note: VT6 = ePTFE tube

Test Performed (Lab Report #) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article and Control(s)	Acceptance Criteria	Conclusions
Subchronic Toxicity **13-Week Systemic Toxicity Study in Rats via subcutaneous implantation** Completed 9/2012 12T_28380_12 ISO 10993-11 OECD 408	No extraction: Test article was directly implanted in each animal as 1cm x 2cm sections (0.07g each) at 6 sites (corresponding to 1.68g material/kg body weight). This corresponds to approximately 87% of what occurs in a worst-case clinical scenario; implantation of more material was not surgically practical.	Test article name: VT6 Lot: SMR108669 Neg. Control = HDPE Pos. Control = N/A	N/A. Information from these studies is used to inform clinicians of potential target organs and associated toxicities at multiples of the intended clinical exposure.	**PASS** – There were no clinical or systemic signs of toxicity (including gross-, microscopic-, and clinical-pathology evaluations). The test article was considered a non-irritant.
Genotoxicity **Bacterial Reverse Mutation Assay** Completed 5/2012 12T_30064_02 12T_30064_03 OECD 471 ISO 10993-3 ISO 10993-12	Test article was extracted at a ratio of 6cm^2/ml in 0.9% USP NaCl and dimethyl sulfoxide (DMSO) at 50°C for 72 hours. A dose range finding study was also performed that used test article extracted at a ratio of 6cm^2/ml in DMSO at 50°C for 72 hours. Test systems: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537; *Escherichia coli* strain WP2uvrA.	Test article name: VT6 Lot: SMR108669 Negative Controls = 0.9% USP NaCl, DMSO; Positive Controls = Sodium azide, methyl methanesulfonate (MMS), 2-aminoanthracene, benzo[a]pyrene, 2-nitrofluorene, ICR-191.	Non-mutagenic: normal background lawn and < 2-fold increase in number of mean revertants over the Neg. Control for strains TA98, TA100, WP2*uvrA*, and < 3-fold increase in number of mean revertants for strains TA1535 and TA1537 in both the presence and absence of metabolic activation.	**PASS** – non mutagenic The test article extracts were not considered to be mutagenic.

Test Performed (Lab Report #) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article and Control(s)	Acceptance Criteria	Conclusions
Mouse Lymphoma Assay Completed 6/2012 12T_30064_04 12T_30064_05 OECD 476 ISO 10993-3 ISO 10993-12	Test article was extracted at a ratio of 6cm^2/ml in serum free cell culture media ($RPMI_0$) at 37°C for 72 hours; test article was extracted at a ratio of 6cm^2/ml in DMSO at 50°C for 72 hours. Test system: Mouse Lymphoma L5178Y/TK$^{+/-}$ cells	Test article name: VT6 Lot: SMR108669 Negative Controls = DMSO, $RPMI_0$. Positive Controls = MMS, 3-methylcholanthrene.	Mutagenic: a ≥ 2-fold increase in mean mutation frequency over the vehicle control. Non-mutagenic: < 2-fold increase. Results from cell cultures with < 10% Rel. Total Growth (RTG) are not biologically relevant due to high cytotoxicity.	**PASS** – non mutagenic The test article extracts did not induce gene mutations or chromosomal damage.
Mouse Peripheral Blood Micronucleus Study Completed 5/2012 12T_30064_06 12T_30064_07 OECD 474 ISO 10993-3 ISO 10993-12	Test article was extracted at a ratio of 6cm^2/ml in 0.9% USP NaCl and sesame oil at 50°C for 72 hours.	Test article name: VT6 Lot: SMR108669 Negative Control = 0.9% USP NaCl, sesame oil; Positive Control =MMS, 50mg/kg	Statistical analyses (p values < 0.05) will be used to determine whether test extract administration induces multi-nucleated reticulocytes. Biological relevance of results will be considered in the final determination of genotoxicity.	**PASS** – non mutagenic The test article extracts did not induce micronuclei formation.
Local Effects after Implantation **Muscle Implantation Study in Rabbits, 4 weeks** Completed 6/2012 12T_28380_11 ISO 10993-6	No extraction. 10mm x 1mm x 1mm sections of the test article representative of all materials in the device were implanted directly into the test system.	Test article name: VT6 Lot: SMR108669 Negative Control = HDPE; Positive Control = N/A	Tissue response (eg, width of inflammation) to the test article in all animals is significantly stronger than that of the Neg. Control.	**PASS** - Non adverse No adverse effects were observed micro- or macroscopically. The test article was a non-irritant.

Note: VT6 = ePTFE tube

Test Performed (Lab Report #) Testing Guideline(s)	Extraction Vehicle(s) Conditions	Test Article and Control(s)	Acceptance Criteria	Conclusions
Hemocompatibility **Hemolysis-Rabbit Blood (Direct and Indirect Contact)** Completed 4/2012 12T_28380_13 ISO 10993-4 ISO 10993-12 ASTM F756	Test article was directly exposed to test system at a ratio of 6cm²/ml for the direct contact test; for the indirect contact test, test article was extracted at a ratio of 6cm²/ml in Ca- and Mg-free phosphate buffered saline at 50°C for 72 hours.	Test article name: VT6 Lot: SMR108669 Negative Control = High density polyethylene. Positive control = Sterile H_2O for injection	Percentage hemolysis must be ≤ 2 % to be non-hemolytic.	PASS – Non-hemolytic. Direct contact: ≤ 2 % hemolysis. Indirect contact: ≤ 2 % hemolysis.
Partial Thromboplastin Time Assay (Direct Contact) Completed 4/2012 12T_28380_14 ISO 10993-4 ISO 10993-12 ASTM F2382	No extraction. Test article was directly exposed to human plasma at a ratio of 4.0cm²/ml at 37°C for 15 minutes.	Test article name: VT6 Lot: SMR108669 Negative Control = Polypropylene tube Positive Controls = Soda lime glass beads	ASTM F2382 defines the test result >50% of the negative control as a passing result.	PASS – No effect on coagulation. The average Partial Thromboplastin Time was 84% of the negative control.
C3a Complement Activation Assay (Direct Contact) Completed 4/2012 12T_28380_15 ISO 10993-4	No extraction. Test article was directly exposed to test system at a ratio of 6cm²/ml at 37°C for 60 minutes.	Test article name: VT6 Lot: SMR108669 Negative Control = LDPE; Positive Controls = latex gloves, Cobra Venom Factor (CVF)	The test article is considered to have no effect on complement activation if the C3a concentration is not statistically higher than activated normal human serum (NHS) and negative control concentrations.	PASS – No activation of complement. The test article sample was not statistically higher ($p<0.05$) than both the activated human serum and negative controls.
SC5b-9 Complement Activation Assay (Direct Contact) Completed 4/2012 12T_28380_16 ISO 10993-4	No extraction. Test article was directly exposed to test system at a ratio of 6cm²/ml at 37°C for 60 minutes.	Test article name: VT6 Lot: SMR108669 Negative Control = LDPE; Positive Controls = latex gloves, CVF	The test article is considered to have no effect on complement activation if the SC5b-9 concentration is not statistically higher than activated NHS and negative control concentrations.	PASS – No activation of complement. The test article sample was not statistically higher ($p<0.05$) than both the activated human serum and negative controls.

[1]Test samples are referred to as VT6 in the test reports.

Note: VT6 = ePTFE tube

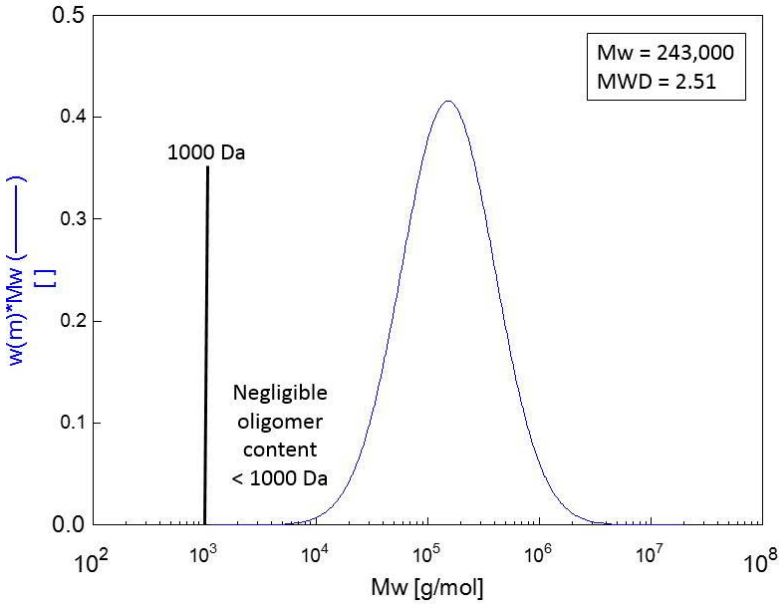
Polymer of Low Concern (PLC) Assessment Criteria

Molecular Weight (MW), Number Average Molecular Weight (M_n) and Molecular Weight Distribution (MWD)

Polymers contain monomer chains of unequal length. The molecular weight of a polymer is not a single value. The polymer exists as a distribution of chain lengths and varying molecular weights. The molecular weight of a polymer must therefore be described as some average molecular weight calculated from the molecular weights of all the chains in the sample. The number average molecular weight (M_n) is the statistical average molecular weight of all the polymer chains in the sample. M_n can be predicted by polymerization mechanisms and is measured by methods that determine the number of molecules in a sample of a given weight; for example, end-group assay. If M_n is quoted for a molecular weight distribution, there are equal numbers of molecules on either side of M_n in the distribution. The OECD Expert Group on Polymers noted: "One of the most striking findings related to the number-average molecular weight (M_n) of a polymer; *the lower the M_n, the higher the potential for health or eco-toxicological concern* (OECD 2009, p9.)."

Molecular Weight Distribution (MWD), aka polydispersity index, measures the heterogeneity of size of polymer molecules in a polymer. MWD is an important parameter for predicting potential biological effects of polymers because while M_n may be a large value, low MW oligomers <1,000 Da may be present which could penetrate the cell.

Figure S2. An FEP Fluoropolymer Molecular Weight Distribution – from a rheological study



Reactive Functional Groups (RFG) and RFG Ratio to MW (FGEW)

Not only does the number of functional groups per polymer M_n impact the health and environmental impact of a polymer, but so does the relative hazard ("low", "moderate, " high" concern) of the functional group itself. The Deloitte report concluded that most polymer of low concern and polymer of low concern-eligible polymers are over 10,000 Da MW and are mostly inert (BIO by Deloitte 2015). Those polymers with MW>1,000 <10,000 Da with RFG of "moderate concern" should have functional group equivalent weight, FGEW >1,000 each and combined FGEW >1,000 (BIO by Deloitte 2015). Those polymers with MW > 1,000 < 10,000 Da with both "high" and "moderate" concern RFGs should have a combined FGEW >5,000; each high concern group should have a FGEW >5,000; each moderate concern group should have a FGEW >1,000 (BIO by Deloitte 2015).

Similar to FGEW, the ratio of residual monomers to MW is a rough metric for whether or not the potential impact of the monomer is substantially diluted by polymeric material. This ratio is used as an indication of the degree of hazard of the polymer. The higher the percent residual monomer in the M_n, the more the polymer would be expected to behave like the monomer. As shown in the Table 1 of the main paper, for PTFE, the ratio of residual TFE monomer to PTFE molecular weight is <0.07%.

As previously discussed, PTFE is surrounded by an envelope of fluorine atoms and has two carboxylic acid end groups per molecule. Both carboxylic acid and halogen RFG (except reactive halogen-containing benzylic or allylic halides) were concluded to be "low concern" functional groups (BIO by Deloitte 2015). See Table S6.

Table S6: US EPA's Chemical Categories of Concern, 2010

US EPA's Chemical Categories of Concern (2010 "current" list)	
Acid Chlorides	Hindered Amines
Acid Dyes and Amphoteric Dyes	Imides
Acrylamides	β-Naphthylamines, Sulfonated
Acrylates/Methacrylates	Lanthanides or Rare Earth Metals
Aldehydes	Neutral Organics
Aliphatic Amines	Nickel Compounds
Alkoxysilanes	Nitriles, allylic/vinyl
Aluminum Compounds	Nonionic Surfactants
Aminobenzothiazole Azo Dyes	Organotins
Anhydrides, Carboxylic Acid	Peroxides
Anilines	Persistent, Bioaccumulative, and Toxic (PBT) Chemicals
Dianilines	Phenolphthaleins
Anionic Surfactants	Phenols
Azides	Phosphates, Inorganic
Benzotriazoles	Phosphinate Esters
Benzotriazole-hindered phenols	Polyanionic Polymers (& Monomers)
Boron Compounds	Polycationic Polymers
Cationic Dyes	Polynitroaromatics
Cationic (quaternary ammonium) surfactants	Respirable, Poorly Soluble Particulates
Cobalt	Rosin
Diazoniums	Stilbene, derivatives of 4,4-bis(triazin-2-ylamino)-
Diisocyanates	Thiols
Dichlorobenzidine-based Pigments	Substituted Triazines
Dithiocarbamates	Triarylmethane Pigments/Dyes with Non-solubilizing Groups
Epoxides Esters	Vinyl Esters
Ethylene Glycol Ethers	Vinyl Sulfones
Hydrazines and Related Compounds	Soluble complexes of Zinc
	Zirconium Compounds

Note: The following is an analytical chemistry report from W.L. Gore & Associates. This report is intended to supplement the information in the main text to the complete PLC criteria table which supports the conclusion that PTFE is equivalent to a Polymer of Low Concern. This analytical report may be reported in a separate technical document for publication in an appropriate journal following peer review.

PTFE Fine Powder Resin Extractable and Leachable Analytical Report for Polymer of Low Concern Concept

Introduction

The global Organisation for Economic Co-operation and Development (OECD) Expert Group on Polymers found that sufficient data existed to create a consensus document identifying the essential data elements to qualify as a Polymer of Low Concern (PLC) to health and the environment (OECD, 2009). Polymers satisfying these essential data elements were deemed to warrant reduced regulatory requirements (OECD, 2009). A recent report commissioned be European Community (EC) compiled existing polymer regulations outside the EU and proposed alternative options for EU polymer registration (BIO by Deloitte, 2015). The BIO by Deloitte report identified the eligibility criteria to be considered a Polymer of Low Concern with respect to potential for adverse impact on health and the environment.

Recent regulatory interest and pending restrictions have caused some concern that fluoropolymers, although stable and benignly persistent, would be included in these restrictions. An avenue toward protecting these valuable polymers from restriction is to demonstrate that they meet the criteria for a Polymer of Low Concern. Many of the defined criteria can be gleaned from the available literature and supplier technical reports. Not all of the necessary information is readily available and must be generated to complete the data set for the Polymer of Low Concern (PLC) assessment. A study was conducted to investigate several PLC properties of fluoropolymers of interest to W.L. Gore & Associates, Inc. The fluoropolymer investigated in this report was polytetrafluoroethylene, PTFE.

Purpose

This analytical study was performed to develop and apply analytical approaches to generate the following PLC data for the fluoropolymer polytetrafluoroethylene, PTFE, with the sensitivity and selectivity needed. The specific properties that are not readily available and will be investigated in this work are:

- low molecular weight leachables and extractables
- % oligomer
- residual monomers

Materials and Methods

The selection of materials for this study was made for their relevance to Gore PTFE resins used broadly in the majority of products sold. Chromatographic techniques were performing using the most appropriate grade and purity and are identified below.

PTFE Samples:

- Polytetrafluoroethylene meeting ASTM4895 Type I fine powder definition (CASRN 9002-84-0, PTFE) selected from raw material inventory by a Gore associate (Joe Carlin), from a Gore facility (Cherry Hill plant), April 2016.

Standards & Analytical chemicals:

- Hexane, Honeywell Burdick and Jackson GC^2 Grade
- Isopropyl alcohol (IPA), EMD Omnisolv High Purity
- Water, Millipore Milli-Q 18 MΩ
- FC-72, 3M Fluorinert FC-72 Electronic Liquid
- Novec 7300, 3M Novec 7300 Engineered Fluid
- Isopar K, Exxon-Mobil Isopar K Solvent (lot number not known)
- Diethylene glycol, Sigma-Aldrich ReagentPlus, 99%
- Butylated hydroxytoluene (BHT), Sigma-Aldrich, >99%
- Dioctyl phthalate, Sigma-Aldrich 99%
- GC/MS standard reference material (SRM): undecane, tridecane, tetradecane, pentadecane, Sigma-Aldrich >99%; 4-chlorophenol, > 98%, TCI America; 1-Dodecylamine, >99%, TCI America; methyl dodecanoate, > 98%, TCI America; 1-dodecanol, 99.5%, ChemService; all blended in hexane
- LC/MS SRM: caffeine, ReagentPlus, Sigma-Aldrich; Carbowax PEG 600, Dow; sulforhodamine B (aka Acid Red 52), 75% dye content, Sigma-Aldrich; bromothymol blue sodium salt, Sigma-Aldrich; calibrant ion 922 = hexakis(1H,1H,3H-tetrafluoropropoxy)phosphazene, calibrant ion 1522 = hexakis(1H,1H,5H-octafluoropentoxy)phosphazene, Synquest Laboratories, all blended in 25% methanol (EMD Omnisolv LC/MS grade) and 75% aqueous 2 mM ammonium acetate (EMD HPLC grade) in 18 MΩ water
- PFC standard: perfluorobutane sulfonic acid, potassium salt, >98%, TCI America; perfluorohexanoic acid, sodium salt, Synquest Laboratories; perfluorooctanoic acid, sodium salt, 97%, Lancaster Synthesis; perfluoroctane sulfonic acid, tetraethylammonium salt, 98%, Sigma-Aldrich; perfluorononanoic acid, 97% Sigma-Aldrich, all blended in EMD Omnisolv LC/MS Grade methanol, nominally 100 ng/mL each Extractables, leachables and oligomers were measured using common extraction techniques and multiple solvents of various polarities (hexane, IPA, 55% water/45% IPA by weight).

PTFE powder was extracted with solvents of varying polarities (hexane, IPA, and 55/45 water/IPA by volume) to recover low molecular weight extractable and leachable compounds, as well as low molecular weight oligomers. The extracts were analyzed for their detectable analytes by gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/mass spectrometry (LC/MS) utilizing electrospray ionization in both positive and negative modes

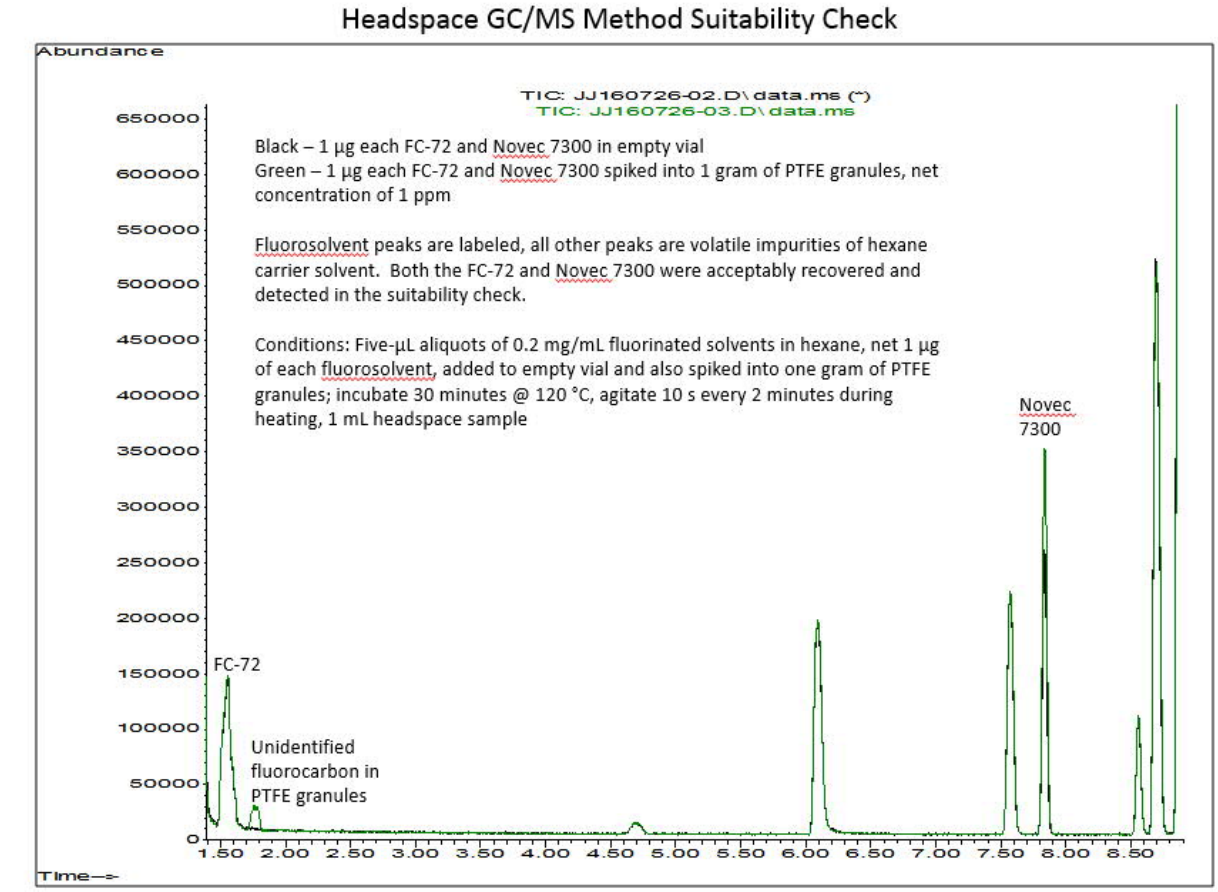
Headspace GC/MS Method

Headspace-GC/MS analysis was carried out on nominally one gram samples of the solid polymer to detect volatile species entrained in the material. The samples were heated for thirty minutes at 120°C, agitated 10 seconds every two minutes, and then a one- mL sample of the headspace gas was drawn for analysis.

Volatile species, such as entrained solvents and residual monomers, are determined by headspace GC/MS analysis of the raw polymer. For example, tetrafluoroethylene (TFE) monomer is the principal component of polytetrafluoroethylene and is a gas at normal ambient conditions. As such, TFE would not be recoverable via extraction but could be detected by headspace analysis.

Headspace GC/MS Method Suitability Check

The suitability of this procedure was verified by performing a replicate test with known quantities of fluorosolvents available for reference. Five-µL aliquots of 0.2 mg/mL mixture of fluorinated solvents in hexane (FC-72 and Novec 7300), was added to the empty vial and also to a vial containing one gram of PTFD powder, resulting in a net spike of one µg of each fluorosolvent, corresponding to a one µg/g concentration in the PTFE if present. The samples were analyzed by headspace GC/MS as described above. Both the FC-72 and Novec 7300 were recovered within acceptable ranges and detected in the suitability check.



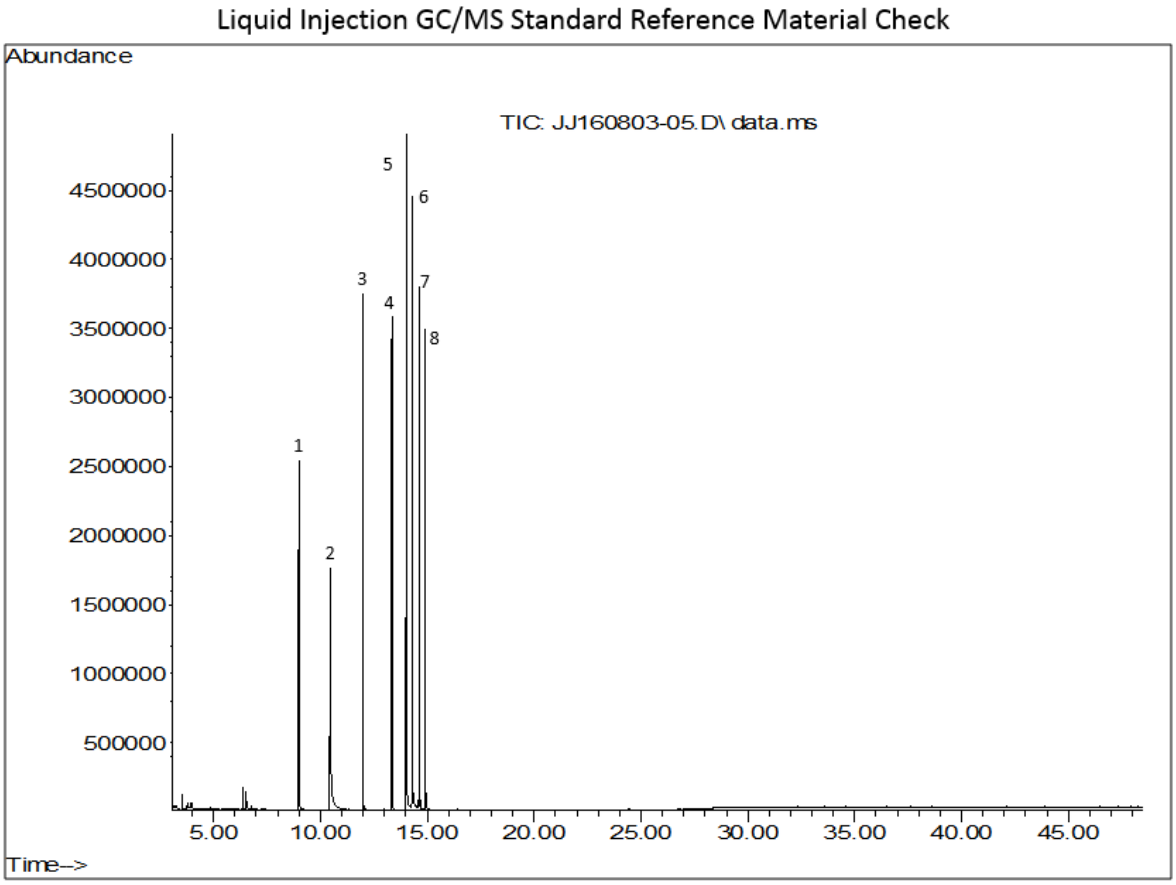
Liquid Injection GC/MS System Suitability and Performance Checks

Additional GC/MS System Suitability tests were conducted for ensuring accurate detection of analytes across the spectral range of interest and verify that the instrument was operating within normal parameters.

The standard reference material (SRM) is used to check the performance of the GC inlet, column, and mass spectrometer. It is a subset of the Grob test mixture for gas chromatography. All of the compounds were detected at their expected retention times with acceptable peak shapes and with the correct mass spectra.

The compounds in the SRM are nominally present at 10-30 µg/mL and are listed below:

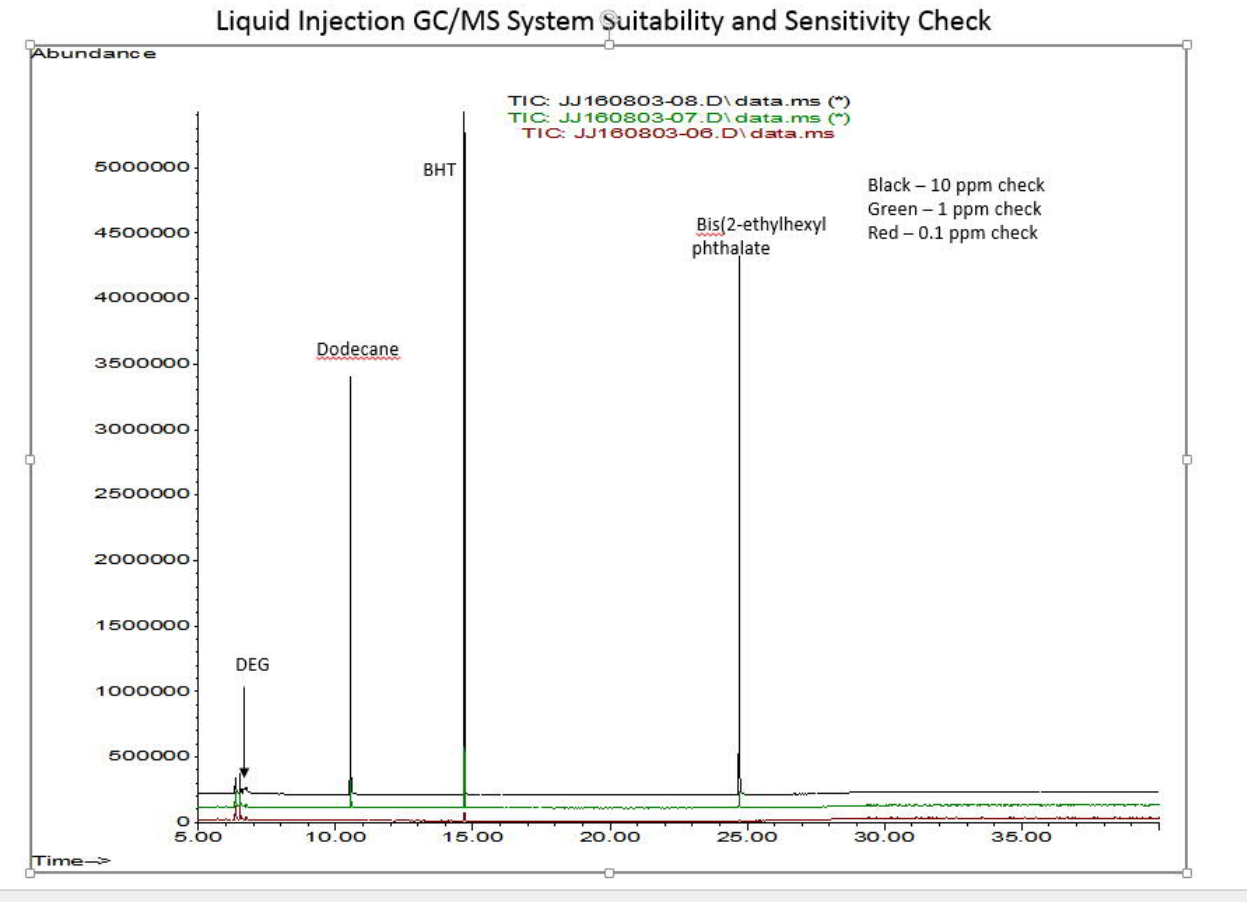
1. Undecane
2. 4-Chlorophenol
3. Tridecane
4. Tetradecane
5. 1-Dodecanamine
6. 1-Dodecanol
7. Pentadecane
8. Methyl dodecanoate



The response of the check standards indicate that the GC/MS system was operating within normal limits.

The system suitability check is intended to verify the ability of the GC/MS system to detect analytes with very different properties and ionization efficiencies. The check standards are blends of diethylene glycol, dodecane, BHT, and bis(2-ethylhexyl)phthalate (DEHP) in hexane prepared at 0.1 ppm, 1 ppm, and 10 ppm. All of the compounds were detected at 10 ppm; diethylene glycol (DEG) was not detected at 0.1 and 1 ppm, an expected result; dodecane was

detected in trace at 0.1 ppm while the others gave visible peaks and easily recognizable mass spectra at this level.



Extractable & Leachable Methods for GC/MS & LC/MS Analysis

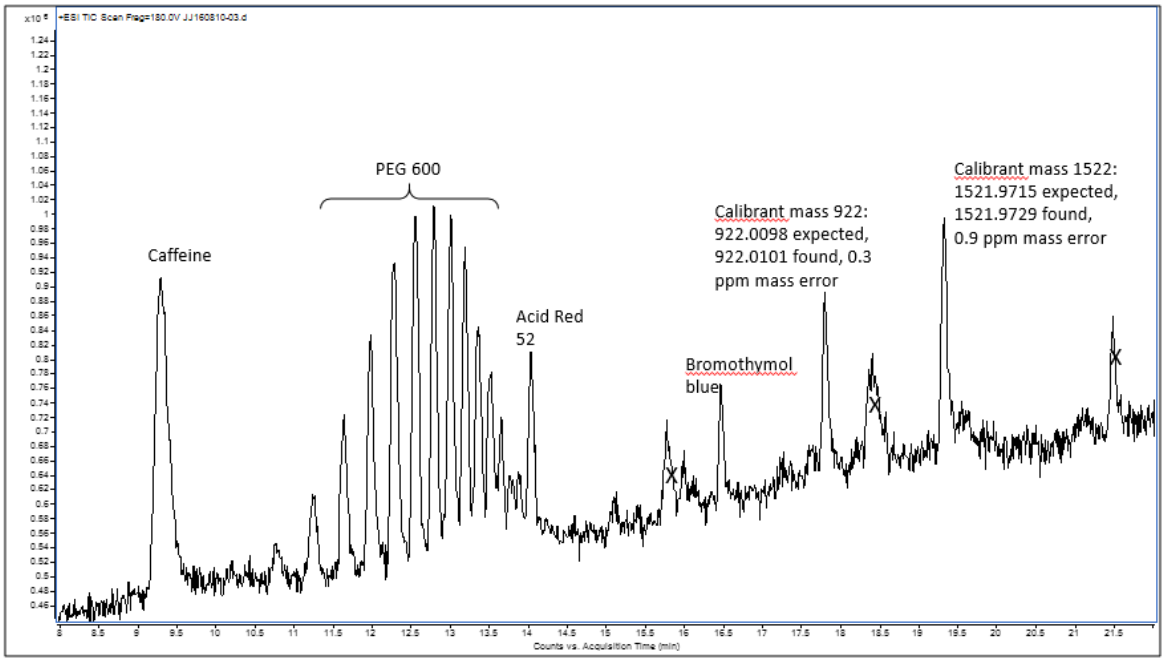
Extractable testing is performed to force any materials present in the polymers into the solvents through aggressive laboratory conditions. Leachable testing is performed to simulate more routine conditions experienced in the direct contact (e.g. aqueous based environments) of a material. Each of the polymers was extracted in two ways:

1. a heated ultrasonic extraction at 55 °C for 3 hours
2. a leachable extraction carried out at 40 °C for 72 hours in a shaking water bath.

Duplicate one-gram portions of the polymers were prepared in 10 mL each of hexane, isopropyl alcohol (IPA), and 55% water / 45% IPA. GC/MS analysis was carried out on the hexane and IPA extracts and LC/MS analysis was carried out on the IPA and 55/45 water/IPA extracts.

A standard reference material (SRM) is used to check the performance of the LC column, UV-Vis detector, and mass spectrometer. The test compounds were detected with appropriate peak shapes and correct mass spectra. Peaks noted with an "X" are system artifacts.

LC/MS Standard Reference Material ESI(+) System Check



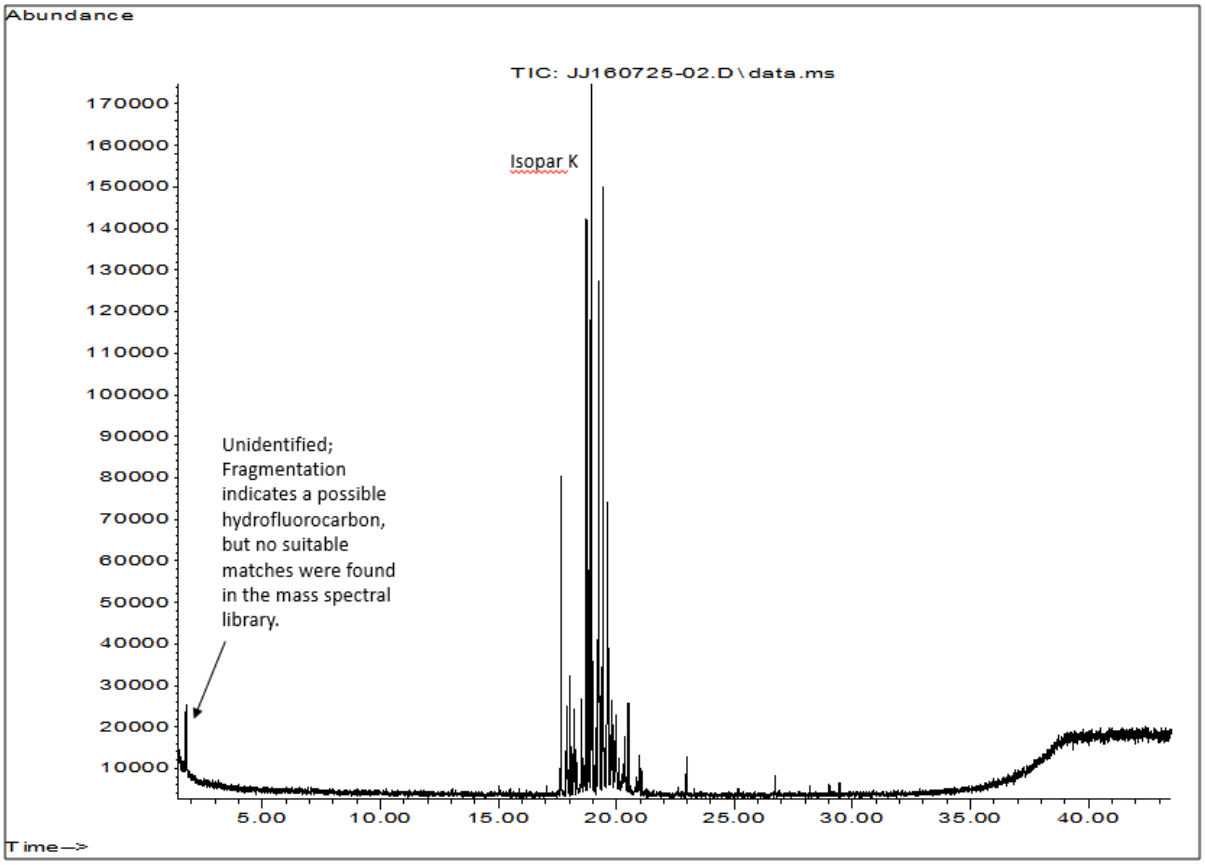
Results

The quantitative results of the tests are shown in the table below. Where quantification was needed, additional analytical methods were employed (e.g. a G/MS method for Isopar K capable down to less than 0.5 µg/g with the extraction conditions here was used). Details are included below in the Analysis section for reference.

Final PTFE Results		
Properties of interest	**Concentration**	**PLC Criterion**
*% oligomer	Not detected	< 2% wt/wt (20,000 ppm)
^residual monomers	Not detected	No Limit Established by OECD, 2009
low molecular weight leachables & extractables	#2 ppm	No Limit Established by OECD, 2009
*Polymers with potential health concern had an increased incidence of higher oligomer content that began at 5% for <1000 Da and 2% for <500 Da oligomeric content (OECD, 2009, page 24). The table lists the lower limit, 2%, which is 20,000 ppm.		
^The data set used by OECD (2009) to establish the PLC criteria was insufficient to establish a universal limit for all residual monomers, though residual monomer content was established as a PLC criteria (OECD, 2009). According to U.S. EPA's Safer Choice criteria (SCP, 2015), tetrafluoroethylene is a residual of concern, which is not allowed to be present in Safer Choice recognized products at 0.01% or higher. There is no specific limit on residual monomer in the PLC criteria (OECD, 2009).		
#Isopar K, an unavoidable ambient air contaminant adsorbed to the PTFE fine powder, was detected at ≤ 2ppm.		

The result of the headspace GC-MS analysis is shown in the figure below for a grade of PTFE.

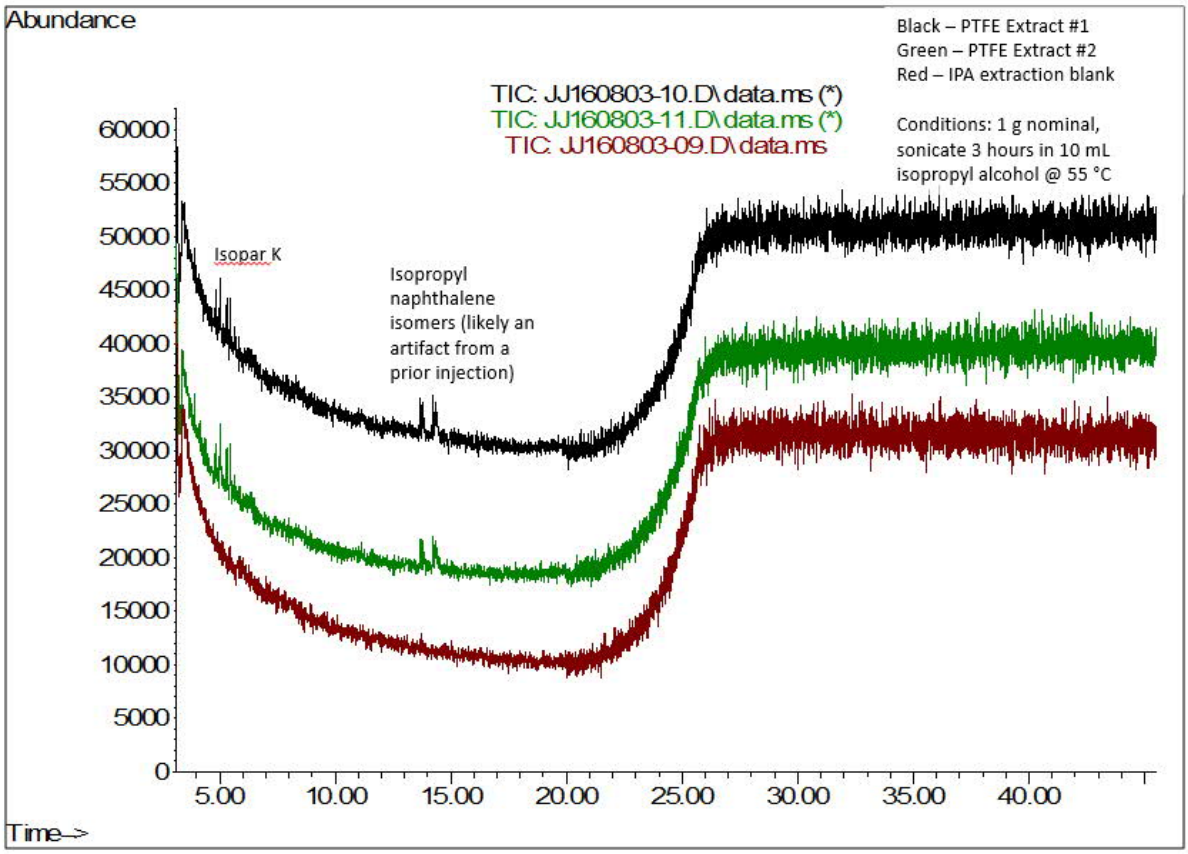
PTFE– Headspace GC/MS Results



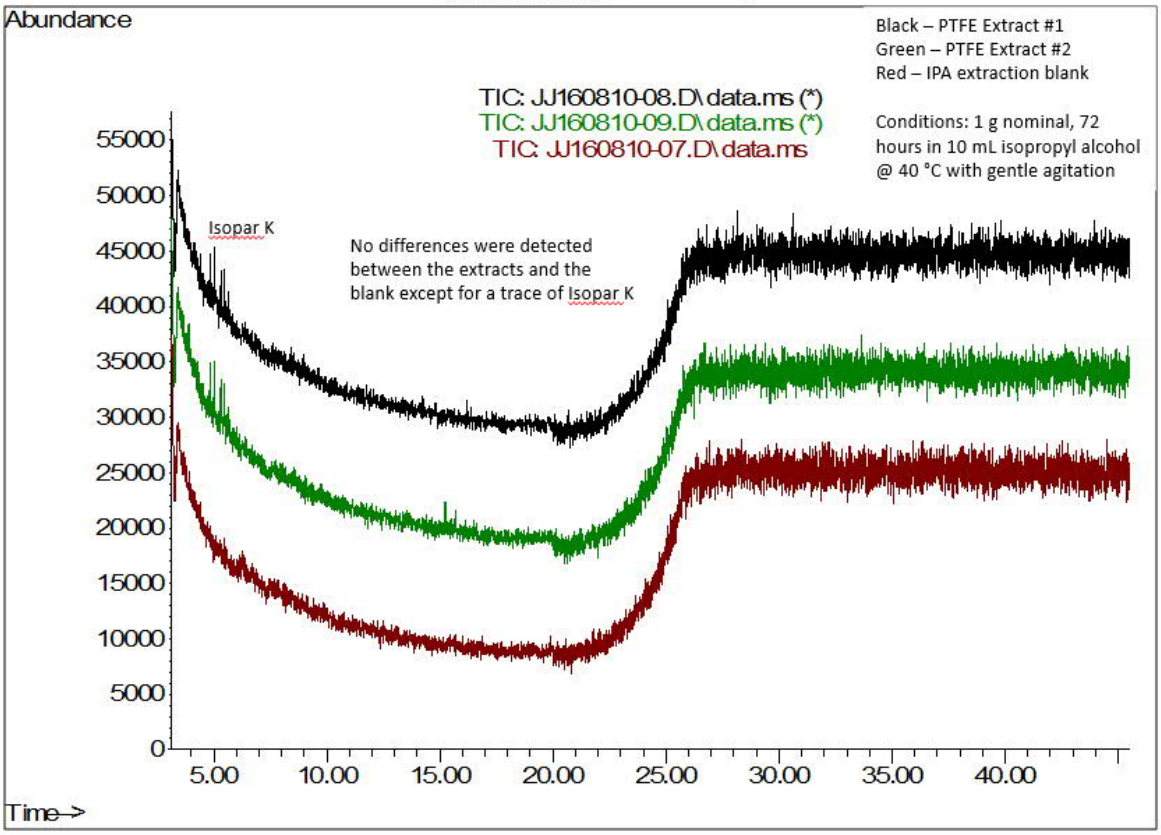
Interestingly, Isopar K was detected in the sample headspace as well as in the hexane and IPA extracts of the PTF powder. Isopar K is a well-known mineral spirit used in PTFE fine powder paste processing, not the PTFE resin manufacturing. It is used in the facility in which the resin sample was collected and is, therefore, most likely an airborne contaminant of the sample. A 2 ppm Isopar K standard was prepared and analyzed to confirm the positive identification. A 0.2 ppm standard was used to give a semi-quantitative estimate of Isopar K in the PTFE sample.

Liquid injection GC/MS results of the solvent extracts of the PTFE are shown in the figures below.

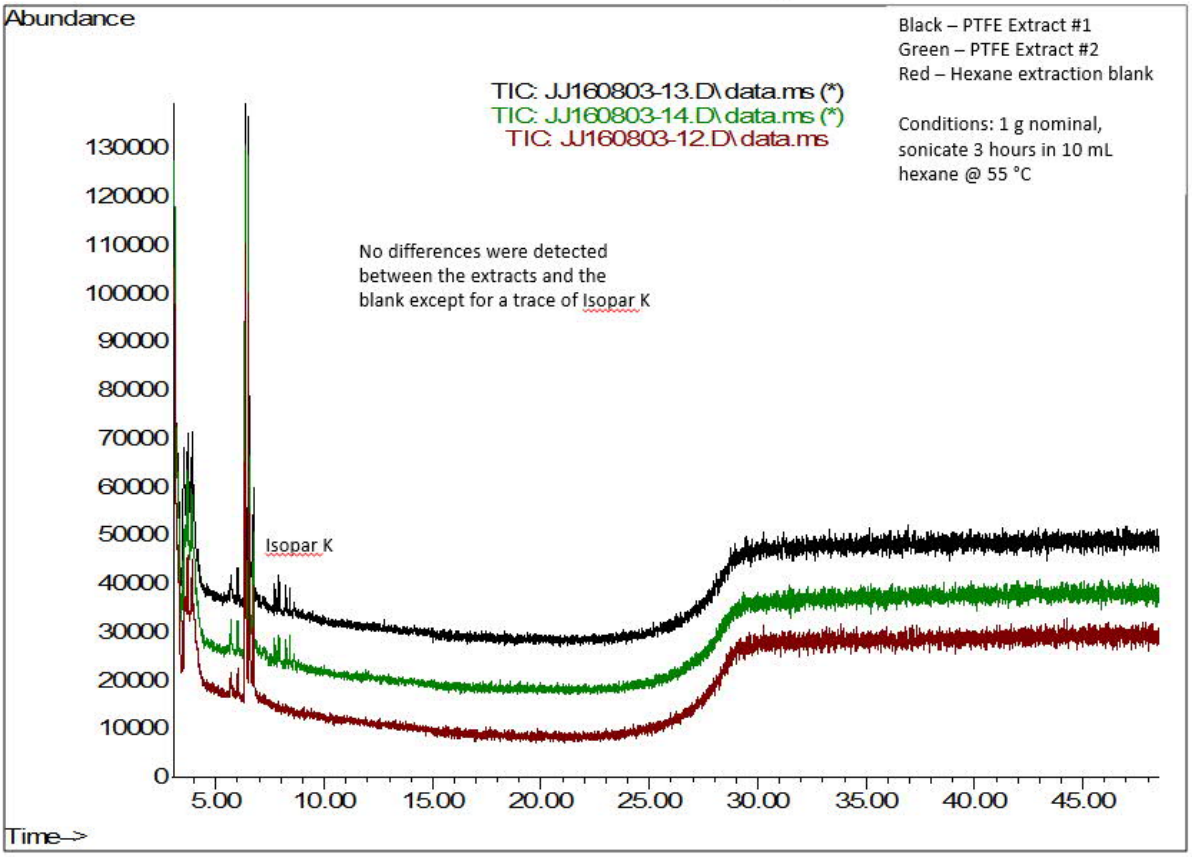
PTFE – Ultrasonic IPA Extraction – GC/MS Results



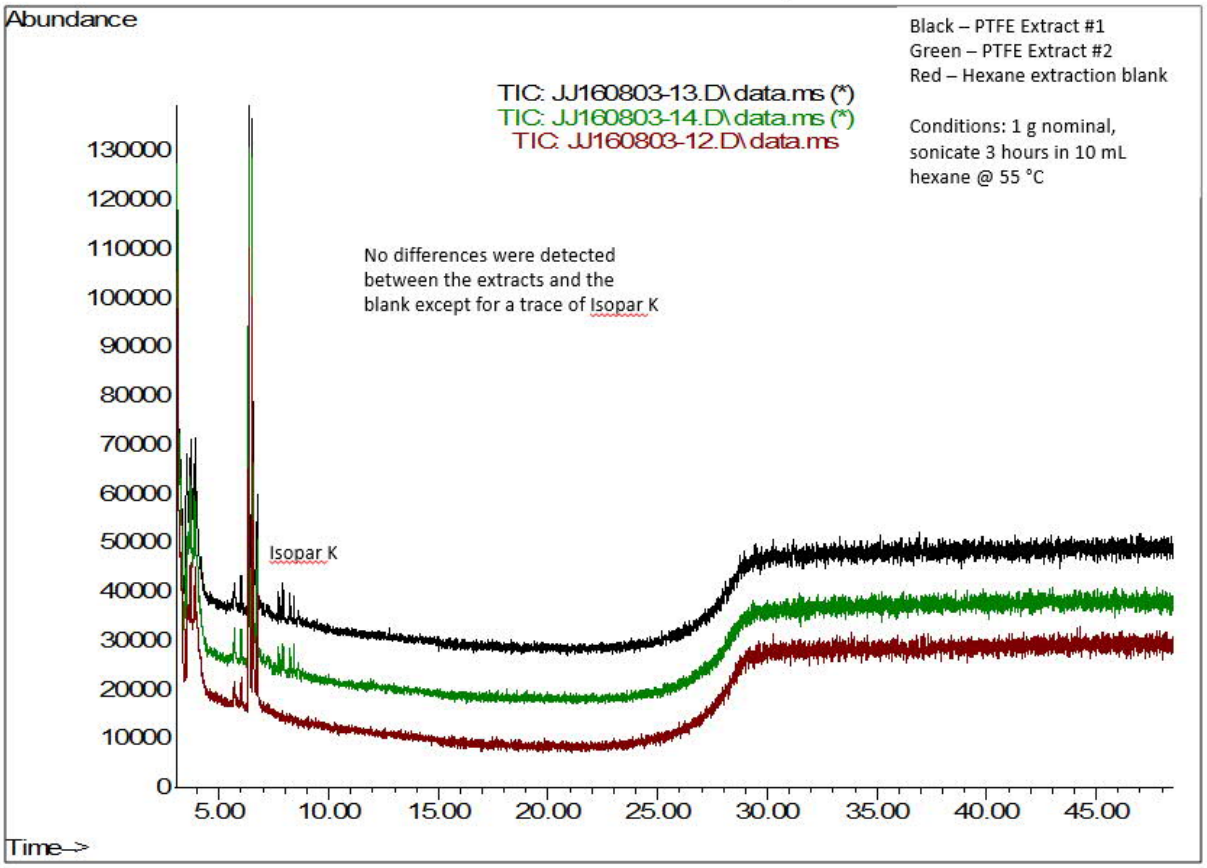
PTFE – 72 hour Extractables in IPA – GC/MS Results



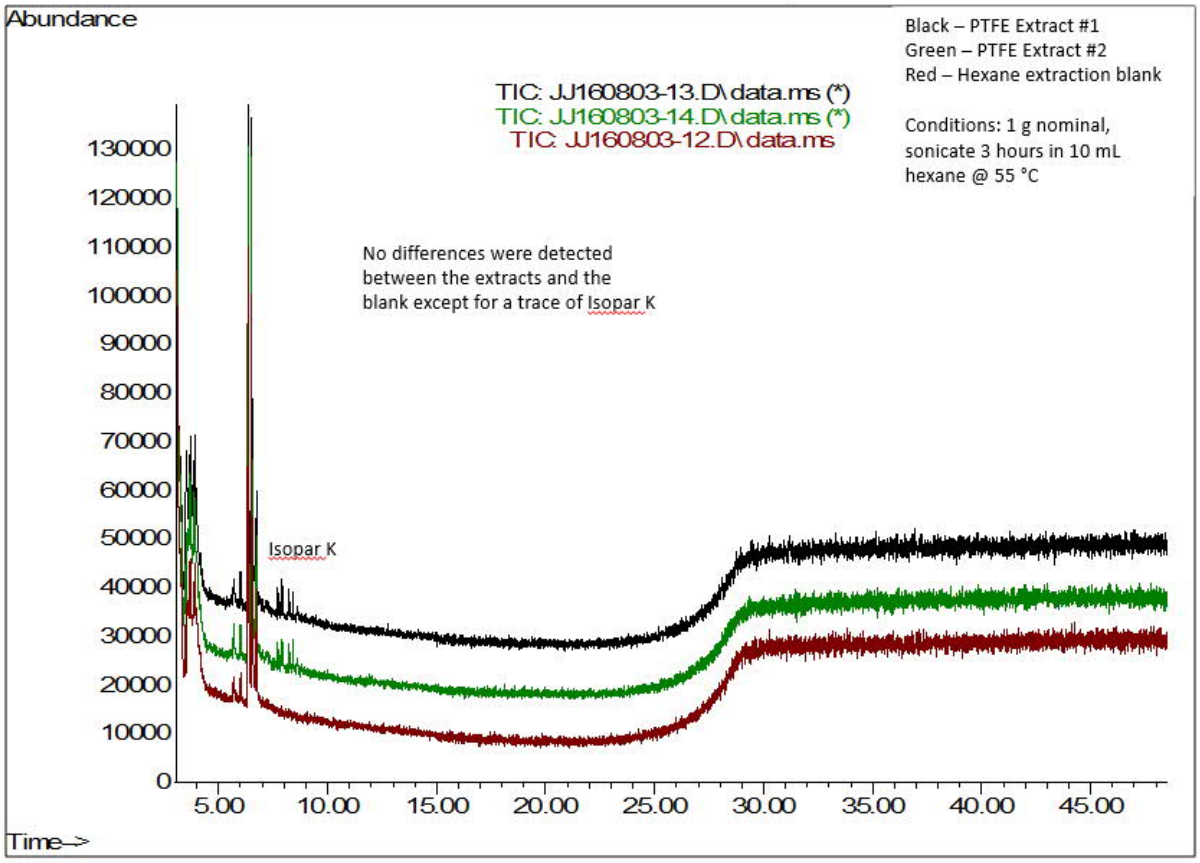
PTFE – Ultrasonic Hexane Extraction – GC/MS Results



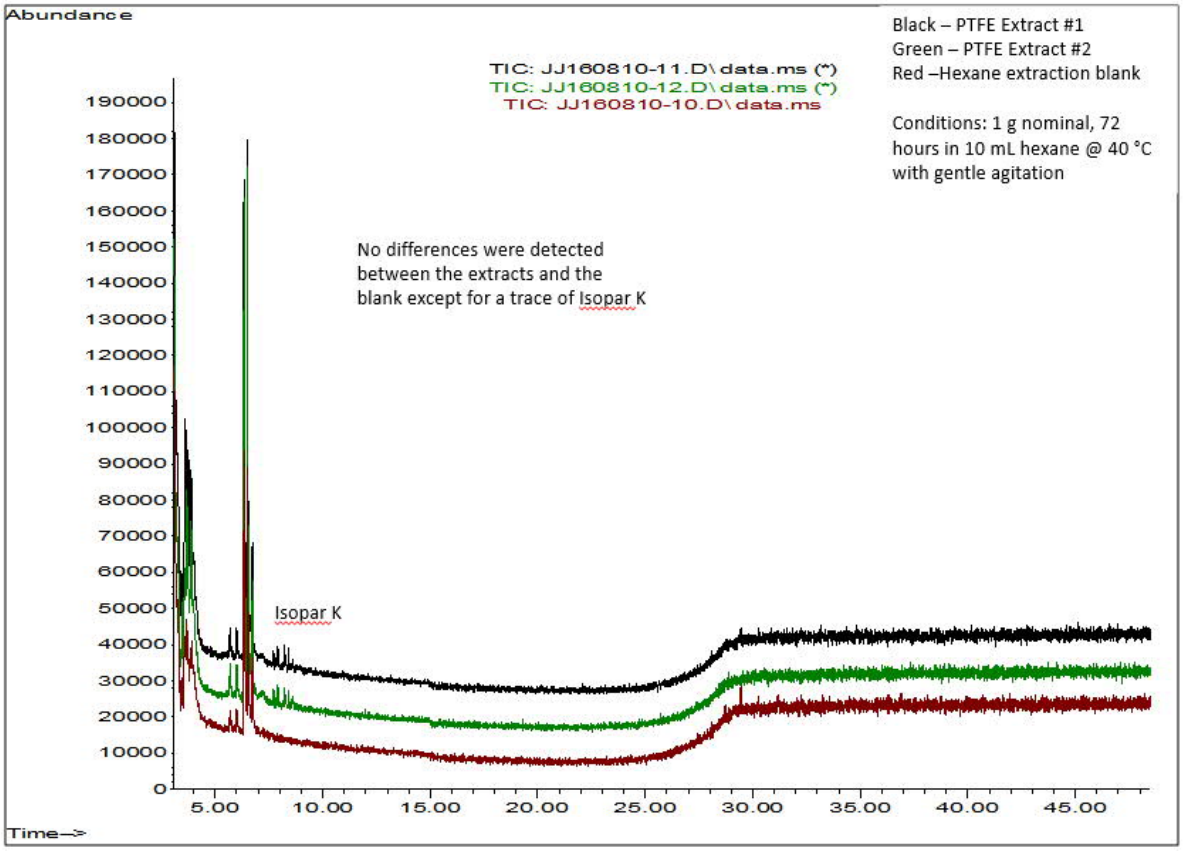
PTFE – Ultrasonic Hexane Extraction – GC/MS Results



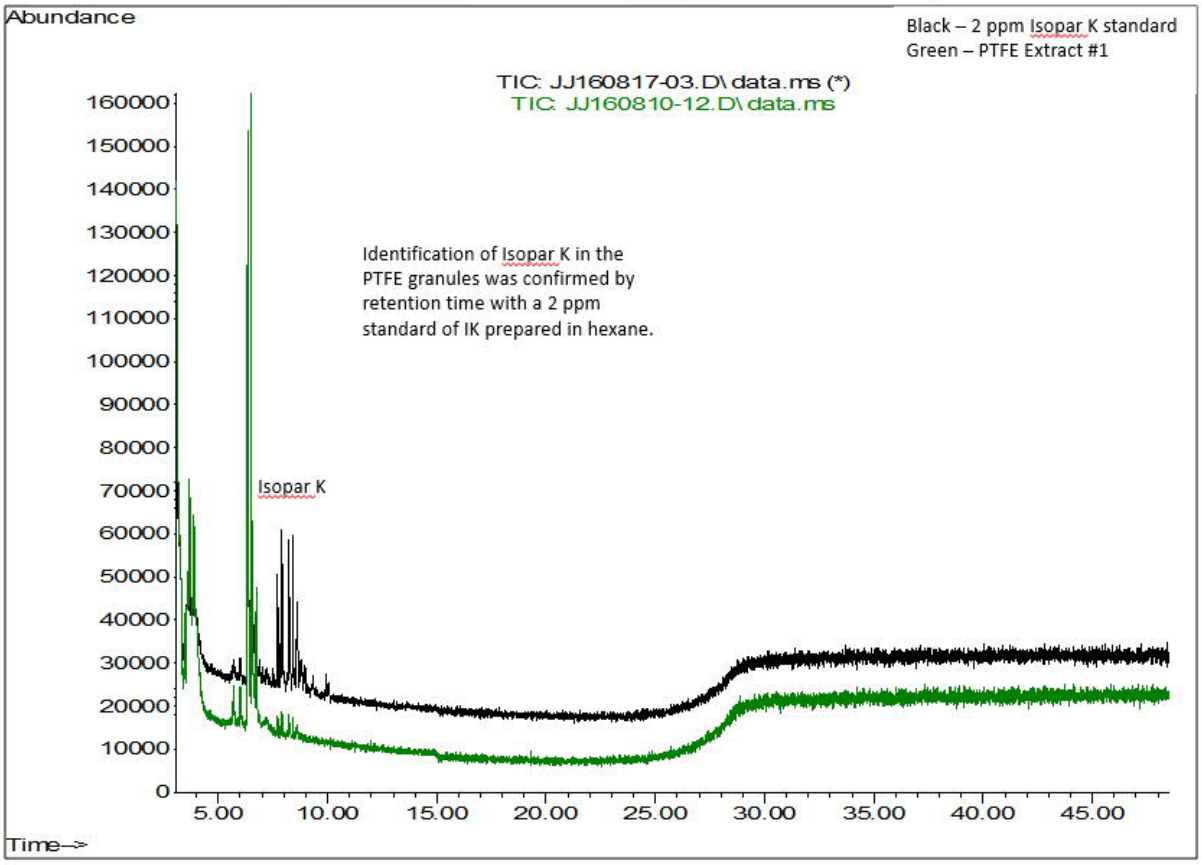
PTFE – Ultrasonic Hexane Extraction – GC/MS Results



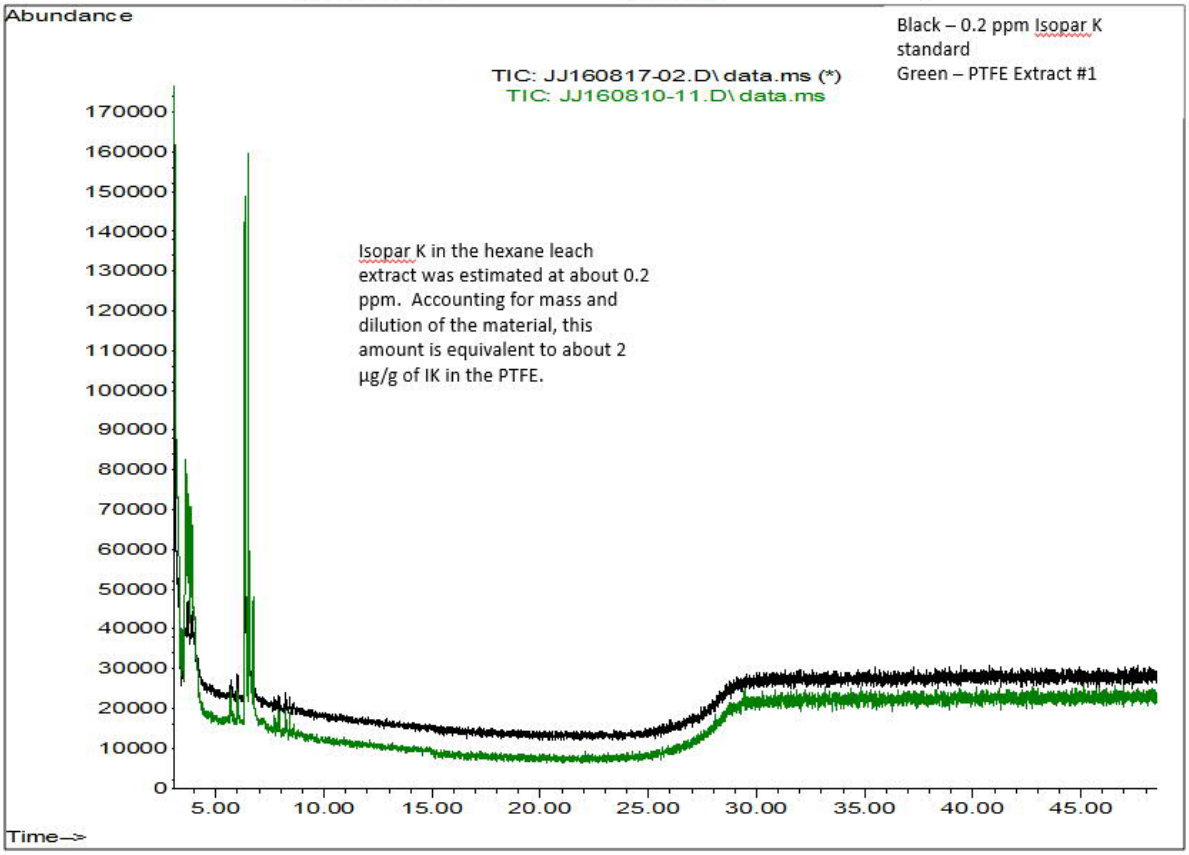
PTFE – 72 hour Extractables in Hexane – GC/MS Results



PTFE – 72 hour Extractables in Hexane vs. Isopar K Standard – GC/MS Results



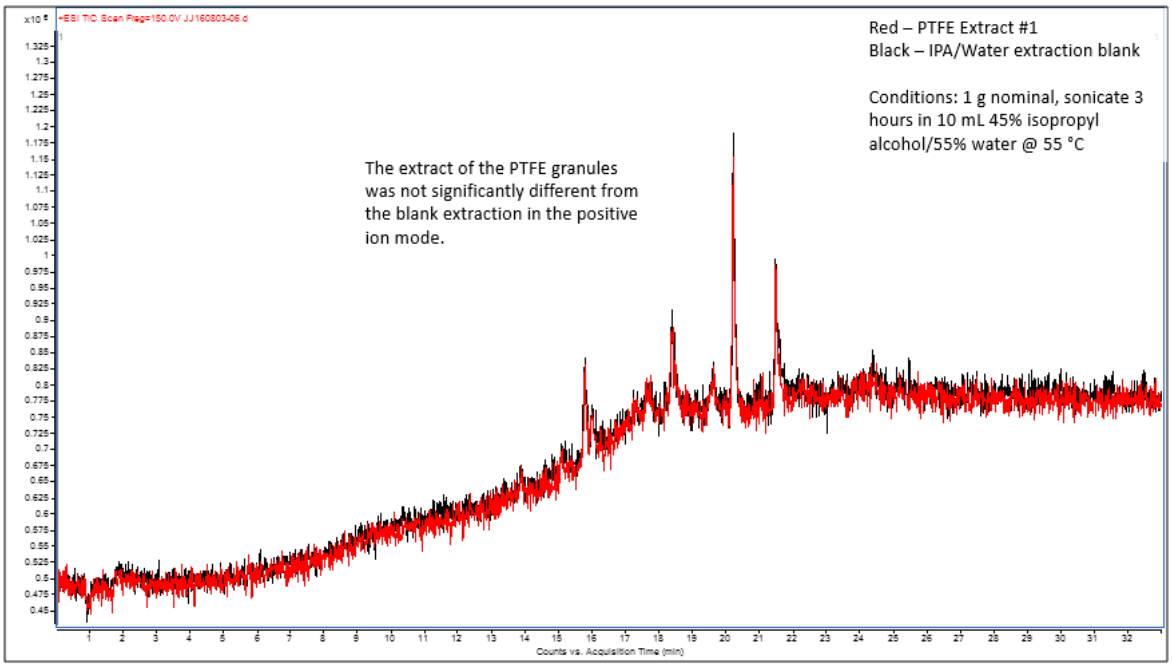
PTFE – 72 hour Extractables in Hexane vs. Isopar K Standard – GC/MS Results



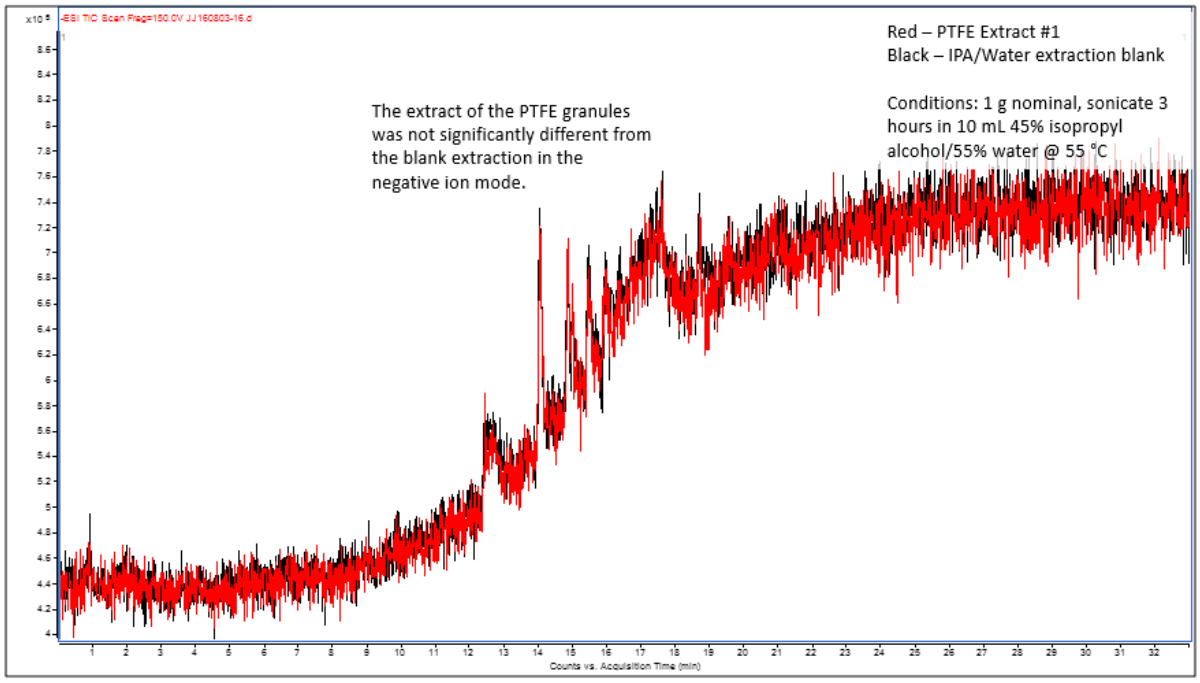
As shown in the GC/MS analysis for IPA and hexane extractions, there is no discernable difference between the PTFE samples and the blanks except for the trace of Isopar K in the extracts. The limit of quantitation for Isopar K is estimated to be < 1.5 µg/g in the PTFE by the method employed.

LC/MS analyses of the IPA and IPA/water extracts in both negative and positive ion modes show results similar to the GC/MS analyses in that the extracts are almost indistinguishable from the blank extractions. There is an erucamide peak present in both the samples and blanks from a persistent contaminant in the LC/MS system. No other peaks were detected in the analyses.

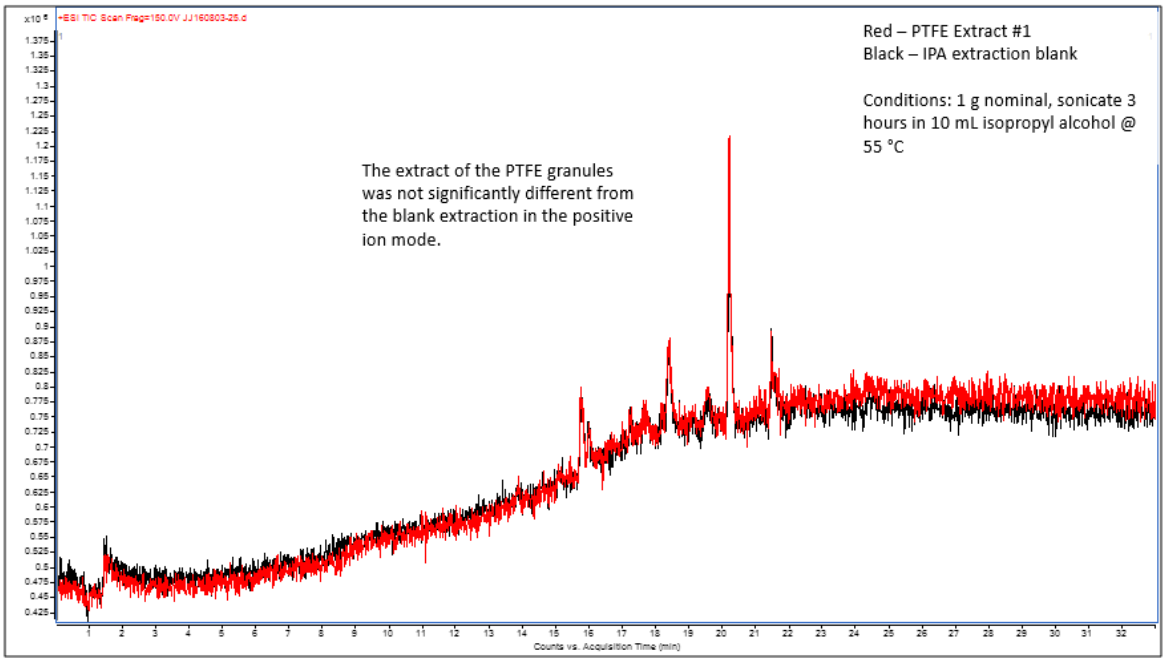
PTFE – Ultrasonic IPA/Water Extraction – ESI(+) LC/MS Results



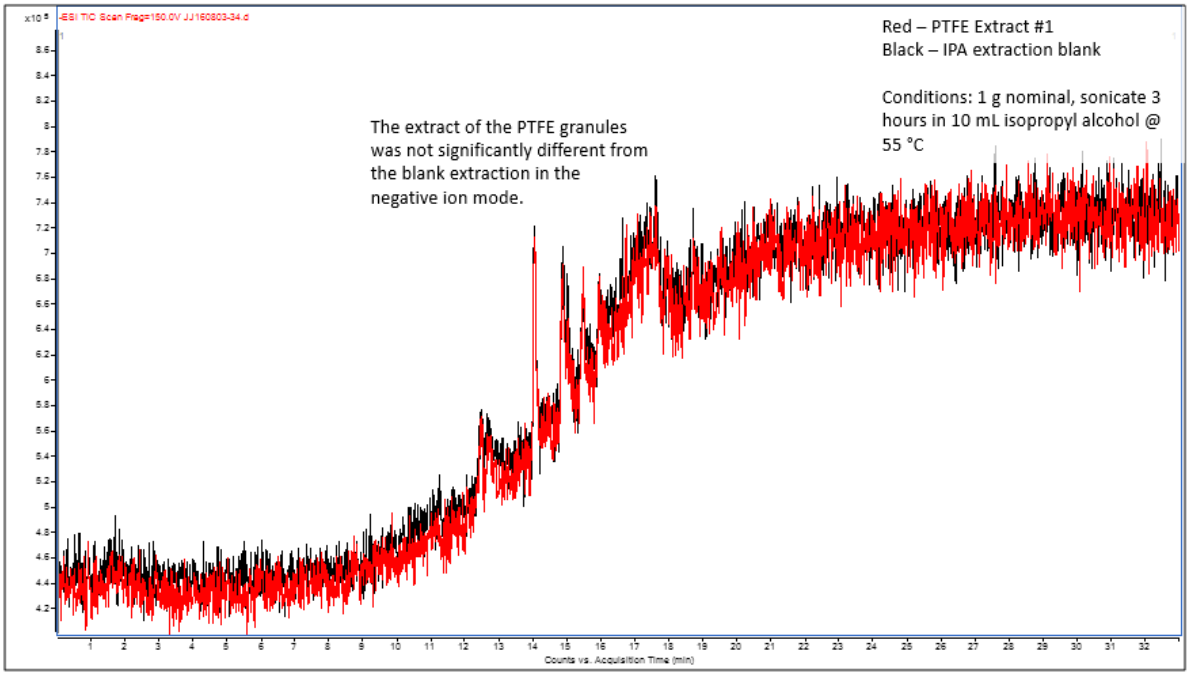
PTFE – Ultrasonic IPA/Water Extraction – ESI(-) LC/MS Results



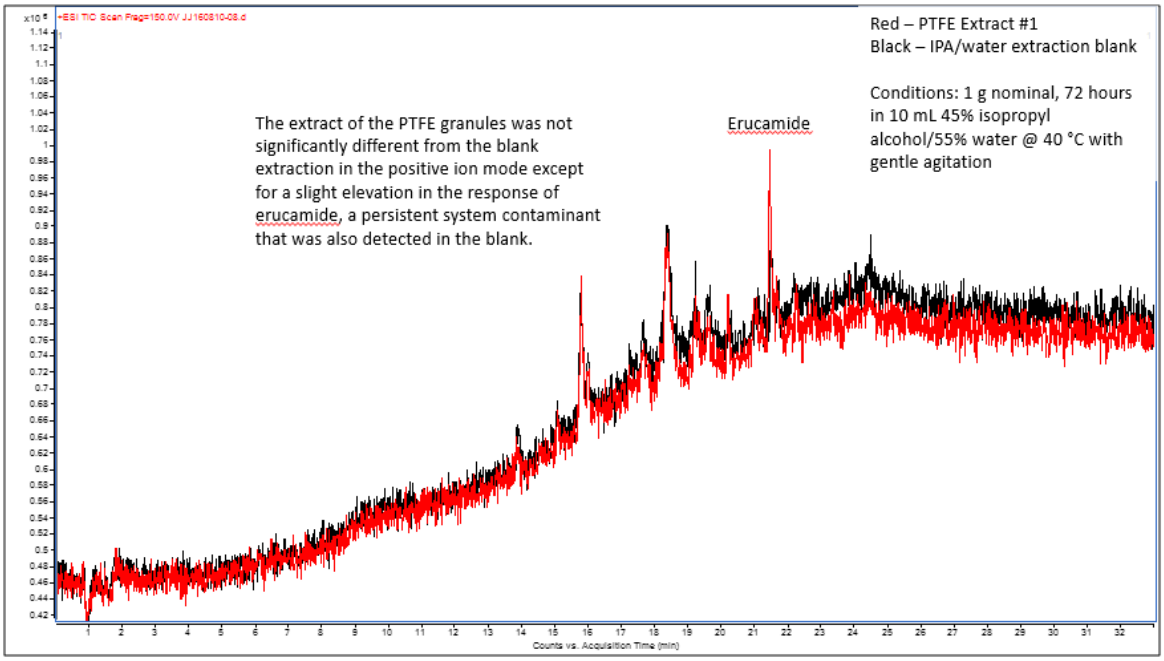
PTFE – Ultrasonic IPA Extraction – ESI(+) LC/MS Results



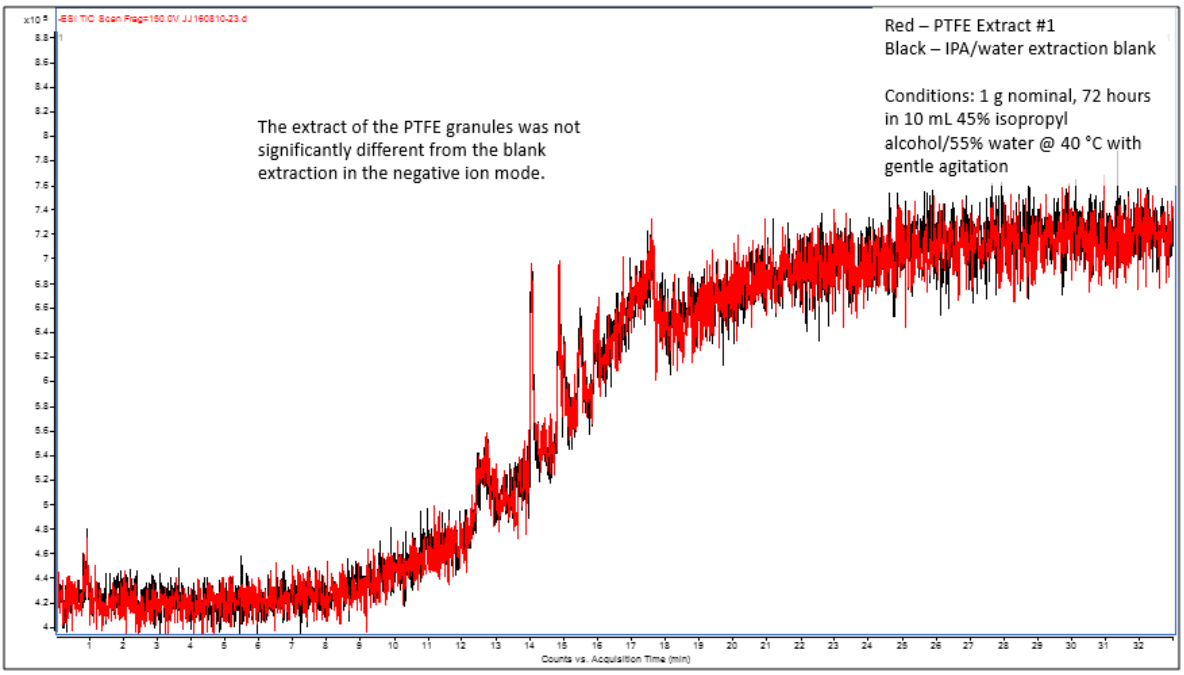
PTFE – Ultrasonic IPA Extraction – ESI(-) LC/MS Results



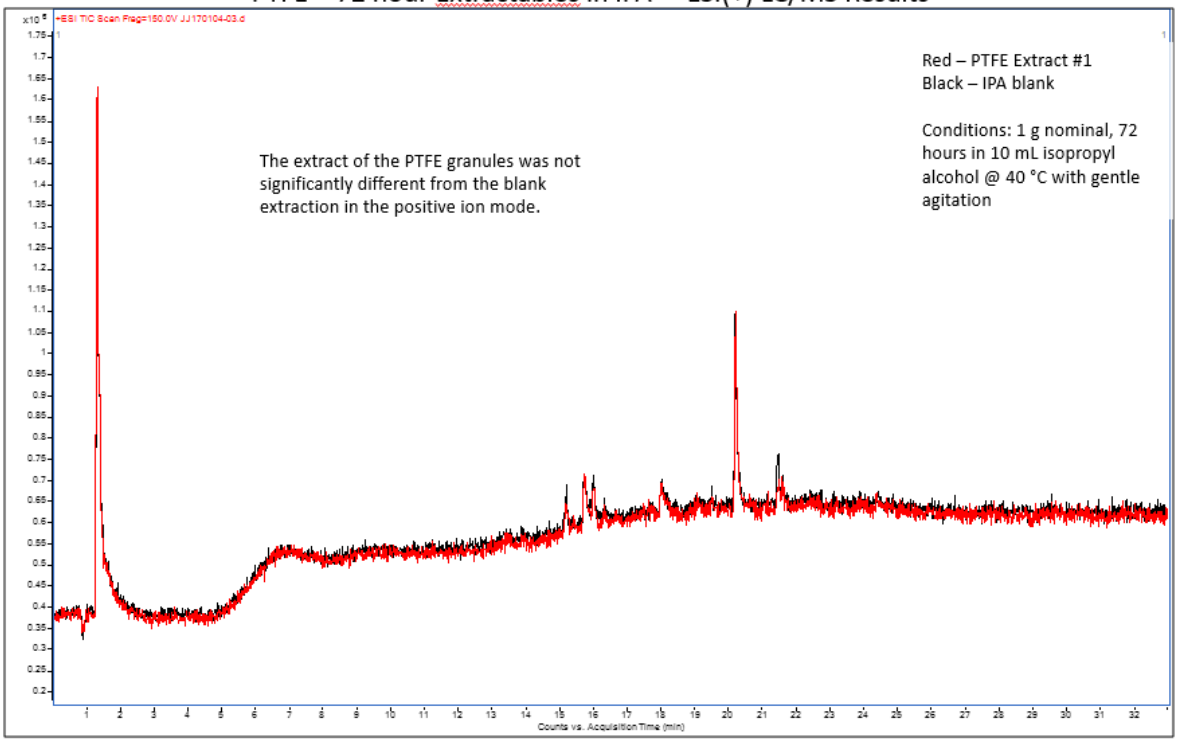
PTFE – 72 hour Extractables in IPA/Water – ESI(+) LC/MS Results



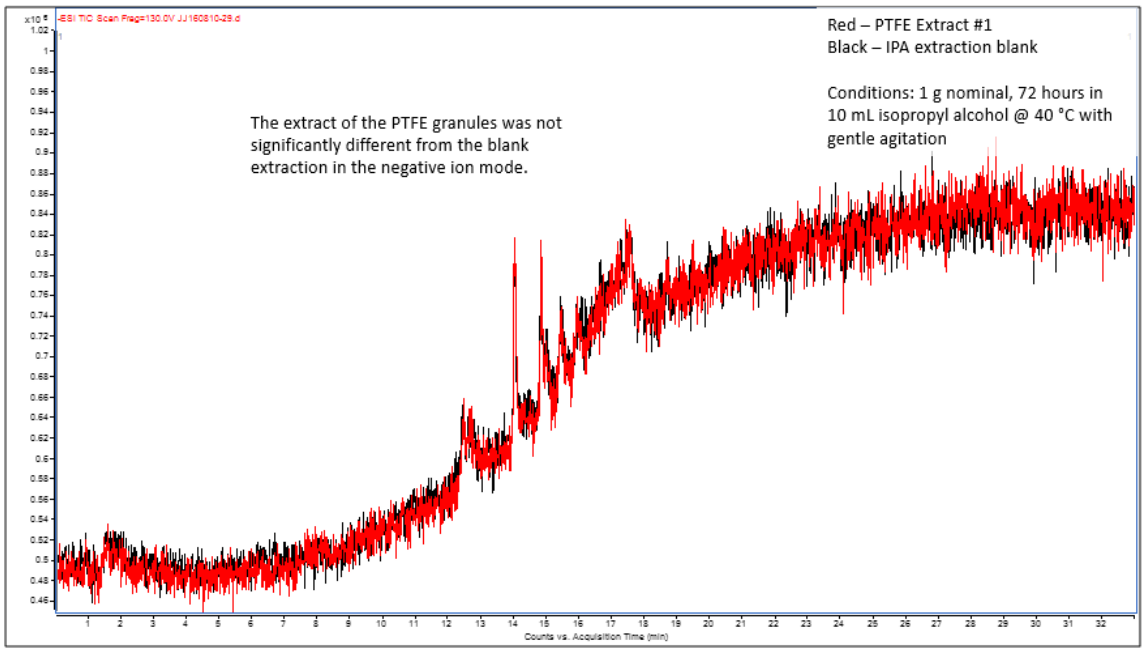
PTFE – 72 hour Extractables in IPA/Water – ESI(-) LC/MS Results



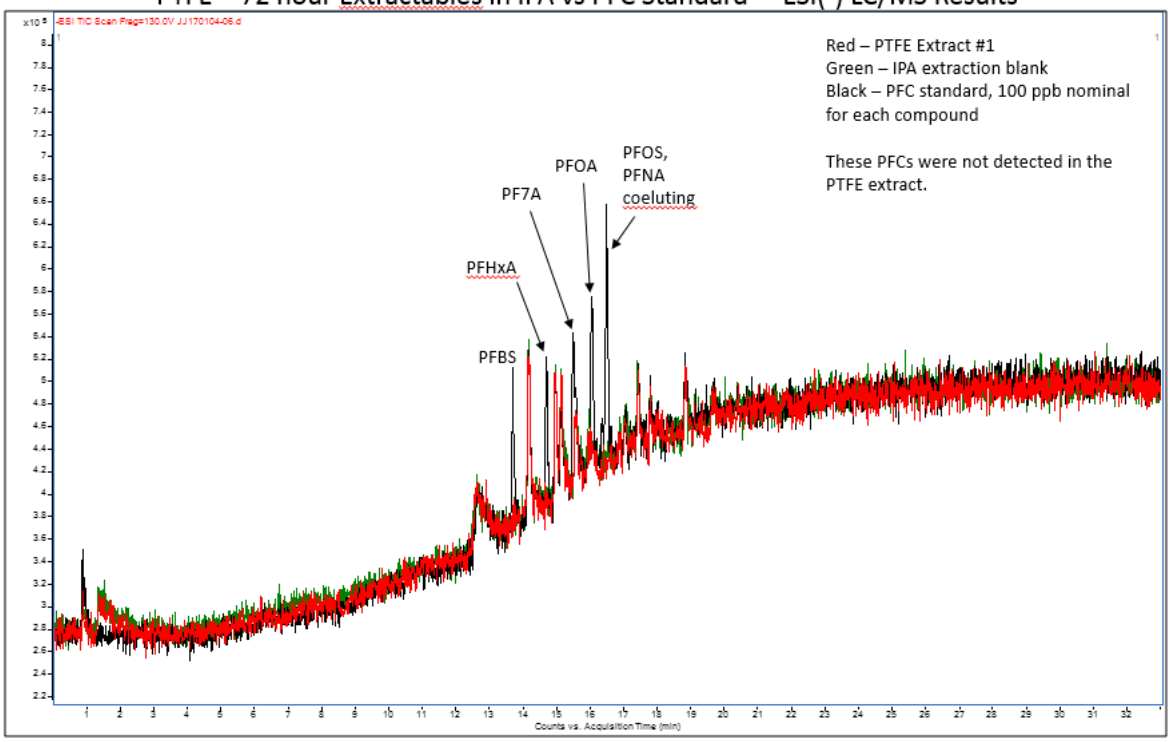
PTFE – 72 hour Extractables in IPA – ESI(+) LC/MS Results



PTFE – 72 hour Extractables in IPA – ESI(-) LC/MS Results



PTFE – 72 hour Extractables in IPA vs PFC Standard – ESI(-) LC/MS Results



The IPA extracts of the PTFE were also tested for the presence of possible common fluorinated surfactants. These compounds were not detected in the extracts.

Extractable/Leachable Analysis of PTFE

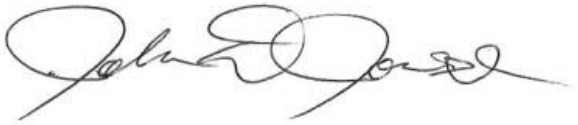
Sample ID	Nominal Sample Mass, g	Headspace GC/MS analysis	Ultrasonic IPA extraction GC/MS	Ultrasonic Hexane extraction GC/MS	Ultrasonic Extraction 55% H2O/45% IPA ESI(+) LC/MS	Ultrasonic Extraction 55% H2O / 45% IPA ESI(-) LC/MS	Ultrasonic Extraction IPA ESI(+) LC/MS	Ultrasonic Extraction IPA ESI(-) LC/MS	72 hr IPA Leachable extraction ESI(+) LC/MS	72 hr IPA Leachable extraction ESI(-) LC/MS	72 hr IPA Leachable extraction GC/MS	72 hr Hexane Leachable extraction GC/MS	72 hr 55% H2O / 45% IPA Leachable extraction ESI(+) LC/MS	72 hr 55% H2O / 45% IPA Leachable extraction ESI(-) LC/MS
PTFE Extract #1	1	trace[a c]	trace [a]	trace [a]	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	trace [a]	trace [a]	< 1 ppm [b]	< 1 ppm
PTFE Extract #2	1	trace[a c]	trace [a]	trace [a]	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	trace [a]	trace [a]	< 1 ppm [b]	< 1 ppm
Blank	1	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm	< 1 ppm

[a] - IK trace only from environmental contamination
[b] - slight erucamide peak, a persistent system contaminant that was also detected in the blank.
[c] - Hydrocarbon, fluorocarbon peaks but below identification threshold

ESI(+) indicates positive ion mode acquisition
ESI(-) indicates negative ion mode acquisition

Conclusions

By all extraction and analytical techniques employed in this study, oligomer and residual monomer were not detected. In addition, an ambient air contaminant (Isopar K) adsorbed to the PTFE fine powder was detected at ≤ 2 ppm. Therefore, PTFE meets the Polymer of Low Concern criterion of < 2% wt/wt or 20,000 ppm of extractable oligomers.



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