Integrated Environmental Assessment and Management — Volume 14, Number 3—pp. 316–334
Received: 26 September 2017 | Returned for Revision: 16 January 2018 | Accepted: 30 January 2018

Critical Review

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

Barbara J Henry,† Joseph P Carlin,† Jon A Hammerschmidt,† Robert C Buck,‡ L William Buxton,‡ Heidelore Fiedler,§ Jennifer Seed,‖ and Oscar Hernandez#*

†WL Gore & Associates, Elkton, Maryland, USA
‡Chemours Company, Wilmington, Delaware, USA
§MTM Research Centre School of Science and Technology, Örebro University, Örebro, Sweden
‖Risk Assessment Consultant, Alexandria, Virginia, USA
#Bergeson & Campbell, Washington, DC, USA

ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) are a group of fluorinated substances that are in the focus of researchers and regulators due to widespread presence in the environment and biota, including humans, of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). Fluoropolymers, high molecular weight polymers, have unique properties that constitute a distinct class within the PFAS group. Fluoropolymers have thermal, chemical, photochemical, hydrolytic, oxidative, and biological stability. They have negligible residual monomer and oligomer content and low to no leachables. Fluoropolymers are practically insoluble in water and not subject to long-range transport. With a molecular weight well over 100 000 Da, fluoropolymers cannot cross the cell membrane. Fluoropolymers are not bioavailable or bioaccumulative, as evidenced by toxicology studies on polytetrafluoroethylene (PTFE): acute and subchronic systemic toxicity, irritation, sensitization, local toxicity on implantation, cytotoxicity, in vitro and in vivo genotoxicity, hemolysis, complement activation, and thrombogenicity. Clinical studies of patients receiving permanently implanted PTFE cardiovascular medical devices demonstrate no chronic toxicity or carcinogenicity and no reproductive, developmental, or endocrine toxicity. This paper brings together fluoropolymer toxicity data, human clinical data, and physical, chemical, thermal, and biological data for review and assessment to show that fluoropolymers satisfy widely accepted assessment criteria to be considered as "polymers of low concern" (PLC). This review concludes that fluoropolymers are distinctly different from other polymeric and nonpolymeric PFAS and should be separated from them for hazard assessment or regulatory purposes. Grouping fluoropolymers with all classes of PFAS for "read across" or structure–activity relationship assessment is not scientifically appropriate. *Integr Environ Assess Manag* 2018;14:316–334. © 2018 The Authors. *Integrated Environmental Assessment and Management* published by Wiley Periodicals, Inc. on behalf of Society of Environmental Toxicology & Chemistry (SETAC)

Keywords: Fluoropolymer International regulation Polytetrafluoroethylene Polymer of low concern PFAS

INTRODUCTION

The carbon–fluorine (C–F) bond is the strongest bond between C and another atom, instilling substances that contain a majority of C–F bonds with stability, inertness, and persistence (Banks et al. 1994). Per- and polyfluoroalkyl substances (PFAS) are a large group of highly fluorinated synthetic substances with diverse properties that have been used in a wide variety of industrial and consumer applications since the 1950s (Buck et al. 2011). Within the group are distinct substances with different properties: polymers and nonpolymers; solids, liquids, and gases; persistent and nonpersistent substances; highly reactive and inert substances; mobile and insoluble substances; and toxic and nontoxic chemicals.

The PFAS are a large, diverse group of substances that, in some respects, challenge easy distinction for assessment and management. A clearer understanding of the origin of PFAS found in the environment and assessment of their properties is needed to be able to determine which classes of PFAS require management action. Per- and polyfluoroalkyl substances must be assessed taking into account their differences in chemical, physical, thermal, and biological properties. A single, globally harmonized system for PFAS classification has not yet been defined, resulting in a lack of distinction between PFAS. As regulatory frameworks continue to evolve, such as the Regulation (EC) No 1907/2006 of the European

This article includes online-only Supplemental Data.

* Address correspondence to [redacted]@wlgore.com

Published 9 February 2018 on wileyonlinelibrary.com/journal/ieam.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (RC 2006), more work is needed to distinguish classes of PFAS to ensure that regulations are appropriate in scope and proportionality.

Two long-chain nonpolymer perfluoroalkyl acids (PFAAs), perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) (both PFAS), found widespread in the environment and living systems, led to regulatory assessment and management efforts in several countries (Buck et al. 2011; OECD 2017; USEPA 2017a). Management actions to curtail manufacture of long-chain PFAAs, including PFOS and PFOA, and substances that may degrade to form them (also known as "precursors") have been taken (EC 2006; ECHA 2015; USEPA 2017a). Both PFOS and PFOA have been determined by regulators to be persistent, bioaccumulative, and toxic (PBT) substances (EC 2006; ECHA 2015). A current concern is the potential for certain side-chain polymer PFAS to degrade in the environment to PFOS and PFOA or lower homologues (Liu and Mejia-Avendaño 2013). In addition, PFOS (a nonpolymeric perfluoroalkyl substance) and related substances have been listed as persistent organic pollutants (POPs) under Annex B of the Stockholm Convention (UNEP 2009), and PFOA and other related substances (UNEP 2011), as well as perfluorohexane sulfonic acid (PFHxS) and related substances are being evaluated for listing (UNEP 2017a). As a result, questions about the health and environmental safety of PFAS as a group have been raised (Scheringer et al. 2014; Blum et al. 2015).

These findings have prompted expanded regulatory interest and concern about PFAS as a group, spurring additional assessment and management actions. The German Environment Agency, Umweltbundesamt (UBA), published a proposal to implement new assessment criteria and procedures for identifying persistent (P), mobile (M), and toxic (T) substances under the European Union REACH chemical registration process (UBA 2017). The UBA has concluded that PM and/or PMT substances constitute "an irreversible threat to sources of drinking water and the quality of drinking water" in Germany. This has prompted the designation of PFAS substances as posing an "equivalent level of concern" under Article 57(f) of REACH and thereby has prompted the need for a new paradigm for chemical assessment and authorization. The Swedish Chemicals Agency, Kemikalieinspektionen (KEMI), announced agreement among 37 government agencies and research institutions in the European Union (EU) to expand cooperation to reduce the risks and increase the knowledge of PFAS, thereby endorsing the UBA view on the hazards posed by all PFAS substances (KEMI Swedish Chemicals Agency 2016). The KEMI announcement indicated that all perfluoralkyl substances should be considered as extremely persistent in the environment, and many are water soluble, mobile in soil, and likely to contaminate waterways and drinking water supplies. A risk assessment report prepared by KEMI is forthcoming (ChemNews 2016).

The PFAS are divided into 2 primary categories: nonpolymers and polymers (Figure 1). Figure 1 shows that these 2 categories are divided into 5 classes of PFAS. The fluoropolymer class of PFAS is the focus of the present paper. The nonpolymer category includes perfluoroalkyl substances and polyfluoroalkyl substances. The polymer category includes fluoropolymers, perfluoropolyethers, and side-chain fluorinated polymers. Polymers generally have very different physical, chemical, and biological properties than do nonpolymer chemical substances of low molecular weight. Precise criteria that distinguish polymers from nonpolymers have been established (OECD 1993).

There are distinct differences between the 5 classes of PFAS. For example, PFOA, in the class nonpolymer perfluoroalkyl substances, is small, mobile, and persistent; has been assessed and determined to be a PBT chemical (ECHA 2015); and is in the final stage for recommendation of listing as a POP under the Stockholm Convention (UNEP 2017b). Regulatory and industry management actions on PFOA include precursor substances that may degrade to form PFOA (USEPA 2017a). An example in the class of nonpolymer polyfluorinated substances, 8:2 fluorotelomer alcohol, is known to degrade under environmentally relevant conditions to form PFOA (Liu and Mejia-Avendaño 2013). It is therefore a precursor substance to PFOA and subject to regulatory management (Liu and Mejia-Avendaño 2013). Polymers derived from 8:2 fluorotelomer alcohol are examples of the side-chain fluorinated polymers class. These polymers may degrade to form PFOA and therefore are subject to regulatory management. Lastly, perfluoropolyethers class is a complex class of PFAS, which contains O linkages in the polymer backbone.

In the present paper, we address fluoropolymers, a class of PFAS polymers (Figure 1). Fluoropolymers are high molecular weight solid plastics that have been studied extensively.

The present paper brings together fluoropolymer toxicity data, human clinical data, and physical, chemical, thermal, and biological data for review and assessment to show that fluoropolymers satisfy widely accepted assessment criteria to be considered as "polymers of low concern" (PLC) and to show that fluoropolymers are distinctly different enough from other classes of PFAS to not be grouped with them for hazard assessment or regulatory purposes.

PERFORMANCE CHARACTERISTICS AND USES OF FLUOROPOLYMERS

Since the discovery of polytetrafluoroethylene (PTFE) in 1938 (Plunkett 1987), the use of fluoropolymers has grown considerably to take advantage of their unique physical–chemical, thermal, and biological properties. The 4 fluoropolymers addressed in the present paper, polytetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), ethylene tetrafluoroethylene (ETFE), and tetrafluoroethylene copolymers with perfluoroalkyl vinyl ethers (e.g., perfluoroalkoxy polymer, PFA), accounted for approximately 70% to 75% of the world fluoropolymer consumption in 2015 (IHS 2016). The representative fluoropolymer discussed in the present paper, PTFE, made up 58% (by weight) of 2015 worldwide fluoropolymer consumption (IHS 2016). Fluoropolymers are high molecular weight plastics with unique properties attributable to the strong C–F bonds, the strongest bond between C and another atom, making

 © 2018 The Authors

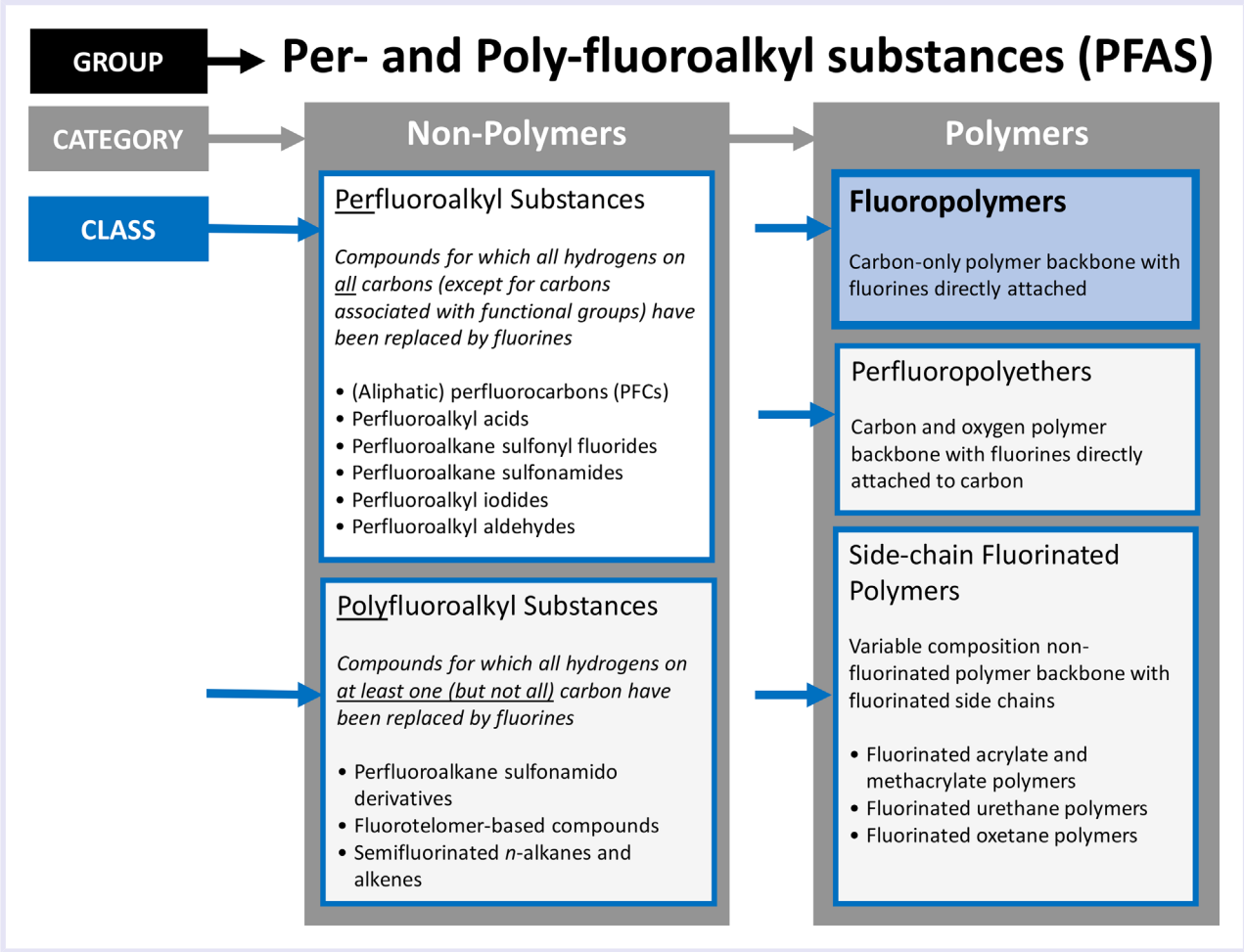


Figure 1. Per- and polyfluoroalkyl substances (PFAS).

them highly stable (Olabisi and Adewale 2015). Carbon atoms alone form the fluoropolymer backbone, each surrounded by an envelope of F atoms. Fluoropolymers are generally very high molecular weight (>100 000 Da); have high thermal, chemical, photochemical, oxidative, hydrolytic, and biological stability; have low flammability, neutral electrical charge, and resistance to degradation; have negligible residual monomers and low molecular weight oligomer content; have limited low molecular weight leachables; and have no reactive functional groups of concern (Gangal and Brothers 2015).

The unique properties of fluoropolymers include durability, mechanical strength, inertness, thermal stability in foreseeable use conditions, and resistance to chemical, biological, and physical degradation (Hougham et al. 1999). Table 1 shows performance characteristics required in various commercial fluoropolymer applications (Gangal and Brothers 2015; Dams and Hintzer 2016). For example, medical devices are successful when they are made from "biocompatible" biomaterials, that is, the material has the ability to perform with an appropriate host response in a specific situation (Williams 1987). The inertness of PTFE allows for its acceptance into the body. Moreover, PTFE flexibility and durability deliver mechanical integrity for the device's lifetime. The microstructure of PTFE can be modified to meet specific physiological needs (e.g., porous and open structure to facilitate tissue ingrowth), enhancing its utility in medical devices. In terms of end-use function, PTFE's inertness, physical properties (Ebnesajjad 2011), and the low level of residual monomer, oligomers, and low molecular weight leachables (Supplemental Data p 32–55) meet the requirements for low levels of contaminants and particulates in manufacturing environments essential for the food and beverage, pharmaceutical, medical, and semiconductor industries (Olabisi and Adewale 2015). Manufacturing applications requiring ultrapure high efficiency particulate air (HEPA) filtration use the finely controlled microporous PTFE membranes. Other components requiring a high degree of contamination control associated with patient care (e.g., dialysis tubing) also find the properties of PTFE essential. Durability in harsh conditions makes PTFE a superior material of choice in aerospace, environmental controls, energy production and storage, and electronics, as well as in technical apparel. The thermal stability of PTFE and FEP fluoropolymers provides improved fire safety risk over other polymers when used in plenums and structural

 DOI: 10.1002/ieam.4035 © 2018 The Authors

Table 1. Fluoropolymer functionality and commercial applications

	Fluoropolymer characteristics									
	Durable		Inert		Functional			Stable		
Commercial application	Mechanical strength	Low particulation	Resistance to chemicals	Nontoxic, biocompatible, biological degradation resistant	Flexibility	Friction resistance	Low dielectric constant	Low leachables	Resistance to photolysis, oxidation, hydrolysis	Stability
Aerospace	X	—	X	—	X	X	X	—	X	X
Automotive industry	X	—	X	—	X	X	X	—	X	x
Medical devices	X	X		X	X	X	—	X	X	X
Pharmaceutical manufacture	X	X	X	X	X	—	—	X	—	X
Consumer outdoor apparel	X	—		X	X	—	—	X	—	—
Technical clothing (military, firefighters, first responders, medical personnel)	X	—	X	X	X	X	—	X	X	X
Consumer electronics	X	—	X	—	X	X	X	—	X	X
Wireless communications	X	—	X	—	X	X	X	—	X	X
Satellite navigation systems	X	—	X	—	X	X	X	—	X	X
Semiconductor industry	—	X	X	—	—	—	X	X	—	—
Building construction	X	—	—	X	X	—	X	—	X	X
Energy production and storage	X	X	—	—	—	—	X	X	X	X
Food and beverage production	X	X	X	X	X	X	—	X	X	—
Food protection and packaging	X	X	X	X	X	—	—	X		—
Drinking water filtration	—	X	X	X	—	—	—	X	X	—
Environmental protection	—	X	X	X	—	—	—	X	X	X

© 2018 The Authors

geometries in aviation and standard building construction (Olabisi and Adewale 2015). In addition, chemical resistance to acids, bases, solvents, and chemical attack, combined with its unique conformable strength, makes PTFE an ideal coating for chemical process equipment, lining for process piping, sealants for gaskets and hoses, and fabricated parts for pumps, gears, and other mechanical parts that need this extreme resistance for functionality (Olabisi and Adewale 2015). The low dielectric constant of PTFE ensures the integrity of high speed–low signal loss systems as employed in the aerospace industry for flight controls, communication, and protection from extreme cold, moisture, and altitude changes (Dams and Hintzer 2016). These are lifesaving applications that are used in satellite systems for navigation, wireless communications, in-flight navigation, and shielding from electronic interference. Civil and military aviation depends on reliable performance of these systems for long service hours with minimal maintenance down times. In addition, PTFE provides reduced friction of moving parts (e.g., cable chains), preventing particulation during automated manufacturing in cleanroom environments (Dams and Hintzer 2016). This friction reduction is also uniquely beneficial in light load bearings, gears, cams, and other mechanical machine parts as well as in weaving fibers, yarns, and greases (Dams and Hintzer 2016).

ASSESSMENT OF POLYMERS

History

Prior to the mid-20th century, regulation of new chemical substances, mixtures, and polymers in general was very limited. National chemical inventories were created with notification requirements for new chemical substances, mixtures, and polymers. In the United States, new chemicals submitted to the US Environmental Protection Agency (USEPA) under the Toxic Substances Control Act (TSCA) (USC 1976) for addition to the US chemical inventory are reviewed for potential physical, chemical, and biological effects (environmental and mammalian), as well as for potential exposure to the environment and human populations. Over time, the USEPA regulatory scientists gained enough knowledge through the review of the thousands of data packages to develop tools to assist in the identification of physical–chemical properties, potential hazard, and potential exposure to assist in and expedite the chemical review and assessment process (Auer et al. 1990; Wagner et al. 1995; USEPA 2012; USEPA 2017b).

The predictive power and reliability of these approaches were tested and refined (Wagner et al. 1995). Over time, it was recognized that many of the physical–chemical properties, such as molecular weight, limit the ability of the chemical to cross the cell membrane and therefore limit its bioavailability. Further examination of general physical–chemical properties and their relationship to hazard potential of a given chemical led to the development of general principles or criteria for the identification of chemicals, including polymers, with low hazard potential. These criteria were developed for use by USEPA for its hazard evaluation of new polymers. The USEPA made this methodology available to the public to assist submitters interested in developing low hazard polymers (USEPA 1997a). In 1984, the USEPA published the polymer exemption rule to exempt low hazard polymers from certain notification requirements under the new chemicals program (USFR 1984). The polymer exemption rule incorporated the hazard criteria as part of the criteria to determine eligibility for exemption (USEPA 1997a, 2010).

The hazard criteria that support the PLC concept represent an extension of these principles and practices developed for (nonpolymeric) chemicals and rely heavily on physical–chemical properties that determine a chemical's bioavailability. In 1993, the 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 a polymer as a PLC to human health and the environment (OECD 1993). By 2007, the OECD Expert Group on Polymers agreed that, "Polymers of low concern are those deemed to have insignificant environmental and human health impacts" (OECD 2009). Thus, there was agreement within the OECD that polymeric chemicals meeting these criteria have a low hazard potential. However, the integration of the criteria into a risk management framework may differ from country to country according to their individual regulatory mandate.

In a recent report commissioned by the European Commission (EC) (BIO by Deloitte 2015), the following countries agreed on the polymer properties predictive of adverse human health and environmental hazard: Australia, Canada, China, Japan, South Korea, Philippines, New Zealand, Taiwan, and the United States. Further, the report identified the eligibility criteria to be considered a PLC with respect to potential for adverse impact on health and the environment. The report also compiled existing polymer regulations outside the EU and proposed alternative options for EU polymer registration, including defining a category of a PLC and grouping polymers into families.

The PLC criteria are described in the following section. Note that there are some policy components, such as elemental composition, as well as the physical–chemical attributes, in the PLC criteria.

POLYMER OF LOW CONCERN CRITERIA

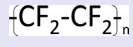
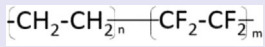
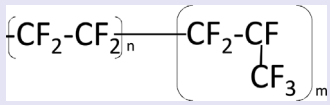
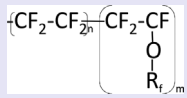
Here we describe each of the eligibility criteria for PLC and provide an assessment for the representative fluoropolymer PTFE. We will show that fluoropolymers, including PTFE, satisfy the widely accepted assessment criteria to be considered PLCs (Table 2) and therefore are considered to be of low hazard to human health and the environment.

Polymer composition

The polymer composition criterion requires structure and elemental composition of the polymer be described and identified (e.g., by Chemical Abstracts Service [CAS] number).

 DOI: 10.1002/ieam.4035 © 2018 The Authors

Table 2. Fluoropolymers and PLC criteria

	Fluoropolymers			
	PTFE	ETFE	FEP	PFA
Assessment criteria[a]	CAS 9002-84-0	CAS 25038-71-5, 68258-85-5	CAS 25067-11-2	CAS 26655-00-5, 31784-04-0
Structure				
Polymer composition (must have C, H, Si, S, F, Cl, Br, or I covalently bound to C)	Yes	Yes	Yes	Yes
Molecular weight	389 000–8 900 000[bc]	—	—	—
(M_n > 1000 Da and oligomer content < 1%)	520 000–45 000 000[bd]	530 000–1 200 000[ef]	241 000–575 000[eg]	200 000–450 000[eh]
Molecular weight distribution MW ÷ number average M_n (M_n and heterogeneity of MW distribution indicate if majority are >1000 or <1000 Da, which could penetrate the cell)	2.3[i]	1.4–2.7[f]	1.55–2.09[g]	1.7[j]
Wt % oligomer (see Figure 2) (<5% for <1000 Da oligomers, <2% for <500 Da oligomers)	Negligible	Negligible	Negligible	Negligible
Ionic character (cationic polymers associated with aquatic toxicity; polycationic with adverse human health effect)	Neutral	Neutral	Neutral	Neutral
RFGs[k] (some highly reactive functional groups associated with adverse human health and ecotoxicology effects, e.g., acrylates, isocyanates, anhydrides, aziridines)	<1 (see section *Reactive functional groups and RFG ratio to MW*)	<1 (see section *Reactive functional groups and RFG ratio to MW*)	<1 (see section *Reactive functional groups and RFG ratio to MW*)	<1 (see section *Reactive functional groups and RFG ratio to MW*)
FGEW[k] (typical value) (the lower the FGEW, the more reactive the polymer and the higher the potential for health and environmental impact)	$>10^5$–10^7	$>10^5$–10^6	$>10^5$	$>10^5$
Low molecular weight leachables (MW < 1000 Da able to enter cell)	<1 ppm	No active leachables by USP class VI[l] (121 °C)	No active leachables by USP class VI[l] (121 °C)	No active leachables by USP class VI[l] (121 °C)
Residual monomers (monomers have lower MW than polymers; typically more hazardous than polymers)	<1 ppm	<50 ppb	<50 ppb	<50 ppb
Ratio of residual monomers to molecular weight (typical value) (more low MW monomer content per mole increases bioavailability and hazard potential)	$\sim10^{-13}$ to 10^{-15}	$\sim10^{-13}$ to 10^{-14}	$\sim10^{-13}$	$\sim 10^{-13}$
Structural similarities to RFG of concern (increases potential risk of adverse effects)	None	None	None	None
Reference standard see also ISO 1133 (ISO 2011), ISO 12086 (ISO 2006)	ASTM D 4894 (ASTM 2015a), D 4895 (ASTM 2015b)	ASTM D 2116 (ASTM 2016a)	ASTM D 3159 (ASTM 2015c)	ASTM D 3307 (ASTM 2016b)

(*Continued*)

 © 2018 The Authors

Table 2. (*Continued*)

	Fluoropolymers			
	PTFE	ETFE	FEP	PFA
Assessment criteria[a]	CAS 9002-84-0	CAS 25038-71-5, 68258-85-5	CAS 25067-11-2	CAS 26655-00-5, 31784-04-0
Physical–chemical properties				
Water solubility (per USP 2011) (water solubility <10 mg/L showed generally low health concerns; 10 mL/L to 10000 mg/L had potential health concern)	Practically insoluble or insoluble (1×10^{-5} mg/L)	Practically insoluble or insoluble	Practically insoluble or insoluble	Practically insoluble or insoluble
Octanol–water partition coefficient, K_{OW} (higher K_{OW} associated with lipophilicity and a high potential to bioaccumulate or bioconcentrate)	NA	NA	NA	NA
Particle size (median mass aerodynamic diameter, MMAD, should be >5 μm)	100–500 μm (powders)	50–250 μm (powders)	50–250 μm (powders)	50–250 μm (powders)
	—	2–4 mm (pellets)	2–4 mm (pellets)	2–4 mm (pellets)
Stability				
Hydrolysis (breaking into M_n < 1000 Da increases hazard potential)	Stable	Stable	Stable	Stable
Light (hν) (breaking into M_n < 1 000 Da increases hazard potential)	Stable	Stable	Stable	Stable
Oxidation (breaking into M_n < 1000 Da increases hazard potential)	Stable	Stable	Stable	Stable
Biodegradation (aerobic and anaerobic) (breaking into M_n < 1000 Da increases hazard potential)	Stable	Stable	Stable	Stable
Thermal stability at normal foreseeable use maximum continuous temp (°C) (breaking into M_n < 1000 Da increases hazard potential)	260	150	200	260
Meets PLC criteria[a] (Y/N)	Yes	Yes	Yes	Yes

ASTM = American Society for Testing and Materials; CAS = Chemical Abstracts Service; Da = dalton; ETFE = ethylene tetrafluoroethylene; FEP = fluorinated ethylene propylene; FGEW = functional group equivalent weight; ISO = International Organization for Standardization; MMAD = median mass aerodynamic diameter; M_n = number average molecular weight; MW = molecular weight; MWD = molecular weight distribution; OECD = Organisation for Economic Co-operation and Development; PFA = perfluoroalkoxy polymer; PFPE = perfluoropolyether; PLC = polymer of low concern; PTFE = polytetrafluoroethylene; PVDF = polyvinylidene fluoride; PVF = polyvinyl fluoride; RFG = reactive functional groups; USEPA = US Environmental Protection Agency; USP = US Pharmacopeia.

[a]See OECD 2009 and BIO by Deloitte 2015 for details on characteristics of a "polymer of low concern."

[b]Molecular weight is number average molecular weight.

[c]Berry and Peterson 1951; Doban et al. 1956.

[d]Suwa et al. 1973.

[e]Molecular weight is weight average molecular weight.

[f]Tuminello et al. 1993.

[g]Tuminello 1989.

[h]Putnam 1986.

[i]Chu et al. 1989.

[j]Frick et al. 2012.

[k]For definition of reactive functional group; lists of low-, moderate-, and high-concern functional groups; and FGEW limits, see USEPA Polymer Exemption Guidance Manual (USEPA 1997b), BIO by Deloitte 2015 (p 191–192), and USEPA 2010. See Supplemental Data.

[l]In the USP<88> testing for "class VI," 2 g of the plastic (e.g., FEP, ETFE, or PFA) were extracted at 121 °C in: 1) 0.9% sodium chloride solution, 2) sesame oil, NF, 3) alcohol saline, and d) polyethylene glycol. The acute systemic toxicity and intracutaneous reactivity tests were conducted with those extracts. The intramuscular implantation was conducted with the plastic. Passing these 3 tests indicates that any leachables were not released in concentrations capable of causing these adverse effects, but does not result in a quantitative concentration of leachables. (See USP 2018.)

Note: The following are not addressed in this paper: PFPEs, side-chain fluorinated polymers, fluoroelastomers, PVF, and PVDF.

 DOI: 10.1002/ieam.4035 © 2018 The Authors

Molecular weight, number average molecular weight, MW distribution, and % oligomer <1000 Da

The number average molecular weight (M_n) and oligomer content are the most commonly used criteria for PLC assessment. The EU assessment report (BIO by Deloitte 2015) states that the "most potential health concern polymers have a number average molecular weight, Mn, < 1000 Da and oligomer content >1%." The higher the oligomeric content, the more likely a polymer is to be a health or ecotoxicological (OECD 2009, p 9). In fact, when comparing the potential health concern of polymers with varying percent oligomer content, "...the distribution of potential health concern polymers showed an increased incidence of higher oligomer content that began at 5% for <1000 Da and 2% for <500 Da oligomeric content" (OECD 2009, p 24).

Molecular weight (MW) is an important predictor of biological effect because very large molecules (>1000–10 000 Da) are too large to penetrate cell membranes (Supplemental Data in Beyer 1993, p 14). Because large molecular weight polymers cannot enter the cell, they cannot react with "target organs," such as the reproductive system, and are not bioavailable. "Therefore, as the M_n of a polymer increases, a reduced incidence of potential health concern effects might be expected" (OECD 2009, p 20).

An additional PLC consideration is the weight percent oligomers <1000 Da. Oligomers may be composed of, for example, dimers, trimmers, and tetramers, meaning they have 2-, 3-, and 4-monomer units, respectively. The EU report (BIO by Deloitte 2015) concluded that most potential health concern polymers have M_n of <1000 Da and oligomer content of >1%: "...the distribution of potential health concern polymers showed an increased incidence of higher oligomer content that began at 5% for <1000 Da and 2% for <500 Da oligomeric content" (OECD 2009, p 24).

Molecular weight distribution (MWD), also known as "polydispersity index," measures the heterogeneity of size of polymer molecules in a polymer. The MWD is an important parameter for predicting potential biological effects of polymers because although M_n may be a large value, low MW oligomers <1000 Da may be present, which could penetrate the cell.

Electrical charge (ionic character)

Electrical charge or ionic character can be anionic, cationic, amphoteric, or nonionic. Specifically, cationic polymers have been associated with aquatic toxicity (Auer et al. 1990; USEPA 1997a). Polycationic polymers that are water soluble or dispersible are of concern due to adverse human health (inhalation) effects (NICNAS 2016).

Reactive functional groups and RFG ratio to MW

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 (USFR 2012). Some highly reactive functional groups (or a high ratio of RFGs per mole) have been associated with adverse human health and ecotoxicology (e.g., acrylates, methacrylates, isocyanates, anhydrides, aziridines) (USEPA 2010). Methods have been demonstrated to identify the functional end groups on fluoropolymers (Pianca et al. 1999).

The functional group equivalent weight (FGEW) is used to determine if the RFGs in a polymer are substantially diluted by polymeric material to allow the polymer to be a PLC (USEPA 1997b). The FGEW of a polymer is defined as the ratio of the M_n to the number of functional groups in the polymer. It is the weight of a polymer that contains 1 formula weight of the functional group. The FGEW is used as an indication of the degree of reactivity of the polymer; the lower the FGEW, the more reactive the polymer and the higher the potential for health and environmental impact (OECD 2009, p 10).

Low MW leachables

Low MW leachables are chemical molecules, either inorganic or organic, that migrate (i.e., leach) out of the polymer. These could be residual monomers or oligomers resulting from incomplete polymerization processes, surface residues, or other chemicals used in the manufacturing processes (e.g., initiators, catalysts, chain transfer agents, surfactants). Chemical analysis, by techniques such as thermal gravimetric analysis (TGA), gas chromatography mass spectrometry (GC-MS), or liquid chromatography mass spectrometry (LC-MS) are used to identify low MW leachables.

Low MW leachables are critically important to the potential for a polymer to affect health and the environment, given that they may be able to migrate out of the polymer and cross cell membranes to potentially react with biomolecules. In a report to the EU (BIO by Deloitte 2015) the polymer policies for 10 countries around the world, including the EU REACH handling of polymers, were reviewed. The report concluded that "Polymers with <1% MW <1000 Da and low water extractivity are not able to cause systemic effects which are toxicologically or ecotoxicologically relevant."

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 2015) 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.

Particle size

Particle size is also a PLC criterion. Particles that are small enough to reach the deep lung upon inhalation are often associated with adverse health effects. Therefore, to qualify as a PLC, median mass aerodynamic diameter (MMAD) of the polymer particle size should be greater than 5 μm.

Structural and elemental composition

In the United States, Chemical Categories of Concern are the result of the review of new chemicals by the USEPA under the TSCA (see https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/chemical-categories-used-review-new). New chemicals submitted to the USEPA

 © 2018 The Authors

under the TSCA for addition to the US chemical inventory are reviewed for potential chemical, physical, and biological effects (environmental and mammalian). The USEPA groups Premanufacture Notice (PMN) chemicals with shared chemical and toxicological properties into categories, enabling both PMN submitters and USEPA reviewers to benefit from the accumulated data and past decisional precedents, allowing reviews to be facilitated. The categories describe the molecular structure, boundary conditions such as MW, equivalent weight, the log of the octanol–water partition coefficient, log P, or water solubility, and standard hazard (mammalian and ecological) and (environmental) fate tests to address concerns. The categories include chemicals for which sufficient history has been accumulated so that hazard concerns and testing recommendations vary little from chemical to chemical within the category. (See Supplemental Data, p 30, for details on USEPA's chemical categories.)

Elemental composition

The elemental composition is a factor in the assessment of the eligibility of polymers for reduced notification requirements. The exclusion of polymers under this step is not a conclusion of hazard but a determination that the elemental composition does not fall within the parameters of the polymer set under which this rule was formulated, and consequently, these polymers would have to follow the standard notification and review process. These elemental requirements differ across jurisdictions as covered in the report to the EU on global regulatory approaches to polymer assessment (BIO by Deloitte 2015). For example, in the EU under REACH it is proposed that polymers composed from among these elements, covalently bound to C, have reduced hazard: H, N, O, Si, S, F, Cl, Br, or I (BIO by Deloitte 2015). In contrast, the USEPA Polymer Exemption Rule states that a polymer is eligible for reduced agency review when it has at least 2 of the following elements: C, H, O, N, S, or Si (USFR 1995).

Water and lipid solubility and the octanol–water partition coefficient

Water solubility is the extent to which a compound will dissolve in water. According to the OECD 2009 meeting of the Expert Group on Polymers, polymers with "negligible" water solubility, or those described as "hydrophobic" have been represented with a water solubility of 0.000001 mg/L (1×10^{-6} mg/L; assigned arbitrarily) (OECD 2009). That is equivalent to 1 ppt, a very conservative definition.

Based on the data set studied, the OECD Expert Group on Polymers concluded "A higher proportion of polymers with intermediate water solubility values (10 mL/L–10 000 mg/L) displayed potential health concern. Polymers with water solubility <10 mg/L showed generally low health concerns" (OECD 2009, p 10). Although not a solubility metric, a polymer capable of absorbing its weight in water was associated with increased inhalation cancer risk in rats (OECD 2009).

The octanol–water partition coefficient (K_{OW}) is another criterion to assess chemicals and their environmental and health impact. The K_{OW} is a physical–chemical property at equilibrium to represent the lipophilic or hydrophilic nature of a chemical, the distribution of a compound in octanol, representing the lipophilic nature, to its solubility in water, representing the aqueous nature. The higher the K_{OW}, the more lipophilic the compound. Typically, a K_{OW} >5000 or a log K_{OW} >5 means high lipophilicity and, thus, a high potential to bioaccumulate or bioconcentrate. Numerous studies showed that K_{OW} was useful for correlating structural changes of drug chemicals with the change observed in some biological, biochemical, or toxic effect (LaGrega et al. 2010). It has been found to be related to water solubility, soil or sediment adsorption coefficients, and bioconcentration factors for aquatic life. According to the Stockholm Convention, a bioconcentration factor of >5000 and a log K_{OW} >5 is used as a criterion for bioaccumulation.

Stability

Stability is resistance to physical, chemical, or biological transformation. Loss of stability in the polymer breaks it down into smaller pieces, producing low MW species. As was previously described in the Polymer of Low Concern section under the *Molecular weight, number average molecular weight, MW distribution, and % oligomer <1000 Da* heading, molecules with M_n <1000 Da are capable of crossing cell membranes, making unstable polymers potentially hazardous to health and the environment.

Abiotic stability

Polymers are stable; monomers are not. Abiotic degradation may involve sunlight, water, or oxygen. Photochemical transformation is a reaction involving the radiation energy of sunlight (ultraviolet radiation) that may break a bond in a molecule to change it to another chemical entity. Hydrolytic degradation of polymers is another potential way to break the polymer bonds, creating smaller oligomers that may be bioavailable. Chemical oxidation is a reaction involving the loss of electrons from 1 atom to another.

Biotic stability: aerobic, anaerobic, and in vivo

Biotic stability is assessed by whether or not the polymer is degraded by microorganisms under oxygenated (aerobic) or anoxic (anaerobic) conditions; in vitro and in vivo stability studies demonstrate this. In vivo biodegradation involves the breaking of the polymer bonds by the action of bacteria, enzymes, and oxidants within the organism.

Thermal stability

Thermal stability of a polymer can be assessed when used as intended under normal, foreseeable use conditions or in extreme temperatures during disposal, such as by incineration. Thermal stability testing may involve Thermal Gravimetric Analysis (TGA), which determines mass loss over time and temperature of a test substance.

ASSESSMENT OF FLUOROPOLYMERS ACCORDING TO PLC CRITERIA

Characteristics of a PLC have been described in the preceding section. These criteria represent the combined

 DOI: 10.1002/ieam.4035 © 2018 The Authors

experience and knowledge of global regulatory authorities on factors demonstrated to be predictive of health and environmental hazards of polymers (OECD 2009; BIO by Deloitte 2015). Four fluoropolymers were assessed according to the PLC criteria. The results are summarized in Table 2, and an expanded discussion on specific criteria is provided in the remainder of this section.

Polymer composition

Fluoropolymers satisfy the PLC criterion of polymer composition. Polytetrafluoroethylene is a homopolymer of tetrafluoroethylene (TFE). Polytetrafluoroethylene can be a homopolymer (1 monomer) or it can be a modified homopolymer containing TFE widely and not more than 1% of another fluoromonomer (see ASTM 2015). Polytetrafluoroethylene contains only C and F having a $–CF_2–$ backbone terminated on both ends of each polymer chain with $–CF_3$. In unique cases, based on production method and ingredients used, commercial PTFE may have end groups that contain O, H, N, or S, depending on the initiator or chain transfer agent used in polymerization (Pianca et al. 1999). Polytetrafluoroethylene meets the compositional criterion to be a PLC.

Molecular weight, M_n, MWD, and % oligomer <1000

Fluoropolymers satisfy the PLC criterion of MW, M_n, MWD, and % oligomer <1000. Fluoropolymers are practically insoluble in water and all organic solvents. Therefore, standard MW methods are not applicable for fluoropolymers like PTFE and have been replaced by standardized indirect methods that use specific gravity and melt flow index to determine MW of PTFE and fluoropolymers (see Supplemental Data, p 27–28). Standard Specific Gravity (SSG) and Melt Flow Rate (MFR) are more conveniently and frequently used with fluoropolymers rather than rheological and dynamic light scattering methods (Chu et al. 1989; Starkweather and Wu 1989; Tuminello 1989; Tuminello et al. 1993). Polytetrafluoroethylene has an M_n of 500 000 to 9 000 000 Da (Berry and Peterson 1951; Doban et al. 1956; Suwa et al. 1973; Putnam 1986; Chu et al. 1989; Tuminello 1989; Tuminello et al. 1993; Frick et al. 2012). Therefore, PTFE, as a very high molecular weight polymer, cannot cross cell membranes, is not bioavailable, and cannot bioaccumulate or be toxic (see Supplemental Data, p 14). High molecular weight fluoropolymers, such as PTFE, therefore meet the PLC criterion for having MW that prevents them from entering the cells. Polytetrafluoroethylene has negligible (<<1%) oligomeric content (Starkweather and Wu 1989), as does FEP (Figure 2.) In summary, fluoropolymers are high molecular weight polymers with narrow MWD and negligible oligomer content.

Reactive functional groups and RFG ratio to MW

Fluoropolymers satisfy the PLC criterion of RFGs and RFG ratio to MW. Polytetrafluoroethylene most typically has a terminal $–CF_3$ group that is not an RFG. When this is not the case, the most common terminal group is –COOH, which is

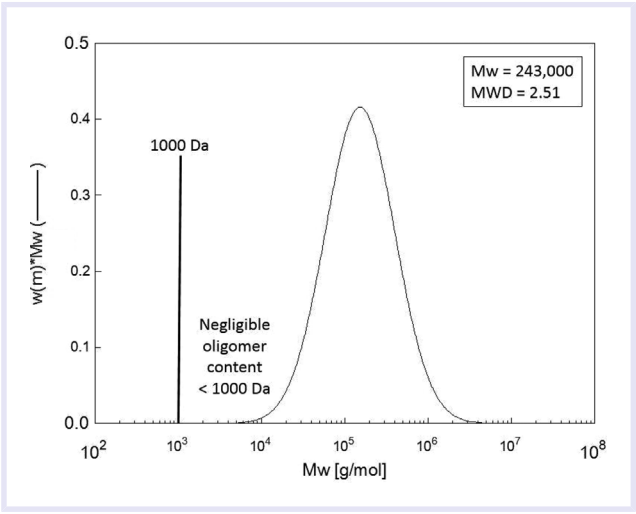


Figure 2. A fluorinated ethylene propylene (FEP) fluoropolymer molecular weight distribution from a rheological study. MW = molecular weight; MWD = molecular weight distribution.

categorized by the USEPA as a low-concern functional group. In unique cases, based on production method and ingredients used, PTFE may have end groups that may contain O, and H, N, or S, depending on the initiator or chain transfer agent used in polymerization. Fluoropolymers have a very high MW, which yields an FGEW on the order of 10^5 or more, well beyond the FGEW threshold of concern.

Low MW leachables

Fluoropolymers satisfy the PLC criterion of low MW leachables. Concentration of leachables from fluoropolymers, particularly PTFE "fine powder" (ASTM [2015] 4895-16 Type I fine powder definition), are typically very low (<1 ppm) (see Supplemental Data). This finding can be explained by the sensitivity of the PTFE polymerization reaction to contamination and is due to the postpolymerization processing steps aggressively exercised to wash out residuals and drive off volatiles. In order to achieve high MW polymerization of TFE, all traces of telogenic H- or Cl-bearing impurities must be removed (Ebnesajjad 2011; Supplemental Data).

In the analysis done on PTFE (see Supplemental Data, p 32), residual TFE monomer was not detected in PTFE resin by headspace GC-MS with a limit of detection of 1 ppm. In addition, publicly available analytical data from independent industry authorities demonstrate that TFE is not detected in finished articles made from fluoropolymers at detection limits down to about 0.01 ppm wt/wt (SPI 2005). Table 3 compares the molecular weight and the 8-h time weighted average (TWA) (American Conference of Governmental Industrial Hygienists [ACGIH], threshold limit value [TLV]), for monomers used to make fluoropolymers (ACGIH 2010). The TWAs are the exposure levels to which a worker could be exposed in an 8-h shift without adverse effects. The monomers have significantly lower MW, have lower TWAs, and are reactive. Note that the fluoropolymers are high MW, have no TWAs, and are inert. Table 3 illustrates that polymers do not have the same health hazards or MWs as their monomers.

 © 2018 The Authors

Table 3. Fluoropolymer and monomer molecular weight and TLV data

Substance	CAS Nr	Molecular weight	ACGIH TLV 8-h TWA
Monomer: TFE	116-14-3	100	2 ppm
Monomer: Ethylene	74-85-1	28	200 ppm
Monomer: HFP	116-15-4	150	0.1 ppm
Monomer: PPVE	1623-05-8	266	200 ppm (vendor limit)
Polymer: PTFE	9002-84-0	389 000–45 000 000	None
Polymer: ETFE	25038-71-5, 68258-85-5	530 000–1 200 000	None
Polymer: FEP	25067-11-2	241 000–575 000	None
Polymer: PFA	26655-00-5, 31784-04-0	200 000–450 000	None

ACGIH = American Conference of Governmental Industrial Hygienists (ACGIH 2010); CAS = Chemical Abstracts Service; ETFE = ethylene tetrafluoroethylene; FEP = fluorinated ethylene propylene; HFP = hexafluoropropene; PFA = perfluoroalkoxy polymer; PPVE = perfluoropropylvinyl ether; PTFE = polytetrafluoroethylene; TFE = tetrafluoroethylene; TLV= threshold limit value; TWA = time weighted average.

Elemental composition

Fluoropolymers meet the widely accepted elemental composition criterion (BIO by Deloitte 2015). The USEPA, in updating its Polymer Exemption Rule, which applies to new polymers only, changed some review procedures to address certain side-chain fluorinated polymers that may degrade into small, mobile, and persistent substances (USFR 2010). This has contributed to confusion regarding the assessment of fluoropolymers. The exclusion of polymers under this step is not a conclusion of hazard, but a determination that the elemental composition does not fall within the parameters of the polymer set under which this rule was formulated, and consequently, these polymers would have to follow the standard notification and review process.

When USEPA updated the polymer exemption rule in 2010, the agency excluded polymers containing $–CF_3$ or larger chains that are covalently bound to C. The agency's rationale for the change was "...because the Agency has receiving information which suggests that polymers containing PFAS (perfluoroalkyl sulfonates) or PFAC (perfluoroalkyl carboxylates) may degrade and release fluorochemical residual compounds in the environment. Once released, PFAS or PFAC are expected to persist in the environment, may bioaccumulate, and may be highly toxic..." (USFR 2006).

Although USEPA recognized that PFAS and PFAC chemicals with longer C chain lengths (C7 and longer) may be of greater concern, it stated that there is insufficient evidence at this time, however, to definitively establish a lower C chain length limit to meet the "will not present an unreasonable risk" finding, which is the determination necessary to support an exemption under section 5(h)(4) of TSCA. The USEPA believes that it is possible for polymers containing these other types of perfluoroalkyl moieties to also degrade over time in the environment, thereby releasing the perfluoroalkyl moiety (USFR 2006).

The updated USEPA polymer exemption definition in 2010, summarized in the Objective and Rationale section for the Final Rule, may imply that new fluoropolymers with pendant or terminal –CF3 groups, such as FEP, do not meet the polymer exemption eligibility for reduced PMN reporting (USFR 2010). However, the summary definition in USFR (2010) lacks critical context found in the preamble to the Final Rule, which elaborates the conditions that would be necessary to exclude a perfluoro chemical from the polymer exemption:

- The first condition is cited above, "...polymers containing PFAS (perfluoroalkyl sulfonates) or PFAC (perfluoroalkyl carboxylates)..." where the C or S atom is an integral part of the polymer molecule; and
- the second condition notes that, polymers containing fluorotelomers or "...perfluoroalkyl moieties that are covalently bound to either a carbon or sulfur atom where the carbon or sulfur atom is an integral part of the polymer molecule can be attached to the polymers using conventional chemical reactions."

For the PFAS and PFAC as described by USEPA, the agency offers a clarification about the nature of the linkage, stating "How these materials are incorporated into the polymer is immaterial (they may be counter ions, terminal/end capping agents, or part of the polymer backbone)" (USFR 2010). The key characteristic is the presence of a –CF3 group that is attached to, or forms part of, the polymer backbone and "this link (between the polymer backbone and the –CF3 group) is susceptible to degradation and cleavage." (USFR 2010). Thus, in USEPA's review, the presence of –CF3 group is important because it is a structural alert to consider potential degradation products. The USEPA will make a determination whether the potential degradation of the polymer in question presents an unreasonable risk to health and the environment under TSCA. As shown in Table 2, these fluoropolymers are not subject to degradation.

Water and lipid solubility and the octanol–water partition coefficient

Fluoropolymers, such as PTFE, are not soluble in octanol or water. Therefore, it is not possible to measure or calculate a

 DOI: 10.1002/ieam.4035 © 2018 The Authors

K_{OW}. Because solubility in octanol is predictive of lipid solubility, PTFE cannot dissolve in cell membrane lipids to gain access to cellular contents, nor is it small enough to enter the cell due to its very high MW. Because PTFE cannot enter the cells, it is not capable of bioaccumulation or bioconcentration in aquatic life.

Stability

Under normal, foreseeable uses, fluoropolymers are stable. Stability is resistance to physical, chemical, or biological transformation. Loss of stability in the polymer breaks it down into smaller pieces, producing low MW species. Molecules with M_n <1000 Da are capable of crossing cell membranes, making unstable polymers potentially hazardous to health and the environment. Fluoropolymers, in general, have exceptional chemical and thermal stability; that is why they are so unique and useful. This is due to very strong C–F bonds that are stable under even extreme conditions (Gangal and Brothers 2015). Polytetrafluoroethylene is inert and chemically resistant to all solvents except molten alkali metals, chlorine trifluoride, and oxygen difluoride. Polytetrafluoroethylene, as a representative fluoropolymer, has the best chemical resistance of all currently known polymers and is insoluble in all known solvents, including water (Drobny 2006).

Abiotic stability

Polymers are stable; monomers are not. Photochemical transformation is a reaction involving the radiation energy of sunlight (ultraviolet radiation) that may break a bond in a molecule to change it to another chemical entity. Although PTFE will rapidly degrade in ionizing radiation (e.g., gamma radiation or high energy electron-beam radiation), it is resistant to photolysis (Drobny 2006). Photoinduced reactions with fluoropolymers do not occur. In addition, hydrolysis is a reaction involving the breaking of a bond in a molecule using water. The fluorine envelope surrounding the C backbone of PTFE is very hydrophobic. Fluoropolymers, such as PTFE, are hydrolytically stable, water resistant, and are not subject to hydrolysis catalyzed degradation (Arkles 1973). Finally, chemical oxidation is a reaction involving the loss of electrons from one atom to another. Because the C–F bond is one of the strongest known, and F is the most electronegative element, the C–F bond is thermodynamically stable, unfavorable to lose electrons (i.e., to oxidize) (Arkles 1973).

Biotic stability: aerobic, anaerobic and in vivo

Fluoropolymers like PTFE are biologically inert and not degraded by microorganisms under oxygenated (aerobic) or anoxic (anaerobic conditions); in vitro and in vivo studies demonstrate this. In vivo degradation involves the breaking of the polymer bonds due to bacteria and other enzymes and oxidants. For example, PTFE hernia patches explanted from patients and examined by scanning electron microscopy, attenuated total reflectance Fourier transform infrared spectroscopy, modulated differential scanning calorimetry, and optical microscope showed no degradation in vivo (King et al. 2013).

Thermal stability

Fluoropolymers, when used as intended under normal, foreseeable use conditions as specified in Table 2 (or "continuous processing temperature") are thermally stable (Puts et al. 2014). The fluoropolymer industry has provided significant information on appropriate use of fluoropolymers (SPI 2005). Thermal gravimetric analysis determines mass loss over time and temperature of a test substance. Polytetrafluoroethylene is one of the most thermally stable polymers. Polytetrafluoroethylene's continuous processing temperature is 260 °C (SPI 2005). This means that PTFE could remain for decades at 260 °C and not decompose (SPI 2005 see percent mass lost per hour at maximum continuous processing temperature).

Outside of normal, foreseeable use conditions (also known as "misuse"), when fluoropolymers are held at temperatures above their recommended processing temperatures, they degrade. Upon decomposition, fluoropolymers generate volatile degradation products (SPI 2005). At 450 °C, the decomposition of PTFE "only proceeds at a rate on the order of one percent per hour. It is not until considerably above the polymer first-order transition temperature (329 °C) that substantial decomposition is observed" (Arkles and Bonnett 1974). As the temperatures increase above recommended processing temperatures, the rate of generation rises and may sufficiently degrade the polymer to produce hazardous gaseous byproducts and polymer (particulate) fume fever (SPI 2005). Temperature, availability of O, the physical form of the polymer article, and the residence time at elevated temperature factor into the ultimate nature of the decomposition products (SPI 2005), mainly fluoroalkenes, hydrogen fluoride, oxides of C, and lower molecular weight fluoropolymer particulates. For PTFE, TFE is the principle gaseous product observed at temperatures near 330 °C. See Supplemental Data for additional information regarding overheating PTFE.

PRODUCT-SPECIFIC REGULATORY REQUIREMENTS

Certain product-specific regulations, such as those for medical devices and food contact for the United States and the EU, require the development of additional data beyond what is required to conduct a PLC evaluation. The following text will discuss food contact requirements for the United States and the EU, and medical device requirements.

Data requirements for food, pharmaceutical, and medical device applications

There are country-specific data requirements for fluoropolymer use in food, pharmaceutical, and medical device applications because the intended use of these products has the potential to directly or indirectly introduce the product into the human body. An extensive fluoropolymer data set has been developed by W.L. Gore for these uses. The clinical history of the safe implantation of more than 40 million PTFE medical devices over 40 y, extensive toxicity data, preclinical

 © 2018 The Authors

data, and chemical extractables and migration testing confirmed that fluoropolymers are not bioavailable. Although the data requirements have evolved over time for contacting food, pharmaceuticals, or use in medical devices, the data (some of which are provided in the present article, the Supplemental Data for the present paper, regulatory submissions, and product literature) confirm the conclusion that fluoropolymers are safe for these intended uses and support the conclusion that fluoropolymers should be considered PLCs.

Polymer of low concern data and US and European Union food contact requirements

In general, the data required to support a PLC determination are helpful, but insufficient to qualify a material for food contact use. Submissions to the US Food and Drug Administration (USFDA) to support new food contact substances require extensive data submissions, including, for example, the nature and amount of nonvolatile extractives (USFDA 2017). Fluoropolymers, however, are not new substances in applications where they come in contact with food and have longstanding acceptance by regulators. In the United States, the USFDA is responsible for regulation of materials that come in contact with food and are considered "indirect food additives," specifically polymers (USFR 2016a). Food storage or food packaging materials, such as the fluoropolymers PTFE, FEP, and PFA, are "perfluorocarbon resins" acceptable for use by application and material type, provided they meet the extractable limits specified in the regulation (USFR 2016b).

Similarly, the European Food Safety Agency (EFSA) provides recommendations to the European Commission (EC) within the EU for the regulation of food contact materials, requirements for their evaluation, and authorization of acceptable uses (EC 2004). Polymer clearance is based in part upon the fact that polymers will not migrate into food due to their high molecular weight. The EU focuses on potential low molecular weight moieties, such as residual monomers and leachables, rather than on the polymer itself. The EU food contact regulation requires that monomers, other starting substances, and additives used to produce food contact polymers should be risk assessed and authorized (EU 2011). The regulation lists authorized substances that are permitted to have food contact (EU 2011). This regulation also sets the specific migration limit (SML), which is the maximum permitted amount of substance in food that has been determined not to pose a risk to human health, specifically for individual chemicals (e.g., monomer) (EU 2011). Note that these limits exist whether or not the substance is present in the food contact material (FCM). The monomers, other starting substances, and additives used to produce fluoropolymers for food contact (e.g., PTFE, FEP, and PFA) have been authorized for food contact uses. Representative SMLs for these monomers, additives, and starting substances relevant for fluoropolymers are given in the Supplemental Data (p 14).

Polymer of low concern data and medical device regulatory requirements

Satisfaction of the PLC criteria is insufficient to satisfy medical device requirements. Formal biocompatibility evaluations are required by the USFDA and other global regulatory authorities to support submissions for approval of medical devices and pharmaceuticals (e.g., combination products, such as drug-eluting stents or prefilled single-dose syringes). The International Organization for Standardization (ISO) 10993 Biocompatibility of Medical Devices standards describe a broad array of biocompatibility tests that require consideration for each new device or significant changes to existing devices (ISO 2009). Over the years, medical devices containing PTFE (or expanded PTFE) have been evaluated using ISO 10993 and US Pharmacopeia (USP) Class VI standards (USP 2011) and have been determined to be biocompatible in their intended uses.

The ISO 10993 standards provide guidance for evaluation of the biological response to a medical device. The USFDA, as well as most international regulatory agencies, recognizes and uses ISO 10993 standards to guide safety evaluations of medical devices submitted for their approval. Requirements to demonstrate the biocompatibility of medical devices are set forth in ISO 10993-1, and regulatory authority–specific requirements (e.g., PMDA 2003; USFDA 2016). In addition, country pharmacopeial organizations also specify testing required for biological reactivity of drugs (e.g., US Pharmacopiea, EU Pharmacopiea, Japan Pharmacopiea). The ISO requirements are categorized by the nature of body contact (e.g., mucosal membrane, circulating blood, tissue, bone, dentin) and duration of contact ($<$24 h, $\geq$1 d $\leq$30 d, $>$30 d). Depending on the nature and duration of contact, requirements include cytotoxicity, irritation, sensitization, implantation, acute–subchronic–chronic systemic toxicity, material-mediated pyrogenicity, hemocompatibility (e.g., hemolysis, thrombogenicity, and complement activation), genotoxicity (in vitro and in vivo), carcinogenicity, and developmental toxicity. (See Supplemental Data p 15 for a list of ISO 10993 biocompatibility tests.)

MEETING PLC CRITERIA PRECLUDES A FINDING THAT A CHEMICAL IS OF HIGH CONCERN

Just as regulatory frameworks have mechanisms to identify materials of low concern such as PLCs, they also have mechanisms to identify chemicals of high concern. For example, under REACH, a mechanism exists to identify substances of very high concern (SVHCs). Having demonstrated that fluoropolymers like PTFE should be considered PLCs, we will also demonstrate that these fluoropolymers cannot be SVHCs under REACH, do not meet the PM and PMT criteria proposed by UBA, and do not meet the criteria for listing as a POP under the Stockholm Convention.

 DOI: 10.1002/ieam.4035 © 2018 The Authors

Fluoropolymers and EU REACH SVHC, CMR, PBT, vPvB, and endocrine disrupting chemical (EDC) criteria

According to the European Chemicals Agency (ECHA), SVHCs are defined in Article 57 of Regulation (EC) Nr 1907/2006 ("the REACH Regulation") (EC 2006) and include substances that are

- "Carcinogenic, mutagenic or toxic to reproduction (CMR), meeting the criteria for classification in category 1 or 2 in accordance with Directive 67/548/EEC. This directive was replaced in beginning of 2009 by the new EU regulation (EC) No 1272/2008 on classification, labeling and packaging of chemical substances and mixtures, the so-called CLP Regulation. According to the new CLP Regulation these substances shall be classified as 1a or 1b."
- "Persistent, Bioaccumulative and Toxic (PBT) or very Persistent and very Bioaccumulative (vPvB) according to the criteria in Annex XIII of the REACH Regulation."
- "Identified, on a case-by-case basis, from scientific evidence as causing probable serious effects to human health or the environment of an equivalent level of concern as those above (e.g., EDCs)."

Under REACH, polymer substances are not registered, but the monomers they are composed of are registered, and the registration must be supported by data submissions that are tiered on the basis of tonnage (see EC 2006, Annex VII). The REACH definition of polymer includes materials with as few as 3 repeating units. But such a small molecule would not meet common industry standard definitions for fluoropolymers (ASTM 2015). It is highly unlikely that fluoropolymers meeting the PLC criteria would exhibit the criteria of an SVHC under REACH. Fluoropolymer data developed for other regulatory needs support the predictive value of the PLC assessment criteria and demonstrate the low hazard potential of this class of PFAS. Due to their physical–chemical properties, PLCs are not bioavailable to cause toxicity or to bioaccumulate. Toxicity study data on PTFE in the Supplemental Data (p 15–27), for example, demonstrate a lack of toxicity, including genotoxicity. Although fluoropolymers are persistent, they are not bioaccumulative or toxic and therefore do not meet the PBT criteria.

Fluoropolymers and German UBA–proposed PMT criteria

As regulatory frameworks continue to evolve, more work is needed in the area of PFAS classification to ensure that regulations are appropriate in scope and proportionality. Although some well-known PFAS would qualify as PM or PMT substances as proposed by the UBA (2017), fluoropolymers do not possess these characteristics. Although fluoropolymers are highly stable (persistent), they do not meet the criteria to be mobile or toxic. To demonstrate this point, PTFE, a high molecular weight fluoropolymer and a member of the PFAS group, is assessed (in the last 4 paragraphs of this section) according to the proposed UBA criteria (UBA 2017).

Briefly, the changes to PM and/or PMT assessment proposed by UBA address applicability, persistence, mobility, and toxicity. The UBA proposes an initial step involving assessment of the chemical composition of a substance to determine if the substance is within the applicability domain of the proposed new assessment criteria. The UBA notes that currently only identifiable organic and organometallic chemicals are considered, and purely inorganic substances or substances of unknown or variable compositions, complex reaction products, or biological material are excluded (UBA 2017).

With respect to persistence, UBA proposes that the criterion for persistence be the same as in Annex XIII of REACH, which considers degradation half-lives in marine water, fresh- or estuarine water, marine sediment, and soil as part of the PBT/very persistent, very bioaccumulative (vPvB) assessment criteria; these degradation half-life criteria range from 40 to 180 d. The UBA proposes that a substance meets the persistent criterion if the degradation half-life in marine water at pH 6 to 8 and 12 °C is higher than 60 d, the half-life in fresh- or estuarine water at pH 6 to 8 and 12 °C is higher than 40 d, the half-life in marine sediment at pH 6 to 8 and 12 °C is higher than 180 d, the half-life in fresh- or estuarine water sediment at pH 6 to 8 and 12 °C is higher than 120 d, or the half-life in soil at pH 6 to 8 and 12 °C is higher than 120 d.

The UBA proposes that the mobility criterion for a persistent chemical should be determined on the basis of 2 considerations. First, the water solubility of a substance at pH 6 to 8 and 12 °C must be greater than or equal to 150 μg/L, and the log K_{OC} at pH 6 to 8 and 12 °C must be less than or equal to 4.5. The UBA notes that the mobility criterion should be applied only to substances that have fulfilled the criterion for persistence.

Lastly, with respect to toxicity, UBA proposes a 5-part test for involving data to understand if the substance is carcinogenic, germ cell mutagenic, or toxic for reproduction; if there is other evidence of chronic toxicity; and if there is evidence for effects on or via lactation. The derived no adverse effect level (DNEL) must be less than or equal to 9 $\mu g \cdot kg^{-1}d^{-1}$. The UBA notes that the first 2 considerations are the same criteria defined in Annex XIII of REACH as part of the PBT/vPvB assessment criteria regarding human health. The next 2 criteria specifically address concerns for drinking water exposure and are based on Regulation EC No 1272/2008 (EC 2008) and Cramer class II (Cramer et al. 1978) for substances exhibiting moderate or low biological activity, respectively. The DNEL criterion is based on Kalberlah et al. (2014).

Regardless of the arguments concerning the scientific foundation and credibility of the changes proposed by UBA to REACH PM and PMT assessment criteria, the central question with respect to PTFE is whether chemical-specific assessment would lead to an outcome different from that assuming PTFE behaved similarly to other PFAS substances. Polymers, including fluoropolymers, are different from non-polymeric chemicals and may be regulated differently. Because of these differences, it is recognized that some data requirements may not be applicable to polymers (EU 2011) For example, as we have shown, the physical–chemical criteria of PLC are predictive of lack of hazard.

 © 2018 The Authors

With respect to applicability, PTFE is not a substance currently registered under REACH because it meets the REACH definition of a polymer substance: "a molecule that contains a sequence of at least 3 monomer units, which are covalently bound to at least one other monomer unit or other reactant" (EC 2006). However, because PTFE is an identifiable organic substance, the proposed UBA framework for assessment using the proposed PMT criteria would be applicable. Further, PTFE is highly stable and persistent in the environment. It is resistant to thermal degradation, being stable for decades at temperatures up to 260 °C (SPI 2005); is stable in terms of hydrolysis, oxidation, and light (Brydson 1999); and is stable in terms of anaerobic and aerobic degradation (King et al. 2013). Therefore, PTFE would fulfill the UBA's proposed persistence criterion.

In contrast, PTFE is practically insoluble in water and, therefore, is not mobile in the environment. Using the descriptive solubility table for the USP (2011), the water solubility of PTFE would be classified as practically insoluble (1×10^{-5} mg/L or 0.01 μg/L) to very slightly soluble (1×10^{-4} mg/L or 0.1 μg/L) (USP 2011). The mobility of PFTE is 1000 to 10 000× lower than UBA's proposed mobility criterion. Therefore, PTFE does not fulfill UBA's proposed mobility criterion and would not be classified as a PM or PMT substance.

A similar negative finding for PTFE pertains to toxicity. The average molecular weight of PTFE is too large for the polymer to cross a cell membrane, which means it is not bioavailable or toxic. Polytetrafluoroethylene has been tested extensively in the United States and European Union to assess commercial applications for food contact and global medical device regulations (see Supplemental Data for additional details). Results demonstrate the absence of toxicity. Therefore, PTFE does not fulfill UBA's proposed toxicity criterion and would not be classified as a PM or PMT substance (Table 4).

Fluoropolymers and the Stockholm Convention POP criteria

In addition to country and regional regulations, there are global legally binding instruments, such as the United Nations Environment Programme–administered conventions on chemicals and waste (UNEP 2001), such as the Stockholm Convention on Persistent Organic Pollutants. The Convention aims to eliminate POPs by eliminating their production, reducing their use, or limiting their use through a cradle-to-grave approach. For the listing of new chemicals into the Convention, numeric or other criteria have been set for the screening of proposed compounds. Stockholm Convention Criteria (annex D) are compared to those of the USEPA, EU REACH, and the UBA-proposed PMT (Table 4). Fluoropolymers meet the persistence criterion only, not the bioaccumulative, toxic, or mobile criteria.

Fluoropolymers satisfy widely accepted criteria to be considered PLCs. Their physical–chemical properties prevent bioavailability, bioaccumulation, toxicity, and degradation. They have negligible monomer, oligomer, and leachable content and no reactive functional groups with high toxicity. These comparisons of PLC and various regulatory assessment criteria demonstrate that, in the realm of PFAS, high molecular weight fluoropolymers like PTFE have vastly different properties than do other PFAS, and therefore, they are truly a separate class of materials that must be assessed on their own merits as has been done here. They also underscore the value of a global regulatory definition of a polymer.

FUTURE WORK

It is important to acknowledge that the manufacture and end-of-life phases of the fluoropolymer life cycle are not the subject of the present paper. The following reflections are provided on how these may be explored in future work. Fluoropolymer manufacture includes fluoromonomers and a wide array of initiators, catalysts, et cetera, including polymer production aids, some of which are fluorosurfactants (non-polymer PFAS) (see Supplemental Data, p 8, for more information about them). Historically, perfluorocarboxylic acids such as PFOA and perfluorononanoic acid (PFNA) were used as polymer production aids in the manufacture of fluoropolymers. They are no longer used by leading global fluoropolymer manufacturers (USEPA 2017a), who are now using alternative substances such as fluorinated polyether carboxylates (see Supplemental Data Table S2). The toxicological and environmental properties (e.g., persistence, bioavailability, and mobility) of these alternatives are very important. Future work should delve into fluoropolymer manufacture and describe the safety, health, and environmental management practices and controls employed; should describe the applicable regulations; and should assess substances used in fluoropolymer manufacture, their human health and environmental attributes, and their mass balance.

At end-of-life when a fluoropolymer has fulfilled its intended use and will be disposed of, the fate of fluoropolymers should be investigated further. Although there are sufficient data to demonstrate that fluoropolymers such as PTFE do not degrade in the environment or release substances of toxicological or environmental concern (Hintzer and Schwertfeger 2014), the downstream, end-of-life process of incineration merits future work. For instance, at temperatures above 450 °C, PTFE begins to degrade, releasing hazardous substances such as hydrofluoric acid. There are published studies on the incineration of fluoropolymers under normal, foreseeable municipal waste incinerator conditions targeting specific analytes (Taylor 2009). Presently, most legislation addresses the release of hydrogen fluoride (HF) as the only critical parameter; limit values are for stack emissions (e.g., EU 2000). Future work should investigate incineration under a range of relevant foreseeable use conditions to determine more comprehensively the substances formed and their amounts. Such an incineration study is underway with results to be published upon completion (W.L. Gore 2017). In addition, the practice of the open burning of fluoropolymers, or for that matter of any polymer, is unacceptable and unsafe. Responsible incineration of fluoropolymers, adhering to regulatory guidelines, at the end of their life cycle is appropriate.

 DOI: 10.1002/ieam.4035 © 2018 The Authors

Table 4. Comparison of United States, Stockholm Convention, EU REACH, and German Criteria

Criterion	United States[a]	Stockholm Convention[b]	REACH[c,d]	Germany[d,e]
Persistence (half-life)				
P	Water, soil, sediment > 60 d	Water >60 d	Marine water > 60 d	Same as REACH
		Soil, sediment >180 d	Estuarine water > 40 d	
			Fresh or estuarine sediment or soil > 120 d	
vP	Water, soil, sediment > 180 d		Marine, fresh, estuarine H_2O > 60 d	
			Marine, fresh, or estuarine sediment > 180 d	
			Soil > 180 d	
Bioaccumulation				
B	Aquatic BCF > 1000	Aquatic BCF or BAF > 5000	BCF > 2000	
		Log K_{OW} > 5		
vB	BCF > 5000		BCF > 5000	
Toxicity				
	Fish	Toxic or ecotoxic	Long-term aquatic NOEC or EC10 < 0.01	1) Carcinogenic, germ cell mutagenic, or toxic for reproduction[d];
	Low > 10 mg/L	(No numeric criteria)	Classified as carcinogen category 1A or 1B; mutagen 1A or 1B; reproductive toxin 1A, 1B, or 2[d]	2) other evidence of chronic toxicity[d]; and
	Moderate 0.1 mg/L–10 mg/L			3) evidence for effects on or via lactation[d].
	High < 0.1 mg/L			4) DNEL[f] ≤ 9 μg · $kg^{-1}d^{-1}$
			Specific target organ toxicity (STOT RE 1 or 2) upon repeated (chronic) exposure)[d]	
Long-range transport (potential for)		Long-range transport (potential for): Presence through monitoring or modeled data; $t_{1/2}$ (air): 2 d		
Mobility				Mobility: water solubility at pH 6–8, 12 °C, must be ≥150 μg/L, and the log K_{OC} at pH 6–8, 12 °C must be ≤4.5.

BAF = bioaccumulation factor; BCF = bioconcentration factor; DNEL = derived no adverse effect level; EU = European Union; M = mobile; P = persistent; REACH = Registration, Evaluation, Authorisation and Restriction of Chemicals; STOT RE = specific target organ of toxicity repeat exposure; T = toxic; v = very.
[a]USEPA 1999.
[b]UNEP 2001
[c]ECHA 2014
[d]EC 2008
[e]UBA 2017
[f]Barlow 2005; Kalberlah et al. 2014.

Recycling, reuse, and closed loop systems are alternative options at the end of life. Recent work has shown, on a small scale, the ability to convert fluoropolymers back to their monomers for capture (Schlipf 2014; Invertec 2017). This approach to a closed loop economy for fluoropolymers merits additional work and discussion, as does the recycling and reuse of melt-processable fluoropolymers, such as FEP.

 © 2018 The Authors

CONCLUSIONS

The present review has brought together fluoropolymer toxicity data, human clinical data, and physical–chemical characteristics, using PTFE as an example to show that fluoropolymers satisfy the widely accepted regulatory assessment criteria to be considered as PLCs. Fluoropolymers are high molecular weight, have narrow molecular weight distribution, and have negligible oligomer content and organic and inorganic leachables. Data show that fluoropolymers have thermal, chemical, photochemical, hydrolytic, and biological stability. Polytetrafluoroethylene has been extensively tested to comply with US and EU food contact and global medical device regulations (e.g., USFDA, CFDA, Korea MFDS, Japan PMDA), including ISO 10993 biocompatibility testing and preclinical animal testing. Toxicology studies on PTFE demonstrate the absence of acute or subchronic systemic toxicity, irritation, sensitization, local toxicity on implantation, in vitro and in vivo genotoxicity, hemolysis, complement activation, or thrombogenicity. The data presented demonstrate that the fluoropolymer class of PFAS is well defined, meets PLC criteria, and should be considered as distinctly different from other classes of PFAS. The grouping of all PFAS together is not supported by the scientific data.

Acknowledgment—The authors would like to thank Laura Hoch and Joel Tickner of the University of MA Lowell for comments on this manuscript; Yasuhiko Matsuoka of AGC Chemicals Americas, Inc.; Mary MaloneyHuss, Greg Hannon, Paul Fisher, David Einum, Catherine Parmeter and Terry Zitzelberger of W.L. Gore for technical assistance; John Jones of W.L. Gore for chemical analyses; Terrie Stike of W.L. Gore for manuscript preparation. We would also like to thank the editors and reviewers for their comments to improve this paper.

Disclaimer—BJ Henry, JP Carlin, and JA Hammerschmidt are employees of W.L. Gore, a global manufacturer of products made with fluoropolymers. RC Buck and LW Buxton are employees of The Chemours Company, a global manufacturer of fluoroproducts. O Hernandez, former Director of the Risk Assessment Division in the USEPA Office of Pollution Prevention and Toxics, is an employee of Bergeson and Campbell, a W.L. Gore contractor. J Seed, former Deputy Director of the Risk Assessment Division in the USEPA Office of Pollution Prevention and Toxics, is an independent risk assessment consultant to W.L. Gore. H Fiedler is a professor of Chemistry at the MTM Research Centre in the School of Science and Technology at Örebro University in Örebro, Sweden. Hernandez and Seed were retained and compensated by W.L. Gore & Associates, Inc., to assist in writing this paper. W.L. Gore & Associates, Inc., the Chemours Company, and the MTM Research Centre School of Science and Technology, Örebro University, Örebro, Sweden donated data and employee time to support this work.

Data Accessibility—All data and information used in this manuscript have been made available in tabulated form (Tables 1–4) by the authors and are included in the paper and the Supplemental Data.

SUPPLEMENTAL DATA

The Supplemental Data contains descriptive and more detailed information as highlighted in the paper.

Figure S1. Where does polytetrafluoroethylene (PTFE) come from?

Figure S2. Fluoropolymer primer: polytetrafluoroethylene (PTFE) polymerization scheme.

Figure S3. Fluoropolymer primer: polytetrafluoroethylene (PTFE) finishing scheme.

Figure S2. A fluorinated ethylene propylene (FEP) fluoropolymer molecular weight distribution from a rheological study.

Table S1. Polytetrafluoroethylene (PTFE) polymerization and post polymerization aids

Table S2. Alterative fluoropolymer processing aids: Sources of data

Table S3. Solubility table from USP 34 NF 29 General Notices, Section 5.3.0, p 6

Table S4. European Union (EU) specific migration limits (SMLs) for monomers in representative fluoropolymers

Table S5. Biocompatibility tests, conditions, and acceptance criteria results for expanded polytetrafluoroethylene patch

Table S6. US Environmental Protection Agency's (USEPA's) chemical categories of concern, 2010

REFERENCES

[ACGIH] American Conference of Governmental Industrial Hygienists. 2010. TLVs and BEIs: Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati (OH): American Conference of Governmental Industrial Hygienists.

Arkles B. 1973. Recycling polytetrafluoroethylene in polymer science and technology. In: Guillet J, editor. Polymers and ecological problems, Vol. 3. New York (NY): Plenum. p 122.

Arkles B, Bonnett R. 1974. Method for the depolymerization of polytetrafluoroethylene, US 3832411A.

[ASTM] American Society for Testing and Materials. 2015a. ASTM D3159-15, Standard specification for modified ETFE fluoropolymer molding and extrusion materials.

[ASTM] American Society for Testing and Materials. 2015b. ASTM D4894, Standard specification for polytetrafluoroethylene (PTFE) granular molding and ram extrusion materials.

[ASTM] American Society for Testing and Materials. 2016a. ASTM D2116-16, Standard specification for FEP-fluorocarbon molding and extrusion materials.

[ASTM] American Society for Testing and Materials. 2016b. ASTM D3307-16, Standard specification for perfluoroalkoxy (PFA) resin molding and extrusion materials.

[ASTM] American Society for Testing and Materials. 2016c. ASTM D4895–16, Standard specification for polytetrafluoroethylene (PTFE) resin produced from dispersion.

Auer CM, Nabholz JV, Baetcke KP. 1990. Mode of action and the assessment of chemical hazards in the presence of limited data: Use of structure-activity relationships (SAR) under TSCA, Section 5. *Environ Health Perspect* 87:183–197.

Banks RE, Smart BE, Tatlow J. 1994. Organofluorine chemistry: Principles and commercial applications. New York (NY): Springer. 644 p.

Barlow S. 2005. Threshold of toxicological concern (TTC): A tool for assessing substances of unknown toxicity present at low levels in the diet. Brussels (BE): ILSI Europe. ILSI Europe Concise Monograph Series.

Berry KL, Peterson JH. 1951. Tracer studies of oxidation—Reduction polymerization and molecular weight of "Teflon" tetrafluoroethylene resin. *J Am Chem Soc* 73:5195–5197.

Beyer EC. 1993. Gap junctions. *Int Rev Cytol* 137:2.

 DOI: 10.1002/ieam.4035 © 2018 The Authors

BIO by Deloitte. 2015. Technical assistance related to the review of REACH with regard to the registration requirements on polymers Final report prepared for the European Commission (DG ENV), in collaboration with PIEP.

Blum A, Balan SA, Scheringer M, Trier X, Goldenman G, Cousins IT, Diamond M, Fletcher T, Higgins C, Lindeman AE, et al. 2015. The Madrid statement on poly- and perfluoroalkyl substances (PFAS). *Environ Health Perspect* 123:A107–A111.

Brydson JA. 1999. Plastics materials. 7th ed. Oxford (UK): Butterworth Heinemann. 920 p.

Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, Jensen AA, Kannan K, Mabury SA, van Leeuwen SPJ. 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. *Integr Environ Assess Manag* 7(4):513–541.

ChemNews. 2016 Jul 7. Sweden's Kemi issues interim report on PFAS. Chemical Watch (Global Risk and Regulation News).

Chu B, Wu C, Buck W. 1989. Light scattering characterization of poly-(tetrafluoroethylene). PTFE in perfluorotetracosane: Molecular weight distribution and solution properties. *Macromolecules* 22:831–837.

Cramer GM, Ford RA, Hall RL. 1978. Estimation of toxic hazard—A decision tree approach. *Food Cosmet Toxicol* 16(3):255–276.

Dams R, Hintzer K. 2016. Industrial aspects of fluorinated oligomers and polymers. In: Ameduri B, Sawada H, editors. Fluorinated polymers, Vol 2: Applications. London (UK): Royal Society of Chemistry. p 1–31.

Doban RC, Knight AC, Peterson JH, Sperati CA. 1956. The molecular weight of polytetrafluoroethylene. Paper presented at 130th Meeting of American Chemical Society; 1956 Sep; Atlantic City, NJ. p 9S.

Drobny JG. 2006. Fluoroplastics. Shropshire (UK): Rapra Technology. p 12.

Ebnesajjad S. 2011. Introduction to fluoropolymers. In: Kutz M, editor. Applied plastics engineering handbook. New York (NY): Elsevier. p 49–60.

[EC] European Commission. 2004. Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC. [cited 2017 July 12]. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02004R1935-20090807&from=EN

[EC] European Commission. 2006. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). [cited 2017 July 12]. https://echa.europa.eu/regulations/reach/legislation

[EC] European Commission. 2008. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (Text with EEA relevance). [cited 2017 July 12]. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32008R1272

[ECHA] European Chemicals Agency. 2014. Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT/vPvB assessment version 2.0 November 2014. [cited 2017 July 12]. https://echa.europa.eu/documents/10162/13632/information_requirements_r11_en.pdf/a8cce23f-a65a-46d2-ac68-92fee1f9e54f

[ECHA] European Chemicals Agency. 2015. Opinion of the Committee for Risk Assessment and Opinion of the Committee for Socio-economic Analysis on an Annex XV dossier proposing restrictions of the manufacture, placing on the market or use of a substance within the EU. [cited 2017 July 12]. https://echa.europa.eu/documents/10162/13641/rest_pfoa_compiled_opinions_en.pdf/2f0dfce0-3dcf-4398-8d6b-2e59c86446be

[EU] European Union. 2000. Directive 2000/76/EC of the European Parliament and of the Council of 4 December 2000 on the incineration of waste.

[EU] European Union. 2011. European Union Guidance on Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food as regards information in the supply chain available on the food safety part of the website of the European Commission, on the page concerning the legislation on Food Contact Materials. [cited 2017 July 12]. http://ec.europa.eu/food/safety/chemical_safety/food_contact_materials/legislation/index_en.htm

Frick A, Sich D, Heinrich G, Stern C, Schlipf M. 2012. Classification of new melt-processable PTFE: Comparison of emulsion- and suspension-polymerized materials. *Macromol Mater Eng* 297:329–341.

Gangal SV, Brothers PD. 2015. Perfluorinated polymers. In: Kirk-Othmer encyclopedia of chemical technology. New York (NY): Wiley. p 1–68.

Hintzer K, Schwertfeger W. 2014. Fluoropolymers – Environmental aspects. In: Smith Jr DW, Iacano ST, Iyer SS, editors. Handbook of fluoropolymer science and technology. New York (NY): Wiley. p 495–520.

Hougham G, Cassidy PE, Johns K, Davidson T. 1999. Topics in applied chemistry. Fluoropolymers 2: Properties. New York (NY): Springer. 408 p.

IHS Markit. 2016. Fluoropolymers chemical economics handbook. Freedonia Group.

Invertec. 2017. Pilot project: Recycling of fluoropolymers (PTFE). [cited 2017 July 12]. https://www.invertec-ev.de/en/projects/environmental-care/ptfe-recycling/

[ISO] International Organization for Standardization. 2006. ISO 12086-1:2006 Plastics – Fluoropolymer dispersions and moulding and extrusion materials. Part 1: Designation system and basis for specifications.

[ISO] International Organization for Standardization. 2009. ISO 10993-1: Biological evaluation of medical devices. Part 1: Evaluation and testing in the risk management process. Geneva (CH).

[ISO] International Organization for Standardization. 2011. ISO 1133-1:2011 Plastics — Determination of the melt mass-flow rate (MFR) and melt volume-flow rate (MVR) of thermoplastics. Part 1: Standard method.

Kalberlah F, Oltmanns J, Schwartz MA, Baumeister J, and Stiffler A. 2014. Guidance for the precautionary protection of raw water destined for drinking water extraction from contaminants regulated under REACH. Dessau-Roßlau (DE): Umweltbundesamt (UBA). Report FKZ 371265416.

Kemi Swedish Chemicals Agency. 2016. Strategy for reducing the use of highly fluorinated substances, PFASs: Interim report as part of a Government assignment. Report 11/16. [cited 2017 July 12]. https://www.kemi.se/global/rapporter/2016/report-11-16-strategy-for-reducing-the-use-of-higly-fluorinated-substances-pfas.pdf

King MW, Gupta BA, Guidoin R. 2013. Biotextiles as medical implants:15. Vascular prostheses for open surgery. Cambridge (UK): Woodhood. p 434–484.

LaGrega M D. Buckingham PL, Evans JC. 2010. Hazardous waste management. 2nd ed. Long Grove (IL): Waveland. 1232 p.

Liu J, Mejia-Avendaño S. 2013. Microbial degradation of polyfluoroalkyl chemicals in the environment: A review. *Environ Int* 61:98–114.

[NICNAS] National Industrial Chemicals Notification and Assessment Scheme. 2016. NICNAS Handbook - Guide for importers and manufacturers of industrial chemicals in Australia. Sydney (AU). [cited 2017 July 12]. http://webarchive.nla.gov.au/gov/20161017033100/https://www.nicnas.gov.au/regulation-and-compliance/nicnas-handbook

[OECD] Organisation for Economic Co-operation and Development. 1993. OECD Expert Group on Polymers. Third Meeting of the Experts on Polymers: Chairman's Report [ENV/MC/CHEM/RD(93)4]; 1993 Apr; Paris (FR).

[OECD] Organisation for Economic Co-operation and Development. 2009. Data analysis of the identification of correlations between polymer characteristics and potential for health or ecotoxicological concern. OECD Task Force on New Chemicals Notification and Assessment, Expert Group Meeting on Polymers; 2007 Mar; Tokyo, Japan. Paris (FR).

[OECD] Organisation for Economic Co-operation and Development. 2017. OECD portal on per and poly fluorinated chemicals. Country Information section. Paris (FR). [cited 2017 July 12]. http://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/

Olabisi O, Adewale K. 2015. Handbook of thermoplastics. 2nd ed. Boca Raton (FL): CRC.

Pianca M, Barchiesi E, Esposto G, Radice S. 1999. End groups in fluoropolymers. *J Fluorine Chem* 95:71–84.

Plunkett RJ. 1987. The history of polytetrafluoroethylene: Discovery and development. In: Seymour RB, Kirshenbaum GS, editors. High performance polymers: Their origin and development. New York (NY): Elsevier. p 261–266.

[PMDA] Japan Pharmaceutical and Medical Device Agency, Ministry of Health, Labour and Welfare. 2003. Basic principles of biological safety evaluation required for application for approval to manufacture (import) medical

 © 2018 The Authors

devices. Tokyo (JP). PFBS/ELD (Iyakushin) Notification No. 0213001. 2003 Feb 13.
Putnam RE. 1986. Development of thermoplastic fluoropolymers. In: Seymour RB, Kirshenbaum GS, editors. High performance polymers: Their origin and development. New York (NY): Elsevier. p 279–286.
Puts G, Crouse P, Ameduri B. 2014. Thermal degradation and pyrolysis of polytetrafluoroethylene. In: Smith DW, Iacano TS, Iyer SS, editors Handbook of fluoropolymer science and technology. New York (NY): Wiley. p 81–104.
Scheringer M, Trier X, Cousins IT, de Voogt P, Fletcher T, Wang, Z, Webster TF. 2014. Helsingor statement on poly- and perfluorinated alkyl substances (PFAS). *Chemosphere* 114:337–339.
Schlipf M, Schwalm T. 2014. Closing the recyling loop. *Kunststoffe Intl* 2014/06. [cited 2017 July 12]. https://www.kunststoffe.de/en/journal/archive/article/up-cycling-of-end-of-life-fluoroplastics-841786.html
[SPI] Society of the Plastics Industry. 2005. SPIs guide to safe handling of fluoropolymers. Washington (DC).
Starkweather Jr HW, Wu S. 1989. Molecular weight distribution in polymers of tetrafluoroethylene. *Polymer* 30:1669–1674.
Suwa T, Takehisa M, Machi S. 1973. Melting and crystallization behavior of poly(tetrafluoroethylene). New method for molecular weight measurement of poly(tetrafluoroethylene) using a differential scanning calorimeter. *J Appl Polym Sci* 17:3253–3257.
Taylor PH, 2009. ECA incineration testing program: Laboratory-scale incineration testing of fluoropolymers. Dayton (OH): USEPA. USEPA Docket No. OPPT-2003-0071.
Tuminello WH. 1989. Molecular weight distributions of tetrafluoroethylene-hexafluoropropylene copolymers. *Polym Eng Sci* 29:645–653.
Tuminello WH, Buck WH, Kerbow DL. 1993. Rheological molecular weight distribution determination of ethylene/ tetrafluoroethylene copolymers: Implications for long-chain branching. *Macromolecules* 26:499–503.
[UBA] Umweltbundesamt. 2017. Protecting the sources of our drinking water from mobile chemicals. A proposal for implementing criteria and an assessment procedure to identify persistent, mobile and toxic (PM or PMT) substances registered under REACH. Dessau-Roßlau (DE). [cited 2017 July 12]. https://www.umweltbundesamt.de/en/publikationen/protecting-the-sources-of-our-drinking-water-from
[UNEP] United Nations Environment Programme. 2001. Conference of Plenipotentiaries on the Stockholm Convention. UNEP/POPS/CONF/2. [cited 2017 July 12]. http://www.wipo.int/edocs/trtdocs/en/unep-pop/trt_unep_pop_2.pdf
[UNEP] United Nations Environment Programme. 2009: Decision SC-4/17. Geneva (CH). [cited 2017 July 12]. http://chm.pops.int/Portals/0/download.aspx?d=UNEP-POPS-COP.4-SC-4-17.English.pdf; also accessible from table of new POPs: http://www.pops.int/TheConvention/ThePOPs/TheNewPOPs/tabid/2511/Default.aspx
[UNEP] United Nations Environment Programme. 2011. UNEP-POPS-POPRC.11-POPRC-11-4.English.docx. Geneva (CH). [cited 2017 July 12]. http://www.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC11/Overview/tabid/4558/mctl/ViewDetails/EventModID/871/EventID/553/xmid/13837/Default.aspx
[UNEP] United Nations Environment Programme. 2017a. Proposal for listing PFHxS (UNEP/POPS/POPRC.13/4). Geneva (CH). [cited 2017 July 12]. http://chm.pops.int/Convention/POPsReviewCommittee/Chemicals/tabid/243/Default.aspx
[UNEP] United Nations Environment Programme. 2017b. Risk management profile for PFOA, (UNEP/POPS/POPRC.13/7/Add.2). Geneva (CH). [cited 2017 July 12]. http://chm.pops.int/Convention/POPsReviewCommittee/Chemicals/tabid/243/Default.aspx
[USC] US Congress. 1976. The Toxic Substance Control Act. 15 U.S.C. 2601-2671. Public Law 94–469.
[USEPA] US Environmental Protection Agency. 1997a. Chemistry assistance manual for premanufacture notification submitters. Washington (DC). EPA 774-R-97-003. March 1997.
[USEPA] US Environmental Protection Agency. 1997b. Polymer exemption guidance manual. Washington (DC). EPA-744-B-97-001. June 1997.
[USEPA] US Environmental Protection Agency. 1999. Category for persistent, bioaccumulative, and toxic new chemical substances. *Fed Regis* 4(213). 1999 Nov 4.
[USEPA] US Environmental Protection Agency. 2010. Reviewing new chemicals under the Toxic Substances Control Act (TSCA) – EPA's Review Process - Chemical categories used to review new chemicals under TSCA: TSCA New Chemicals Program (NCP) Chemical Categories. Washington (DC): USEPA Office of Pollution Prevention and Toxics. [cited 2017 July 12]. http://www.epa.gov/oppt/newchems/pubs/npcchemicalcategories.pdf
[USEPA] US Environmental Protection Agency. 2012. Sustainable futures/P2 framework manual.
[USEPA] US Environmental Protection Agency. 2017a. US Environmental Protection Agency, PFOA Stewardship Program. Washington (DC). [cited 2017 July 12]. https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-and-polyfluoroalkyl-substances-pfass#tab-3
[USEPA] US Environmental Protection Agency. 2017b. Using predictive methods to assess hazard under TSCA. Washington (DC). [cited 2017 July 12]. https://www.epa.gov/tsca-screening-tools/using-predictive-methods-assess-hazard-under-tsca
[USFDA] US Food and Drug Administration. 2017. Guidance for industry: Preparation of premarket submissions for food contact substances: Chemistry recommendations. College Park (MD). [cited 2017 July 12]. https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm081818.htm#iid2
[USFDA] US Food and Drug Administration Center for Drug Safety and Radiological Health. 2016. Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" Guidance for Industry and Food and Drug Administration Staff Document. Silver Spring (MD). [cited 2017 July 12]. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm348890.pdf
[USFR] US Federal Register. 1984. Premanufacture Notification Exemptions for polymers; Final rule 49 FR 46066, 1984 Nov 21. FRL-2439-1.
[USFR] US Federal Register. 1995. Premanufacture notification exemptions; Revisions of exemptions for polymers; Final rule. *Fed Regist* 60(60): 16316–16336. Environmental Protection Agency. 60 FR 16316. 1995 Mar 29. FRL–4929–8.
[USFR] US Federal Register. 2006. Premanufacture notification exemption for polymers; Amendment of polymer exemption rule to exclude certain perfluorinated polymers. 40 CFR Part 723. 2006 Mar 7. Fed Reg No 06-02152.
[USFR] US Federal Register. 2010. Premanufacture notification exemption for polymers; Amendment of polymer exemption rule to exclude certain perfluorinated polymers. 40 CFR Part 723. 2010 Jan 27. EPA-HQ-OPPT-2002-0051; FRL-8805-5. RIN 2070-AD58.
[USFR] US Federal Register. 2012. Polymers (b). 40 CFR Sect 723.250.
[USFR] US Federal Register. 2016a. Indirect food additives. 21 CFR, Sect 174–178.
[USFR] US Federal Register. 2016b. Perfluorocarbon resins. 21 CFR, Sect 177.1550.
[USP] US Pharmacopeia 40. 2018. National Formulary 35 (USP), General Chapter 88, Biological Reactivity Tests, In Vivo.
[USP] US Pharmacopeial Convention. 2011. US Pharmacopeia National Formulary 2011: USP 34 NF 29. Rockville (MD). General Notices, Section 5.3.0, p 6.
Wagner PM, Nabholz JV, Kent RJ. 1995. The new chemicals process at the Environmental Protection Agency (EPA): Structure-activity relationships for hazard identification and risk assessment. *Toxicol Lett* 79:67–73.
Williams DF. 1987. Definitions in biomaterials. Amsterdam (NL): Elsevier. 72 p.
W.L. Gore. 2017. Fabrics goal for eliminating PFCs of environmental concern. [cited 2017 July 12]. https://www.gore-tex.com/pfcgoal

 © 2018 The Authors