

Testimony of Dr. Maricel V. Maffini, Independent Consultant, in support of LD 1433, “An Act To Protect the Environment and Public Health by Further Reducing Toxic Chemicals in Packaging” before the Committee on Environment and Natural Resources of the State of Maine Legislature.

April 17, 2019

Dear Committee Members:

My name is Dr. Maricel V. Maffini. I am a scientist and independent consultant based in Frederick, Maryland. I hold a doctorate in Biological Sciences. My work focuses on safety assessment of chemicals in food and the scientific basis for safety determinations. I work with public interest organizations and the private sector. I have also co-authored petitions to the U.S. Food and Drug Administration (FDA) to revoke uses of toxic chemicals in food and food packaging including carcinogenic flavors, long-chain perfluorinated chemicals, perchlorate and ortho-phthalates. My testimony is in SUPPORT of LD 1433.

Both, per and polyfluorinated alkyl substances (PFAS) and ortho-phthalates (hereafter phthalates) have a few things in common:

- They are families or classes of chemicals;
- Many of them are commonly found in the body of most Americans tested by the Centers for Disease Control and Prevention;¹
- Scientists have reported long-term developmental, reproductive, intellectual and behavioral effects of chemicals that have been studied in each class at very low levels of exposure;
- Contaminate our food and our environment;
- FDA regulates their multiple uses in packaging and handling equipment.

Per and polyfluorinated alkyl substances

Also known as PFAS, members of this class of chemicals have been measured in [drinking water](#), [ground water](#) and food. PFAS have also been found in fast food packaging,² [take out packaging](#) at grocery stores and [popcorn bags](#). Most studies have measured the amount of fluorine in the packaging as a surrogate for the PFAS class. It is important to note, that there aren't harmonized analytical methods and best practice to measure individual PFAS mostly due to the lack of information on identity of the chemicals or standards for identification.

The FDA regulates food contact substances also referred to as packaging chemicals. When a company seeks FDA's pre-market approval of packaging chemicals, it is [required](#) to provide the agency with all relevant [chemistry](#), [toxicology](#) and [environmental](#) data so it can conduct a safety assessment. While the agency typically conducts a literature search of its own and of public databases, the company that is

¹ [Per- and Polyfluorinated Substances \(PFAS\) Factsheet](#). [Phthalates Factsheet](#).

² Schaider et al. (2017). Fluorinated Compounds in U.S. Fast Food Packaging. [Environ Sci Technol Lett. 4\(3\):105-111](#)

claiming the chemical's use is safe is obligated to include any data that is inconsistent with the company's conclusion.

This requirement is essential because, as part of the safety assessment, the agency must determine that there is a reasonable certainty of no harm from the chemical's intended use considering three factors: 1) the probable consumption of the chemical due to the use; 2) the cumulative effect of chemically- and pharmacologically-related substances in the diet; and 3) appropriate safety factors. When data are omitted, the agency could miss critical information that would prompt it to raise questions, demand more studies, and possibly refuse to approve the use.

As a practical matter, this review is critical because it is FDA's best chance to get it right; the agency rarely looks back at the safety of a chemical unless there is a later notice or other request for the same substance. For instance, FDA has never withdrawn an approval for a food contact substance notification (FCN), not even when it raised [concerns about the safety of long-chain PFASs](#). When the agency asked manufacturers of these toxic PFAS BASF, DuPont and Clariant for more safety information, the manufacturers responded by voluntarily ceasing the use of chemicals and stop distribution of products containing long-chain PFAS. Because this was a voluntary action by industry and not a formal revocation of use by FDA, there is no enforcement. Therefore, it does not preclude other actors, both domestic and foreign, to ignore it and continue their use without the agency's or the public's knowledge.

Even when it was aware of all the health concerns about PFAS in the early-2000s, FDA continued to approved them. Between 2002 and 2016, the agency approved an additional 33 [food contact notifications](#) for PFAS uses to coat paper and paperboard, and for repeat uses in bakeware and food handling equipment. The notifications were submitted by six companies for 19 distinct mixtures of PFAS. Appendix 1 contains the list of all effective PFAS food contact notifications and the PFAS monomers used in the manufacturing of the PFAS polymers.

One challenge to effectively evaluating the health impacts of PFASs is that there is very little information on where these chemicals are being used and the toxicology information available. In response to a [Freedom of Information Act request](#), we identified serious breakdown in the safety assessment of PFAS. Specifically, we identified Daikin's serious breach of its obligation to provide FDA with all relevant toxicology data.³

Other revealing information we learned from the response to the FOIA request is that companies did not present any information on the persistence of PFAS in animals; neither did FDA request such information. A decade ago, industry led us to believe that the new technology replacing toxic long-chain PFAS such as PFOS and PFOA would be "more favorable" to human health and the environment. As a result, FDA has been approving the so-called 'short-chain' PFAS for use in contact with food without information on the potential biopersistence of the chemicals themselves or their breakdown products.⁴

It is becoming clear that the bright line between short-chain (less than eight fully fluorinated carbons) and long-chain (eight or more fully fluorinated carbons) PFAS is not as clear as industry would like it. FDA's own scientists have shown a commonly used raw material to make greaseproof paper is likely to

³ [FDA-approved PFAS: A serious breakdown in assessing food additive safety](#).

⁴ [The elephant in the room: Potential biopersistence of short-chain PFAS](#). (attached as Appendix 5)

persist in the human body.⁵ FDA scientists' sophisticated analysis and remarkable conclusion raises questions about the broad assumption that short-chain perfluorinated alkyl substances (PFAS), as a class, did not accumulate. Appendix 2 is a copy of the FDA's scientists peer-reviewed publication.

Industry expected that these C6 compounds (chemicals with six fully fluorinated carbons), among them 6:2 FTOH and its main manufacturing impurity perfluorohexanoic acid (PFHxA), would: 1) be less toxic than long-chain PFAS such as 8:2 FTOH, PFOA and PFOS; and 2) not accumulate in the body. However, these expectations do not hold up under scrutiny because there are significant data gaps remaining and evidence of potential biopersistence.⁶ (Appendix 3)

Additionally, a new study by scientists from the U.S. Environmental Protection Agency and the National Institute of Environmental Health Sciences concluded that the effects of a short-chain PFAS (HFPO-DA or GenX) in rats were similar to those caused by the toxic PFOS and PFOA.⁷ Once again, the toxicity of these short-chain PFAS may not be as low as it was suggested.

In conclusion, the evidence strongly suggests that there the old assumptions about clear-cut distinctions between PFAS based on carbon-length chain and toxicity may not hold to current empirical data. The integration of evidence is conducive towards treating PFAS as a class as defined in LD 1433.

Phthalates

Phthalates have been used in food manufacturing even before the Food Additive Amendment of 1958 to the Federal Food Drug and Cosmetic Act of 1938 was enacted. FDA has approved 28 phthalates uses as diverse as plasticizers (most commonly to polyvinyl chloride plastic), binders, coating agents, defoamers, gasket closures and slimicide agents to process packaged food. The agency allows them to be used in cellophane, paper, paperboard, and plastics that come in contact with food. All of the chemicals were approved by the agency before 1985 and, although the scientific knowledge has advanced, there hasn't been a reevaluation of their safety since then.

FDA does not have limits to how much phthalates can be present in food; the agency recommends that the manufacturer follows good manufacturing practice, in other words, it can add as much phthalate as needed for the product's functionality but not more. Because phthalates are not tightly bound to the materials they are added, they migrate into the food very easily.

⁵ Kabadi et al. (2018). Internal exposure-based pharmacokinetic evaluation of potential for biopersistence of 6:2 fluorotelomer alcohol (FTOH) and its metabolites. [Food and Chemical Toxicology 112:375-382](#).

⁶ Maffini and Neltner. (2019). Overgeneralization by Anderson et al. and Luz et al. regarding safety of fluorotelomer-base chemistry.

<https://www.sciencedirect.com/science/article/pii/S0273230019300935?via%3Dihub>

⁷ Conley et al. (2019). Adverse Maternal, Fetal, and Postnatal Effects of Hexafluoropropylene Oxide Dimer Acid (GenX) from Oral Gestational Exposure in Sprague-Dawley Rats. [Environmental Health Perspectives 127\(3\) March 2019](#)

They have been found in a wide variety of foods from fresh fruits and vegetables⁸ to baby food and more complex processed foods where it is not uncommon to find two or more phthalates present in the same food.⁹ They are also found in foods packaged in different materials such as plastic, glass or paper.

Academic studies have linked some of these chemicals to various reproductive, developmental and endocrine health problems. In fact, every phthalate that has been studied for these types of health effects has been found to pose a risk. From lower IQ in young children¹⁰ to malformation of the male genital tract,¹¹ the evidence of health effects in humans continues to grow.

Although phthalates are better known for their effects in blocking the normal production or function of androgens—the male hormones—risk of health effects have been documented in female reproduction,¹² metabolism,¹³ and obesity.¹⁴ The molecular mechanisms underpinning these effects are unclear.

It's worth noting that eight phthalates allowed in food without limiting quantities have been banned for use in children's toys and other articles;¹⁵ however, food is the main source of phthalates exposure for many people. The Consumer Product Safety Commission (CPSC)'s [Chronic Hazard Advisory Panel](#) evaluated the cumulative risk of phthalates grouped by their common effect on male reproductive development. Their advice was to permanently ban eight phthalates due to their increased health risk to children.

Like CPSC's approach, the [European Chemical Agency](#) also evaluated the cumulative risk of phthalates of four phthalates and the [European Food Safety Authority](#) has recently released its draft scientific opinion on the safety assessment of five phthalates and estimated a tolerable daily intake for the group. One may disagree with some of rationale these agencies have put forward, but it is clear that regulating phthalates as a class is the best approach.

Unlike its counterparts, FDA has not taken any measures to deal with phthalates in food. The agency has yet to decide on three overlapping petitions requesting the agency take action on uses of ortho-phthalates in contact with food. Two of the petitions—a [food additive petition](#) and a [citizen petition](#)—were submitted by 10 public interest organizations. In those petitions, FDA was asked to revoke all uses

⁸ Cao et al. (2015). Di-(2-ethylhexyl) adipate and 20 phthalates in composite food samples from the 2013 Canadian Total Diet Study. [Food Additives & Contaminants, Part A. 32\(11\):1893-1901](#)

⁹ Schechter et al. (2013). Phthalate Concentrations and Dietary Exposure from Food Purchased in New York State. *Environmental Health Perspectives* 121:473-479

¹⁰ Factor-Litvak et al. (2014). Persistent association between maternal prenatal exposure to phthalates on child IQ at age 7 years. [PLoS One 9\(12\):e114003](#)

¹¹ Swan et al. (2015). First trimester phthalate exposure and anogenital distance in newborns. [Human Reproduction 30\(4\):963-972](#)

¹² Kay et al. (2013). Reproductive and developmental effects of phthalate diesters in females. [Critical Reviews in Toxicology 43\(3\):200-219](#)

¹³ Huang et al. (2014). Gender and racial/ethnic differences in the associations of urinary phthalate metabolites with markers of diabetes risk: National Health and Nutrition Examination Survey 2001-2008. [Environ Health 13:6](#).

¹⁴ Hatch et al. (2008). Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: a cross-sectional study of NHANES data, 1999-2002. [Environmental Health 7:27](#)

¹⁵ [CPSC Prohibits Certain Phthalates in Children's Toys and Child Care Products](#).

of this class of chemicals in food because of human health concerns. The [third petition](#) was submitted by an industry group claiming that only four (out of 28) phthalates remain in use.¹⁶

The petition from the public interest groups showed that phthalates are a class of chemically- and pharmacologically-related substances associated with reproductive, developmental, and endocrine health effects. It demonstrated that, when the cumulative effect of these chemicals in the diet are considered as required by law, the FDA cannot conclude their use as food contact substance is safe. Given these health risks, the petition requested FDA to remove all food uses it had previously approved including those for paper, plastic, adhesives, coatings, and metal lubricants. The group also asked that FDA explicitly prohibit use of the eight banned for use in toys that children put in their mouths, reasoning that if the chemicals are not safe in such toys, they have no place in children's food.

Although FDA has a duty to act, it has been very slow to protect public health even in the presence of overwhelming evidence.

In closing, for the last nine years, my colleagues and I have documented how broken the FDA food additive regulatory system is. (Appendix 4). A well-intentioned law with a strong safety standard has been swallowed by a loophole that allows manufacturers to determine the use of chemicals they profit from is safe in secret, without informing FDA. In addition, FDA is not using modern scientific principles when reviews packaging chemicals and it doesn't look back to reassess whether chemicals approved decades ago—some with little or no data—are still safe.

I am encouraged by the approach laid out by LD 1433. Regulating phthalates and PFAS as a class should be a no-brainer to reduce exposure to toxic chemicals. Continuing to wait for FDA to act is to continue putting the health of our most vulnerable populations—pregnant women, children and the elderly—unnecessarily at risk.

I fully support LD 1433 and respectfully urge you to vote "ought to pass".

Sincerely,



Maricel V. Maffini, Ph.D.

¹⁶ [How and when will FDA rule on ortho-phthalates in food? It's anyone's guess.](#)

Appendix 1: PFAS Food Contact Substances Approved by U.S. Food and Drug Administration

PFAS Monomers included in [Food Contact Notifications](#) (FCNs) submitted to FDA for pre-market approval

Unique PFAS monomers and its variations used across 33 FCNs by 6 companies:

- 1- 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate
- 2- 2-propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester
- 3- 1, 1-difluoroethylene
- 4- hexafluoropropene
- 5- tetrafluoroethylene
- 6- trifluoromethyl trifluorovinyl ether
- 7- 4-bromo-3,3,4,4-tetrafluoro-1-butene
- 8- 3,3,3-trifluoropropene
- 9- 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octanol
- 10- hexafluoropropylene,
- 11- perfluoroethyl vinyl ether
- 12- 1,1,2-trifluoro-2-(1,1,2,2,2-pentafluoroethoxy)ethane
- 13- pentafluoroiodoethane-tetrafluoroethylene telomer
- 14- 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane
- 15- perfluoropolyether diol (NOTE: it appears to be the same as tetrafluoroethylene)
- 16- Perfluoropolyether dicarboxylic acid

Company FCN#	Food Contact Substance	PFAS monomer	Comments
Archroma 1493	2-Propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester, polymer with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, N-oxides, acetates (CAS Reg. No. 1440528-04-0)	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate	2-methyl-2-propeonate is also called methyl methacrylate and methacrylate Tridecafluorooctyl is also called perfluorohexyl ethyl

Company FCN#	Food Contact Substance	PFAS monomer	Comments
			The monomer is also known as C6SFMA
Asahi 599	Copolymer of 3,3,4,4,5,5,6,6, 7, 7,8,8,8-tridecafluorooctylmethacrylate, 2-N,N-diethylaminoethylmethacrylate, 2-hydroxyethylmethacrylate, and 2,2'-ethylenedioxydiethylmethacrylate	3,3,4,4,5,5,6,6, 7, 7,8,8,8-tridecafluorooctylmethacrylate	Same as FCN 1493
Asahi 604	Copolymer of polyfluorooctyl methacrylate, 2-N,N-diethylaminoethylmethacrylate, 2-hydroxyethylmethacrylate, and 2,2'-ethylenedioxydiethylmethacrylate	polyfluorooctyl methacrylate	Same as FCN 1493?
Asahi 1186	Butanedioic acid, 2-methylene-, polymer with 2-hydroxyethyl, 2-methyl-2-propenoate, 2-methyl-2-propenoic acid and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, sodium salt (CAS. Reg. No. 1345817-52-8).	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, sodium salt	Same as 1493
Asahi 1676	2-propenoic acid, 2-methyl-, 2-hydroxyethyl ester, polymer with 2-propenoic acid and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, sodium salt [CAS Reg. No. 1878204-24-0]	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, sodium salt	Same as 1493
Chemours 510	Copolymer of 1, 1-difluoroethylene (CASRN 75-38-7), hexafluoropropene	1, 1-difluoroethylene, hexafluoropropene, tetrafluoroethylene	

Company FCN#	Food Contact Substance	PFAS monomer	Comments
	(CASRN 116-15-4), and tetrafluoroethylene (CASRN 116-14-3)		
Chemours 511	Copolymer of 1, 1,-difluoroethylene (CASRN 75-38-7), tetrafluoroethylene (CASRN 116-14-3), and trifluoromethyl trifluorovinyl ether (CASRN 1187-93-5)	1, 1-difluoroethylene, tetrafluoroethylene, trifluoromethyl trifluorovinyl ether	
Chemours 539	Copolymer of 4-bromo-3,3,4,4-tetrafluoro-l-butene, ethylene, tetrafluoroethylene and trifluoromethyl trifluorovinyl ether optionally cured with triallyl isocyanurate and 2,5-dimethyl-2,5-di(tert-butylperoxy)hexane. (CASReg. No.105656-63-1)	4-bromo-3,3,4,4-tetrafluoro-l-butene, tetrafluoroethylene, trifluoromethyl trifluorovinyl ether	
Chemours 598	Copolymer of propylene, tetrafluoroethylene and 3,3,3-trifluoropropene	Tetrafluoroethylene, 3,3,3-trifluoropropene	
Chemours 885	2-propenoic acid, 2-methyl-, polymer with 2-(diethylamino)ethyl 2-methyl-2-propenoate, 2-propenoic acid and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, acetate (CAS Reg. No. 1071022-26-8)	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, acetate	Same as FCN 1493 (acetate instead of propenoate)
Chemours 940	hexane, 1,6-diisocyanato-, homopolymer, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octanol-blocked	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octanol	6:8 fluorotelomer alcohol
Chemours 947	Copolymer of hexafluoropropylene, tetrafluoroethene and perfluoroethyl vinyl ether	hexafluoropropylene, tetrafluoroethene, perfluoroethyl vinyl ether	

Company FCN#	Food Contact Substance	PFAS monomer	Comments
Chemours 948	Ethene, 1,1,2,2-tetrafluoro-, polymer with 1,1,2-trifluoro-2-(1,1,2,2,2-pentafluoroethoxy)ethane	Ethene, 1,1,2,2-tetrafluoro, 1,1,2-trifluoro-2-(1,1,2,2,2-pentafluoroethoxy)ethane	Ethene, 1,1,2,2-tetrafluoro is the same as tetrafluoroethene
Chemours 1027	2-Propenoic acid, 2-methyl-, polymer with 2-(diethylamino)ethyl 2-methyl-2-propenoate, 2-propenoic acid and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, acetate	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, acetate	Same as FCN 1493 (acetate instead of propenoate)
Daikin 820	2-propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester, polymer with alpha-(1-oxo-2-propen-1-yl)-omega-hydroxypoly(oxy-1,2-ethanediyl)	2-propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester	The monomer is also known as 13FA, C6SFA and perfluorohexyl ethyl acrylate
Daikin 827	1-propenoic acid, 2-hydroxyethyl ester, polymer with alpha-(1-oxo-2-propen-1-yl)-omega-hydroxypoly(oxy-1,2-ethanediyl), alpha-(1-oxo-2-propen-1-yl)-omega-[(1-oxo-2-propen-1-yl)oxy]poly(oxy-1,2-ethanediyl) and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate	Same as 820
Daikin 888	2-Propenoic acid, 2-hydroxyethyl ester, polymer with alpha-(1-oxo-2-propen-1-yl)-omega-hydroxypoly(oxy-1,2-ethanediyl), alpha-(1-oxo-2-propen-1-yl)-omega-[(1-oxo-2-propen-1-yl)oxy]poly(oxy-1,2-ethanediyl), and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate	Same as 820

Company FCN#	Food Contact Substance	PFAS monomer	Comments
Daikin 933	2-propenoic acid, 2-methyl-, polymer with 2-hydroxyethyl 2-methyl-2-propenoate, α -(1-oxo-2-propen-1-yl)- ω -hydroxypoly(oxy-1,2-ethanediyl), and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate, sodium salt.	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate	Same as 820
Daikin 1044	2-Propenoic acid, 2-methyl-, 2-hydroxyethyl ester, polymer with 1-ethenyl-2-pyrrolidinone, 2-propenoic acid and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate, sodium salt	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate	Same as 820
Daikin 1360	2-Propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester, polymer with 1-ethenyl-2-pyrrolidinone and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate, acetate (CAS Reg. No. 1334473-84-5).	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate	Same as 820
Daikin 1451	2-Propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester, polymer with 1-ethenyl-2-pyrrolidinone and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate, acetate (CAS Reg. No. 1334473-84-5)	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate	Same as 820
Solenis 314	2-propen-1-ol, reaction products with pentafluoroiodoethane-tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and	pentafluoroiodoethane-tetrafluoroethylene telomer	

Company FCN#	Food Contact Substance	PFAS monomer	Comments
	triethylenetetramine (CAS Reg. No. 464178-90-3)		
Solenis 487	2-propen-1-ol, reaction products with pentafluoroiodoethane-tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine (CAS Reg. No. 464178-90-3)	pentafluoroiodoethane-tetrafluoroethylene telomer	Same as 487
Solenis 518	2-Propen-1-01, reaction products with pentafluoroiodoethane-tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine	pentafluoroiodoethane-tetrafluoroethylene telomer	Same as 487
Solenis 542	2-propen-1-ol, reaction products with 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine (CAS Reg. No. 464178-94-7)	1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane	
Solenis 746	2-Propen-1-ol, reaction products with 1,1,1,2,2,3,3,4,4,4,5,5,6,6-tridecafluoro-6-iodohexane, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine	1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane	Same as 542
Solenis 783	2-propen-1-ol, reaction products with 1,1, 1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane, dehydroiodinated, reaction products with epichlorohydrin	1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane	Same as 542

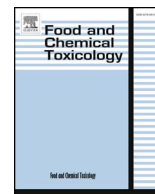
Company FCN#	Food Contact Substance	PFAS monomer	Comments
	and triethylenetetramine (CAS Reg. No. 464178-94-7)		
Solvay 187	Fluorinated polyurethane anionic resin (CAS Reg. No. 328389-91-9) prepared by reacting perfluoropolyether diol (CAS Reg. No. 88645-29-8), isophorone diisocyanate (CAS Reg. No. 4098-71-9), 2,2-dimethylpropionic acid (CAS Reg. No. 4767-03-7), and triethylamine (CAS Reg. No. 121-44-8).	perfluoropolyether diol	Also known as polyperfluoroethoxymethoxy difluoroethyl peg ether; Tetrafluoroethylene; Ethene, 1,1,2,2-tetrafluoro-
Solvay 195	Phosphate esters of ethoxylated perfluoroether. Starting materials: Ethoxylated perfluoroether diol (CAS# 162492-15-1), Phosphorous pentoxide (CAS# 1314-56-3), Pyrophosphoric acid (CAS# 2466-09-3)	perfluoroether diol	Same as 187
Solvay 398	Perfluoropolyether dicarboxylic acid (CAS Reg. No. 69991-62-4), ammonium salt.	Perfluoropolyether dicarboxylic acid	Acid form of perfluoroether diol
Solvay 416	Diphosphoric acid, polymers with ethoxylated reduced methyl esters of reduced polymerized oxidized tetrafluoroethylene (CAS 200013-65-6)	tetrafluoroethylene	Same as 510
Solvay 538	Perfluoropolyether dicarboxylic acid (CAS Reg. No. 69991-62-4), ammonium salt	Perfluoropolyether dicarboxylic acid	Same as 398
Solvay 962	Diphosphoric acid, polymers with ethoxylated reduced methyl esters of reduced polymerized oxidized tetrafluoroethylene (CAS Reg. No.	tetrafluoroethylene	Same as 510

Company FCN#	Food Contact Substance	PFAS monomer	Comments
	200013-65-6). FCS is also known as phosphate esters of ethoxylated perfluoroether, prepared by reaction of ethoxylated perfluoroether diol (EPFED, CAS Reg. No. 162492-15-1) with phosphorous pentoxide (CAS Reg. No. 1314-56-3) or pyrophosphoric acid (CAS Reg. No. 2466-09-3)		



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Short communication

Internal exposure-based pharmacokinetic evaluation of potential for biopersistence of 6:2 fluorotelomer alcohol (FTOH) and its metabolites

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Area under the curve
Allometric scaling
Biopersistence

ABSTRACT

Polyfluorinated compounds (PFCs) are authorized for use as greaseproofing agents in food contact paper. As C8-PFCs (8-carbons) are known to accumulate in tissues, shorter-chain C6-PFCs (6-carbons) have replaced C8-PFCs in many food contact applications. However, the potential of C6-PFCs for human biopersistence has not been fully evaluated. For the first time, we provide internal exposure estimates to key metabolites of 6:2 fluorotelomer alcohol (6:2 FTOH), a monomeric component of C6-PFCs, to extend our understanding of exposure beyond estimates of external exposure. Pharmacokinetic data from published rat and human studies on 6:2 FTOH were used to estimate clearance and area under the curve (AUC) for its metabolites: 5:3 fluorotelomer carboxylic acid (5:3 A), perfluorohexanoic acid (PFHxA) and perfluoroheptanoic acid (PFHpA). Internal exposure to 5:3 A was the highest of evaluated metabolites across species and it had the slowest clearance. Additionally, 5:3 A clearance decreased with increasing 6:2 FTOH exposure. Our analysis provides insight into association of increased internal 5:3 A exposure with high biopersistence potential of 6:2 FTOH. Our results identify 5:3 A as an important biomarker of internal 6:2 FTOH exposure for use in biomonitoring studies, and are potentially useful for toxicological assessment of chronic dietary 6:2 FTOH exposure.

1. Introduction

Polyfluorinated polymers have been authorized for use as greaseproofing agents in paper and paperboard food contact applications under several Food Contact Notifications (FCNs) and Title 21 of the Code of Federal Regulations (21 CFR) (Rice, 2015). These products include microwave popcorn bag susceptors, and greaseproofing films in paper and paperboard in contact with oily foods, such as fast food containers and pizza boxes (Rice, 2015). Fluorotelomer alcohols (FTOHs) are components of high-molecular weight polymeric food contact substances (FCSs) used as coatings which are subject of several FCNs for use as greaseproofing agents in food contact paper and paperboard. In recent years, epidemiological studies, *in vivo* animal studies and *in vitro* studies have demonstrated the potential of certain C8-PFCs (8 carbons in length), particularly perfluorinated carboxylic acids (PFCAs) such as perfluorooctanoic acid (PFOA), and 8:2 FTOH; to accumulate in the environment, and persist in mammalian tissues leading to cancer and other potent adverse effects related to systemic and developmental toxicity (Ladics et al., 2008; Martin et al., 2009; Nabb et al., 2007; Nilsson et al., 2010a, 2010b, 2013; Perkins et al., 2004). Concerns from these data led to regulatory actions by several agencies,

including the United States Environmental Protection Agency (US EPA) and Food and Drug Administration (FDA), towards discontinuing the use of C8-PFCs in the production of polyfluorinated FCSs by voluntary agreements with industry to phase out these compounds from all uses, particularly those involving direct contact with food (Rice, 2015). The European Union (Juncker, 2017) and Canada (2012) have also restricted use of PFOA, its salts and its polymeric precursors in food contact applications. As a result, industry replaced C8-PFCs with shorter-chain C6-PFCs (6 carbons in length) with similar greaseproofing properties, as a safer alternative. Generally, shorter-chain PFCs such as perfluorohexanoic acid (PFHxA) and perfluorobutanoic acid (PFBA), have been reported to have shorter serum elimination half-lives ($t_{1/2}$; hours versus days) than C8-PFCs, such as PFOA (Wang et al., 2013). However, the pharmacokinetic profiles of the C6-FTOHs, crucial components of the C6-polyfluorinated replacement FCSs, have not been elucidated, and their potential for biopersistence in mammalian tissues has not been fully evaluated yet. To understand the potential for biopersistence from chronic dietary exposure of C6-PFC compounds like the C6-FTOH, data on their pharmacokinetic properties in humans and animal models are necessary. C8-PFCs have been well-known to have extremely long elimination half-lives in humans versus animal models.

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Safety assessments may need to account for higher accumulated body burden per given daily dose in humans versus animal models. Given the structural similarity of C6-FTOH to the biopersistent C8-PFCs, it is imperative to assess whether the C6-FTOH also displays bioaccumulative properties in human and animal model tissues. For the first time, we provided internal exposure estimates of key metabolites of a type of C6-FTOH; 6:2 FTOH (CASRN: 647-42-7) in rats and humans, in an effort to extend our understanding of exposure beyond estimates of administered dose of 6:2 FTOH.

We performed a preliminary assessment of the potential of C6-FTOH to persist in mammalian tissues using noncompartmental pharmacokinetic analysis of published data from inhalation exposure to 6:2 FTOH (5 ppm and 50 ppm, one-day) in rats and occupational exposure to a mixture of PFCAs and polyfluoroalkyl compounds consisting of 6:2 FTOH (in fluorinated ski wax, 30 h per week in winter months for 4 years) in humans, respectively, reported in a publication by Russell et al. (2015). A noncompartmental pharmacokinetic approach describes estimation of total internal exposure, commonly represented by the area under the curve (AUC) of the plasma or blood concentration versus time curve. Our analysis represents a quantitative and reliable approach based on a noncompartmental pharmacokinetic analysis for novel interpretation of published data to evaluate the potential of 6:2 FTOH, and, by extension, C6-PFCs manufactured from this compound to cause human biopersistence. Furthermore, our preliminary internal exposure-based assessment provided a valuable insight into disposition of 6:2 FTOH and its metabolites and helped identify some factors that may increase their internal exposures. This information is important to better understand the pharmacokinetic profile of 6:2 FTOH and similar C6-PFCs in the human body and can further be used for designing additional pharmacokinetic and toxicological studies needed for generating appropriate data to conclusively determine whether 6:2 FTOH leads to biopersistence and contributes to systemic toxicity in humans after long-term exposure. Therefore, our work represents the first step towards identifying the mechanism by which 6:2 FTOH, similar C6-PFCs, and its metabolites could accumulate in the body to potentially cause adverse effects.

1.1. Pharmacokinetics

Although inhalation and oral pharmacokinetic studies of 6:2 FTOH in different species have been published, there is insufficient information available in the literature to elucidate a complete pharmacokinetic profile of 6:2 FTOH under conditions of chronic oral exposure. Most of the published reports are in the form of abstracts or journal articles with no data on individual animals and limited or no data on metabolite plasma or tissue concentrations, respectively. Furthermore, the shorter duration (single exposure or repeated exposure for days instead of weeks to months) and low numbers of doses used in these studies make the dose response analysis challenging. In contrast, more pharmacokinetic data have been generated and published on single and repeated exposure of 8:2 FTOHs using *in vivo* and *in vitro* systems, and the biopersistence of 8:2 FTOH has been associated with the long-term internal exposure to some of its metabolites, particularly PFCAs such as PFOA (Himmelstein et al., 2012a, b; Martin et al., 2009; Nabb et al., 2007; Nilsson et al., 2010a, 2010b, 2013; Yang et al., 2009).

To better understand the pharmacokinetic profile of 6:2 FTOH, it is important to examine the metabolism of this compound and evaluate the contribution of its metabolism to the potential for toxicity. The biotransformation reactions involved in the metabolism of 8:2 FTOH and 6:2 FTOH appear to be similar. However, the $t_{1/2}$ of PFHxA has been observed to be significantly shorter than PFOA in rats, monkeys, and humans across exposure routes (Wang et al., 2013). This decreased systemic $t_{1/2}$ of PFHxA is associated with a marked decrease in toxic potency of approximately 100-fold in male rats under the conditions of 90-day repeated exposure (Chengelis et al., 2009; Perkins et al., 2004). In contrast, the no observed effect levels (NOELs) for systemic toxicity

in rats of 8:2 FTOH and 6:2 FTOH have been observed to be similar in 90-day oral toxicity studies (Ladics et al., 2008; Serex et al., 2014), implying no decrease in toxic potency with shortening of the perfluorinated chain length in short-term studies. This finding raises questions regarding potential accumulation and toxicity of 6:2 FTOH in tissues, as the bioaccumulation previously observed with C8-PFCs, such as 8:2 FTOH and PFOA, has been reportedly linked with cancer and adverse effects related to developmental toxicity (Ladics et al., 2008; Martin et al., 2009; Nabb et al., 2007; Nilsson et al., 2010a, 2010b, 2013; Perkins et al., 2004). Furthermore, an analysis of structure-toxicity relationship using isolated rat hepatocytes revealed that the lethal concentration 50 (LC50) value for 8:2 FTOH was lower than 6:2 FTOH (1.4 ± 0.37 mM versus 3.7 ± 0.54 mM), indicating the higher potency of 8:2 FTOH for cytotoxicity under the conditions of the study (Martin et al., 2009). Therefore, pharmacokinetic data on 8:2 FTOH cannot be supplemented to perform a pharmacokinetic assessment of 6:2 FTOH, and it is necessary to examine the potential of biopersistence of 6:2 FTOH by evaluating data from pharmacokinetic studies performed specifically on 6:2 FTOH.

1.2. Scheme of metabolism of 6:2 FTOH

Pharmacokinetic modeling and metabolism studies using rodents (Gannon et al., 2011; Gannon et al., 2012) and comparative studies in rodent and human hepatocytes (Gannon et al., 2010; Ruan et al., 2014) have identified liver as the primary site of 6:2 FTOH metabolism, followed by the kidneys. Glutathione, glucuronide, and sulfate conjugates are the primary metabolites. Furthermore, 5:3 fluorotelomer carboxylic acid (5:3 A), perfluoropentanoic acid (PFPeA), and PFHxA are minor metabolites of 6:2 FTOH (Gannon et al., 2012; Gannon et al., 2010; Kelly et al., 2011; Russell et al. (2015)). Some *in vivo* studies (DeLorme et al., 2011; Gannon et al., 2012; Kelly et al., 2011; Russell et al., 2015) have demonstrated that 6:2 FTOH is rapidly systemically absorbed after oral as well as inhalation exposure, with no difference in metabolism between the two routes of administration. Based on the reviewed information (Gannon et al., 2012; Gannon et al., 2010; Kelly et al., 2011; Ruan et al., 2014; Russell et al., 2015), we propose a scheme for the metabolism of 6:2 FTOH (Fig. 1). 6:2 FTOH is metabolized to first form transient intermediates, 6:2 fluorotelomer aldehyde (6:2 FTAL) and saturated and unsaturated fluorotelomer carboxylic acids (6:2 FTCA and 6:2 FTUCA), across species, which represents Phase I metabolism. The parent 6:2 FTOH and the intermediates then undergo phase II competitive conjugation reactions to form glutathione, glucuronide, and sulfate conjugates, which are the major routes of metabolism (Ruan et al., 2014; Russell et al., 2015). The transient intermediates may follow another metabolic pathway to form terminal products that include PFCAs, such as PFBA, PFPeA, PFHxA, PFHpA, 5:3 A, and 4:3 fluorotelomer carboxylic acid (4:3 A), which is also representative of Phase I metabolism. It has been hypothesized that these terminal metabolites lead to a long-term internal exposure that contributes to systemic toxicity of 6:2 FTOH (Russell et al., 2015). The Phase II conjugates further undergo Phase III metabolism to be eliminated mainly in the urine and to some extent in the bile. The Phase III metabolism involves facilitation of uptake or efflux of the Phase II conjugates by transporters. Studies have suggested the involvement of organic anion transporting polypeptide (OATP) and organic anion transporters (OAT) in the cellular reabsorption and secretion, respectively, of the PFCAs, such as PFOA in the kidneys (Weaver et al., 2010; Worley and Fisher, 2015; Yang et al., 2009; Nakagawa et al., 2009). However, additional metabolism studies are necessary to examine the role of specific transporters, particularly in the kidneys, in Phase III metabolism and elimination of Phase II conjugates of 6:2 FTOH.

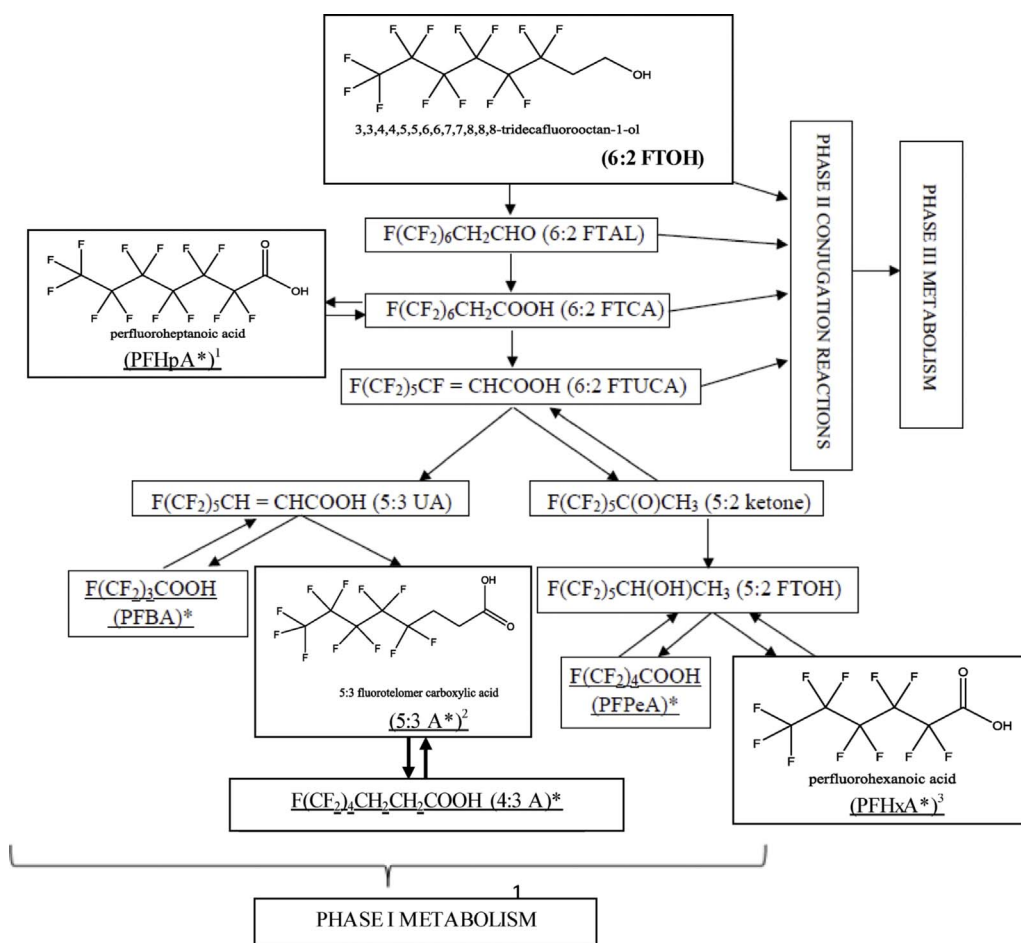


Fig. 1. Proposed Scheme for Metabolism of 6:2 FTOH with a representation of Phase I, Phase II and Phase III metabolism.

* represents metabolites linked with the potential biopersistence.

^{1,2,3} represent the metabolites (structures drawn using ChemDraw Professional 16.0) whose internal exposures were estimated.

2. Materials & methods

2.1. Strategy for pharmacokinetic assessment

In vivo studies have demonstrated that 6:2 FTOH is rapidly systemically absorbed after oral and inhalation exposure, without any route-specific toxicity, and the metabolic profile of 6:2 FTOH remains consistent across exposure routes in all species (DeLorme et al., 2011; Gannon et al., 2012; Gannon et al., 2010; Kelly et al., 2011; Russell et al., 2015). Extrahepatic metabolism of 6:2 FTOH may play an important role in its disposition; however sufficient data are not available to describe the relative contribution of extrahepatic metabolism of 6:2 FTOH to the internal exposure of its metabolites.

We used published data from rat and human studies (Russell et al., 2015) to estimate certain pharmacokinetic parameters as markers of internal exposure for 6:2 FTOH and its metabolites. The publication by Russell et al. (2015) provided a comprehensive compilation of results from single and repeated-exposure studies performed in rats (DeLorme et al., 2011; Himmelstein et al., 2012a, b; Serex et al., 2012) and humans (Nilsson et al., 2013). Notably, this publication reported plasma concentration versus time data on key metabolites of 6:2 FTOH; 5:3 A, PFHxA and PFHpA from single exposure rat studies (DeLorme et al., 2011; Himmelstein et al., 2012a, b; Serex et al., 2012) at two exposure levels for both sexes as well as from an occupational exposure study (Nilsson et al., 2013) performed in ski-wax technicians. We utilized the plasma concentration versus time data (Russell et al., 2015) to evaluate the relative potential of metabolites of 6:2 FTOH for biopersistence in these test systems. A description of the design of studies that were reviewed from the Russell et al. (2015) paper and utilized for our preliminary pharmacokinetic analysis has been provided in Table 1. The

code for a one compartment multi-species toxicokinetic model for inhalation exposure to 6:2 FTOH to rats developed by Russell et al. (2015) was described under supplementary material (Russell et al., 2015) of the paper. We reviewed the model code and the model-based predictions provided under supplementary material of Russell et al. paper (2015). Furthermore, the supplementary material in the Russell et al. (2015) paper described the estimation of potential concentrations of 5:3 A, PFHxA and PFHpA from the human occupational exposure study (Nilsson et al., 2013) for biomonitoring purposes based on the conventional equation of a one compartment steady-state model (Russell et al., 2015). We concluded that there were sufficient details, particularly the reported plasma concentrations at different time points, that could be used for performing a preliminary pharmacokinetic analysis for biomonitoring purposes. More importantly, our objective was to review available pharmacokinetic data and utilize information from published studies which could be used for identifying specific factors that could lead to prolonged internal exposure (i.e. biopersistence) of metabolites of 6:2 FTOH.

Russell et al. (2015) paper did not report any data on tissue concentrations. Furthermore, Russell et al. (2015) reported that serum concentrations of 5:3 A reached steady state after repeated inhalation exposure; however, all model parameters, except for $t_{1/2}$ of the metabolites, were constrained to the values obtained from the one-day inhalation exposure study. Upon reviewing the publication and the data reported therein, we concluded that Russell et al. (2015) paper served as a resourceful repository of pharmacokinetic data from inhalation exposure studies in rats (DeLorme et al., 2011; Himmelstein et al., 2012a, b; Serex et al., 2012) and an occupational exposure study in humans (Nilsson et al., 2013), that could be used to perform a preliminary internal exposure-based pharmacokinetic evaluation of 6:2

Table 1

Summary of studies from Russell et al. (2015) and related publications (DeLorme et al., 2011; Himmelstein et al., 2012a,b; Serex et al., 2010; Nilsson et al., 2013) that were reviewed and utilized for a preliminary pharmacokinetic analysis followed by estimation of internal exposure.

Study type (Route of exposure)	Species/Sex	Test Substance	External Exposure (ppm)	Time-course of blood collection (hours)	Estimated markers of internal exposure
Single-exposure (one-day) inhalation (6-h)	Male and female rats	6:2 FTOH	0.5 and 5.0	0, 1, 3, 6, 12 and 24	Elimination rate constant (k_e); clearance (Cl); area under the curve ($AUC_{0-\infty}$)
Repeated (occupational; primarily inhalation) exposure (30 h/week; December through March 2007–2011)	Male ski wax technicians (humans)	Mixture of PFCAs and polyfluoroalkyl compounds including 6:2 FTOH	Occupational exposure (not defined)	Once every day (end of working day) from December through March, followed by monthly from April to August	$AUC_{0-\infty}$

FTOH for biomonitoring purposes. We utilized these data for estimation of markers of internal exposure, particularly clearance (Cl) and AUC using a noncompartmental pharmacokinetic analysis (Appendix) followed by allometric scaling of some data. A noncompartmental approach simplifies the system by reducing it into a finite number of components and is dependent on the estimation of the total internal exposure. The AUC representing internal exposure of metabolites was estimated using the trapezoidal rule (numerical integration) by calculating and adding the areas of trapezoids in the respective plasma concentration versus time curves (Appendix). The data generated from our preliminary analysis could further be interpreted for identifying factors that affected the internal exposure levels of 6:2 FTOH and its metabolites, and therefore, would be taken into consideration for designing future pharmacokinetic studies and toxicological evaluation of long-term exposure to 6:2 FTOH.

2.2. Rat studies

The article by Russell et al., 2015 summarizes results from one-day single exposure and, five-day, and 23-day repeated-dose inhalation studies (DeLorme et al., 2011; Himmelstein et al., 2012a, b; Serex et al., 2012) conducted in male and female rats. The exposures in the one-day study were 0.5 and 5 ppm for 6 h. The longer-term studies were performed with concentrations of 1, 10, and 100 ppm for 6 h per day. In the one-day study, plasma concentrations of 6:2 FTOH and its metabolites; PFBA, PFPeA, PFHxA, PFHpA, 4:3 A, 5:3 A, 6:2 FTCA, and 6:2 FTUCA were determined at designated time points. In contrast, in the longer-term studies plasma concentrations of 6:2 FTOH and its metabolites were reported only at a single time point at the end of the study. Although these studies provided plasma levels of these metabolites after cessation of last exposure, the data were not sufficient for estimating pharmacokinetic parameters. Tissue concentrations from sites, such as liver, were not estimated in these studies.

The plasma concentration over time data from the one-day rat study (Russell et al., 2015) showed that plasma concentrations of 6:2 FTOH at later time points were below the level of quantification (LOQ), confirming that 6:2 FTOH was rapidly absorbed and metabolized. This finding was consistent across all studies and the terminal metabolites of 6:2 FTOH were identified as PFBA, PFHxA, PFHpA, and 5:3 A. Furthermore, the plasma concentrations of 5:3 A, PFHxA, and PFHpA were reported to be higher than other metabolites at the final time point across studies (Russell et al., 2015). The levels of other metabolites at several time points of the one-day study were below the LOQ (Russell et al., 2015).

The study authors used a one compartment model for metabolism of 6:2 FTOH upon inhalation exposure (Himmelstein et al., 2012a, b; Russell et al., 2015; Serex et al., 2012). We verified the model-based predictions and authors' conclusions using data from the one-day inhalation study. The data were extracted using GetData Graph digitizer software (version 2.26.0.20). Across sexes, the metabolite with the highest molar yield at all time points was 5:3 A. The Russell et al. (2015) study reported that the $t_{1/2}$ of 5:3 A after an exposure of 0.5 ppm

was 5.2 h in both male and female rats, and the $t_{1/2}$ values after an exposure of 5 ppm were 11.7 and 14.7 h in male and female rats, respectively. The $t_{1/2}$ values of PFHxA after both exposures were 1.3 h and 0.5 h in male and female rats, respectively (Russell et al., 2015). In contrast, the $t_{1/2}$ values of PFHpA after an exposure of 0.5 ppm were 15.4 h and 2.1 h in male and female rats, respectively; and after an exposure of 5 ppm were 23.2 h and 1.2 h in male and female rats, respectively (Russell et al., 2015).

Using a noncompartmental pharmacokinetic approach (Appendix), we performed a preliminary pharmacokinetic assessment using data from the one-day rat study (Russell et al., 2015). We calculated values for elimination rate constant (k_e ; hr^{-1}), and Cl ($lhr^{-1}kg^{-1}$). We used the “area under the curve, from time zero to infinity” ($AUC_{0-\infty}$) approach to mathematically determine the area of the plasma concentration versus time plots using the trapezoidal rule (Appendix) as a representative of the internal exposure of 5:3 A, PFHxA, and PFHpA.

2.3. Human (occupational) exposure study

A biomonitoring study of occupational exposure of professional ski wax technicians ($n = 11$) was conducted in which the workplace exposure occurred every year for several months in winter from 2007 to 2011 as fluorinated glide waxes were applied with heat to cross-country skis in enclosed settings. The technicians (males only) were exposed via inhalation in the workplace to a chemical mixture comprising PFCAs and polyfluoroalkyl substances, including 6:2 FTOH (Nilsson et al., 2013; Russell et al., 2015). The blood levels of 6:2 FTOH and some of its metabolites (5:3 A, PFHxA, and PFHpA) were analyzed. The blood concentration data over time were provided in the supplementary data tables of the published study report (Nilsson et al., 2013). Russell et al., 2015 used longitudinal blood analysis to estimate geometric mean apparent human $t_{1/2}$ values for 5:3 A, PFHxA, and PFHpA of 43, 32 and 70 days, respectively. We performed a preliminary pharmacokinetic assessment of the human occupational study by estimating $AUC_{0-\infty}$ of the blood concentration versus time graphs of the 6:2 FTOH metabolites as a marker of their internal exposure.

3. Results and analysis

3.1. Rat studies

Using noncompartmental pharmacokinetic analysis, we calculated values for elimination rate constant (k_e ; hr^{-1}), and clearance (Cl; $lhr^{-1}kg^{-1}$) for the three metabolites of 6:2 FTOH: 5:3 A, PFHxA and PFHpA (Table 2). The calculated Cl for 5:3 A was found to be slower than PFHxA across exposure levels and sexes, indicating a potentially higher internal exposure of 5:3 A versus PFHxA under the conditions of the one-day inhalation study. The Cl of PFHpA appeared to be slower than PFHxA across exposure levels but was generally faster than 5:3 A.

Although Russell et al., 2015 study did not provide any tissue concentrations, supplementary data tables of the study report provided mean plasma concentrations of 6:2 FTOH and its metabolites at time

Table 2

Elimination rate constants (k_e) and clearance (Cl) for 5:3 A, PFHxA, and PFHpA after inhalation exposure to 6:2 FTOH in male and female rats.

External Exposure (ppm)	Metabolite	Species	Elimination half-life; $t_{1/2}$ (hours)	Elimination Rate Constant; k_e (h^{-1})	Clearance; Cl ($l\text{kg}^{-1}h^{-1}$)
0.5	5:3 A	Male rats	5.2	0.133	0.027
		Female rats	5.2	0.133	0.027
	PFHxA	Male rats	1.3	0.533	0.107
		Female rats	0.5	1.386	0.277
	PFHpA	Male rats	15.4	0.045	0.009
		Female rats	2.1	0.330	0.066
5.0	5:3 A	Male rats	11.7	0.059	0.012
		Female rats	14.7	0.047	0.009
	PFHxA	Male rats	1.3	0.533	0.107
		Female rats	0.5	1.386	0.277
	PFHpA	Male rats	23.3	0.029	0.006
		Female rats	1.2	0.577	0.116

points of 1, 3, 6, 12, and 24 h. We used the $AUC_{0-\infty}$ approach to mathematically determine (Appendix) the area of the plasma concentration versus time plots using as a representative of the internal exposure over time of 5:3 A, PFHxA, and PFHpA (Table 3). The $AUC_{0-\infty}$ values (nanomoles/l.hr) for concentration versus time curves of 5:3 A, PFHxA, and PFHpA increased with the exposure level which demonstrated that the internal exposure over time of these metabolites increased in a dose-dependent manner. More importantly, the $AUC_{0-\infty}$ values for 5:3 A were estimated to be the highest of the three metabolites irrespective of the species and the exposure levels. Furthermore, the $AUC_{0-\infty}$ values of PFHpA were higher than that of PFHxA in male rats but lower than PFHxA in female rats at both exposure levels. Therefore, we concluded that the Cl of 5:3 A in rats after single inhalation exposure is slower than PFHxA and PFHpA, resulting in a significantly higher internal 5:3 A exposure over time. Furthermore, the internal exposure of 5:3 A did not significantly differ across sexes indicating that there were no sex-based differences in metabolite kinetics of 5:3 A under the conditions of the study. In contrast, higher internal exposure of PFHxA and PFHpA in males than females indicated that male rats could produce higher levels of these metabolites due to a slower clearance (Table 2). These sex-based differences in the pharmacokinetic profiles of PFHxA and PFHpA need to be investigated further.

We located data from a 90-day rat oral study (Gannon et al., 2011), where the animals were administered 5, 25, 125, and 250 mg/kg bw/d of 6:2 FTOH. Terminal concentrations of 6:2 FTOH, PFBA, PFPeA, PFHxA, PFHpA, 4:3 A, 5:3 A, 6:2 FTCA, and 6:2 FTUCA in the plasma were determined. Due to a lack of data on plasma and tissue concentrations of 6:2 FTOH and its metabolites at multiple time points, we could not estimate $AUC_{0-\infty}$ or Cl after repeated oral exposure in this

Table 3

AUC values for 5:3 A, PFHxA, and PFHpA after inhalation exposure to 6:2 FTOH in male and female rats.

External Exposure (ppm)	Metabolite	Species	AUC_{0-t} (nanomoles/l.hr)	$AUC_{t-\infty}$ (nanomoles/l.hr)	$AUC_{0-\infty}$ (nanomoles/l.hr)
0.5	5:3 A	Male rats	4846.2	549.3	5395.5
		Female rats	4885.5	780.4	5665.9
	PFHxA	Male rats	1096.02	12.5	1108.5
		Female rats	490.95	0	490.9
	PFHpA	Male rats	2291.5	1566.7	3858.2
		Female rats	247.13	0	247.1
5.0	5:3 A	Male rats	38955	17254.5	56209.5
		Female rats	33914	24690.9	58604.9
	PFHxA	Male rats	4079	87.2	4166.2
		Female rats	985.13	5.7	990.8
	PFHpA	Male rats	4598.8	6421.8	11010.6
		Female rats	295.7	11.2	306.9

Table 4

AUC values for 5:3 A, PFHxA, and PFHpA after occupational exposure to 6:2 FTOH (mixture of PFCAs and polyfluoroalkyl substances) in humans.

Metabolite	AUC_{0-t} (ng/ml.d)	$AUC_{t-\infty}$ (ng/ml.d)	$AUC_{0-\infty}$ (ng/ml.d)
5:3 A	326.102	27.9	354.0
PFHxA	329.297	6.0	335.3
PFHpA	127.916	3.0	130.9

study. However, similar to the rat inhalation studies, the terminal plasma concentration of 5:3 A was found to be the highest of all the analyzed metabolites.

3.2. Human (occupational) exposure study

We performed a preliminary pharmacokinetic assessment of the human occupational study by calculating $AUC_{0-\infty}$ (Table 4) of the concentration versus time curves as an estimate of the internal exposure of 5:3 A, PFHxA and PFHpA. Similar to the one-day rat inhalation study, the internal exposure of 5:3 A was found to be slightly higher than that of PFHxA but markedly higher than PFHpA, indicating that of the three metabolites, 5:3 A has the slowest Cl. Furthermore, the internal exposure of PFHxA was estimated to be about 2.5 times higher than PFHpA. It is important to note that the occupational exposure in the study represented inhalation as well as dermal exposure routes, and the test substance was a chemical mixture. Therefore, the confounding effects of different exposure routes and varied characteristics of the chemical mixture would need to be evaluated in the future.

3.3. Allometric scaling of human clearance

To predict the human Cl of 6:2 FTOH, we used the calculated Cl data (Table 2) from the one-day rat study (Russell et al., 2015) and scaled Cl values by allometric scaling (Table 5). Allometric scaling is a commonly applied pharmacokinetic approach based on empirical power law of predicting parameters in humans from corresponding parameters in animals (Boxenbaum, 1982; Hu and Hayton, 2001; Mordenti, 1986; Sawada et al., 1984). The allometric equation is based on the dependency of biological variables on body mass, as shown below:

$$\text{Equation (Boxenbaum, 1982)} Y = a BW^b$$

$$\text{Equation (Canada, 2012)} \log(Y) = \log(a) + (b) \log(BW)$$

Where, Y is the dependent biological variable of interest, a is the normalization constant called the allometric coefficient, BW is the body weight, and b is the allometric exponent.

We calculated Cl values in humans for the three metabolites using an average BW of 0.213 kg for rats (Russell et al., 2015), a BW of 60 kg

Table 5
Predicted (Scaled) human clearance values for 5:3 A, PFHxA, and PFHpA from one-day inhalation 6:2 FTOH exposure rat study by allometric scaling.

Metabolite	External Exposure (ppm)	Average Estimated Rat Clearance ($\text{kg}^{-1}\text{h}^{-1}$)	Predicted Human Clearance ($\text{kg}^{-1}\text{h}^{-1}$)
5:3 A	0.5	0.027	0.582
	5	0.010	0.226
PFHxA	0.5	0.192	4.139
	5	0.192	4.139
PFHpA	0.5	0.037	0.808
	5	0.061	1.315

for humans and b of 0.75 (Hu and Hayton, 2001). The predicted (scaled) Cl values in humans suggested that Cl of PFHpA increased with an increase in exposure, whereas that of PFHxA did not change at higher exposure levels. In contrast, the Cl of 5:3 A decreased as the exposure increased, which indicated that elimination of 5:3 A slowed down with an increase in exposure, suggesting its potential for causing human biopersistence. Furthermore, PFHxA showed the fastest human Cl among the three metabolites at both exposure levels, whereas 5:3 A had the slowest Cl, further implying the relatively higher potential of 5:3 A to exhibit biopersistence than the other metabolites. However, additional studies are necessary to evaluate the effect of certain determining factors, such as sex-based differences, and stimulated reabsorption by transporters or saturation of transporters involved in urinary secretion in the kidneys that could have an impact on the internal exposure of 6:2 FTOH metabolites.

4. Discussion

We examined the available data from rat inhalation and human occupational exposure studies and performed a preliminary pharmacokinetic assessment of 6:2 FTOH and its metabolites using non-compartmental pharmacokinetic analysis. The metabolic profile of 6:2 FTOH remained consistent across exposure routes, and no route-specific toxicity was reported. The three metabolites of 6:2 FTOH whose pharmacokinetic profiles were examined were 5:3 A, PFHxA, and PFHpA. Cl and $\text{AUC}_{0-\infty}$ were estimated as markers of internal exposure of 6:2 FTOH metabolites.

The internal exposure of PFHpA was estimated to be higher than PFHxA in male rats but lower in female rats in the one-day inhalation exposure study (Table 3), suggesting that there may be sex-based differences in the disposition of these metabolites. However, sex was not evaluated as a factor in the disposition of the metabolites of 6:2 FTOH in our analysis. Sex-based differences in pharmacokinetic profiles of some PFCAs, such as PFOA have been observed in rats (Vanden Heuvel et al., 1991; Worley and Fisher, 2015). The urinary elimination of PFOA in female rats was reported to be faster than that in male rats due to faster metabolism into PFOA-glucuronide or sulfate ester in female rats (Vanden Heuvel et al., 1991). More recently, Worley and Fisher (2015) utilized physiologically based pharmacokinetic (PBPK) modeling to demonstrate that sex-based differences in serum $t_{1/2}$ values of PFOA are related to differences in the expression of certain transporters in the kidneys, such as OATPs and OATs. Therefore, the effects of sex-based differences on the metabolism of 6:2 FTOH and the internal exposure of its metabolites in different species need to be investigated for comparing and conclusively determining their potential for biopersistence in both sexes. The internal exposure of PFHxA was 2.5 times higher than PFHpA in the human occupational exposure study (Table 4), implying that the Cl of PFHxA was slower than PFHpA in humans after repeated exposure. The human occupational exposure study was performed only in males. The effects of sex on the pharmacokinetic profiles of PFHpA and PFHxA in humans were not evaluated, and need to be considered for future examination of disposition of these metabolites in

humans.

We used allometric scaling to estimate the Cl of the metabolites of 6:2 FTOH in humans (Table 5) from the estimated Cl (Table 2) under the single inhalation exposure one-day rat study as an internal exposure estimate of these metabolites for a preliminary pharmacokinetic assessment. Cl from animal studies is commonly scaled to humans using allometric scaling as it provides an estimate for the elimination of a compound (or its metabolite) and helps determine the kinetics of mechanisms involved in the metabolism and/or elimination of a compound at different exposure levels in humans (Hu and Hayton, 2001; Mordenti, 1986). We determined that human Cl of PFHxA was the fastest of the three metabolites. In addition, the human Cl of PFHxA did not change with an increase in exposure, whereas the human Cl of PFHpA increased at the higher exposure level. In general, if the elimination follows first-order kinetics Cl remains constant irrespective of the changes in the levels of external exposure. Our findings on the elimination of PFHxA are in agreement with this principle. However, increase in human Cl of PFHpA at a higher external exposure level indicates that there may be mechanisms involved in the elimination of PFHpA that introduce non-linearity in the system. An increase in Cl with increased external exposure could potentially be a result of dose-dependent saturation of any processes involved in the metabolism or elimination of PFHpA, such as its renal reabsorption by transporters, that lead to increased elimination of PFHpA with dose. The effect of increasing external exposure on the kinetics of metabolism and elimination of PFHpA needs to be further examined to better understand the mechanisms behind the increased Cl of PFHpA at a higher external exposure level.

In contrast, the internal exposure of 5:3 A after inhalation 6:2 FTOH exposure was higher than PFHxA and PFHpA in rats (Table 3) as well as humans (Table 4). Furthermore, the scaled human Cl of 5:3 A decreased with an increase in exposure (Table 5). The higher internal exposure and reduced Cl of 5:3 A at a higher external exposure level suggests that its disposition follows “non-linear pharmacokinetics.” Studies have suggested that OATP transporters in the kidneys play a significant role in the renal reabsorption of PFCAs and therefore, reduce their Cl (Weaver et al., 2010; Worley and Fisher, 2015; Yang et al., 2009). Although 5:3 A has not been specifically demonstrated to be a substrate of renal OATP transporters, the reduced Cl at a higher exposure across species indicates that the renal reuptake transport mechanisms may contribute to the prolonged internal exposure of 5:3 A via increased renal reabsorption. Another mechanism which could lead to increased internal exposure to 5:3 A is the saturation of transporters, such as OATs, that are involved in active secretion of the metabolite into urine. However, additional studies and modeling are required to determine whether stimulated renal reabsorption or saturation of urinary secretion have a dominant role to play in increasing the internal exposure of 5:3 A. Based on this observation, we propose that the disposition of 5:3 A potentially follows steady-state kinetics as its elimination rate decreases with an increase in exposure and may eventually become equal to its rate of formation, with change in concentration over time being zero. In other words, 5:3 A has the potential to reach steady state after repeated prolonged exposure to 6:2 FTOH. Therefore, 5:3 A could serve as an important biomarker for the potential for biopersistence of 6:2 FTOH. The Russell et al., 2015 study predicted that the serum concentrations of 5:3 A reached steady state after repeated inhalation exposure; however, all model parameters, except for $t_{1/2}$ for the metabolites, were constrained to the values obtained from the one-day inhalation exposure study. Additional studies are necessary to determine whether 5:3 A reaches steady state after long-term exposure to 6:2 FTOH, and therefore, conclusively establish that 5:3 A is the metabolite which is primarily responsible for human biopersistence resulting from prolonged exposure to the parent compound. An aspect of metabolism of 6:2 FTOH which we did not explore in this study is the reversible conversion of 5:3 A into 4:3 A (Fig. 1) as the plasma concentration versus time data on 4:3 A was not reported in the studies

summarized in the Russell et al. (2015) paper. Furthermore, concentrations both 5:3 A and 4:3 A have been reported in the fat and liver of rats after 90-day oral exposure to 6:2 FTOH (Gannon et al., 2012). However, there is insufficient information available on the kinetics of the reversible reaction between 5:3 A and 4:3 A to determine the role of 4:3 A in the potential biopersistence of long-term exposure to 6:2 FTOH. Therefore, there is a need to evaluate the impact of kinetics of the reversible reaction between 5:3 A and 4:3 A on the internal exposure of 5:3 A.

More recently, the pharmacokinetic profile of PFOA was examined by application of PBPK modeling, and the role of kidney OATP transporters in the renal reabsorption of PFOA was investigated using reported datasets of PFOA concentrations in serum, urine, feces, liver, and other tissues in rats following single intravenous and oral administration (Worley and Fisher, 2015). If appropriate datasets are available, the pharmacokinetic profile of 6:2 FTOH metabolites can be further evaluated by building and validating a PBPK model and utilizing a similar approach. Therefore, for generating these data appropriate pharmacokinetic studies are necessary to expand our understanding of internal exposure-based and toxicological implications of 6:2 FTOH and its metabolites. A recent human biomonitoring study (Poothong et al., 2017) conducted in Oslo (Norway) on men and women analyzed concentrations of different PFCAs, perfluoroalkyl sulfonates (PFASs) and perfluoroalkyl sulfonamides (FOSAs) in serum, plasma and blood, and reported that for some compounds, including PFHxA, the highest concentrations were observed in whole blood instead of serum and plasma. Therefore, based on the results of this study (Poothong et al., 2017) whole blood may provide a more accurate measurement of the concentration of 6:2 FTOH and some of its metabolites than serum and plasma for performing exposure assessment and toxicological evaluation.

To summarize, our analysis represents a preliminary internal exposure-based evaluation following a thorough review of published pharmacokinetic data on 6:2 FTOH exposure. Such internal exposure estimations may be valuable for biomonitoring purposes and for contributing to future toxicological assessments. Additional pharmacokinetic studies are necessary for generating appropriate data for further evaluating the potential of 6:2 FTOH to result in human biopersistence and related systemic toxicity.

5. Conclusion

Our preliminary pharmacokinetic analysis, based on a thorough review of published pharmacokinetic data on rat and human 6:2 FTOH exposure studies, calculated internal exposure estimates for key metabolites of 6:2 FTOH and provided a valuable insight into the pharmacokinetics of this compound (and its metabolites), which could be useful for biomonitoring purposes and toxicological evaluation. More importantly, we determined that 5:3 A is an important biomarker for assessment of long-term exposure to 6:2 FTOH as 5:3 A had the highest internal exposure and slowest clearance across species. Furthermore, we concluded that 5:3 A has the potential to reach steady state upon repeated exposure to 6:2 FTOH as its clearance was determined to reduce with increasing 6:2 FTOH exposure. We also identified specific factors, such as the stimulated renal reabsorption of 5:3 A by transporters or saturation of transporters involved in urinary secretion of 5:3 A in the kidneys, and sex-based differences in pharmacokinetics of PFHxA and PFHpA that need to be evaluated further as they can significantly impact the internal exposure of the evaluated 6:2 FTOH metabolites. Our results provided important information required for designing additional pharmacokinetic studies that are necessary to conclusively determine whether levels of 5:3 A reach steady state after prolonged repeated exposure to 6:2 FTOH, therefore resulting in biopersistence which could contribute to systemic toxicity.

Disclaimer

The data and interpretations expressed in this article represent that of the authors and not necessarily that of the US FDA.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2018.01.012>.

Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2018.01.012>.

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Overgeneralization by Anderson et al. and Luz et al. regarding safety of fluorotelomer-based chemistry

To the Co-Editors-in-Chief Drs. Aylward and van den Berg

We read with great interest the recent articles by Luz et al. and Anderson et al. published in Volume 103 issue of Regulatory Toxicology and Pharmacology. The two-part publications reported on per-fluorohexanoic acid (PFHxA) toxicity, exposure and biomonitoring data available for the chemical. The analysis included the estimation of a toxicity reference dose and drinking water and residential groundwater screening levels. Significant conclusions included 1) PFHxA “is less hazardous to human health than PFOA”; 2) PFHxA is not expected to bioaccumulate due to its “rapid and nearly complete elimination” from the body; and 3) “PFHxA levels currently present in the environment are well below levels that may present a concern for human health.”

Even though the authors narrowly focused on a single chemical, they extended their conclusion to the entire fluorotelomer-based chemical process when they say that 1) “**PFHxA and related fluorotelomer precursors** currently appear to present negligible human health risk to the general population and are not likely to drive or substantially contribute to risk at sites contaminated with PFAS mixtures”, and 2) “**PFHxA may also represent a suitable marker for the safety of fluorotelomer replacement chemistry** used today.” [Emphasis added] These broad statements, however were not fully explained and deserve a closer look based on previously published data from scientists at the U.S. Food and Drug Administration (FDA) (Kabadi et al., 2018).

Evidence from Kabadi et al. appears to contradict Luz et al. (2019) and Anderson et al. (2019) wide-ranging conclusions about the safety of the entire C6 class of per- and poly-fluorinated alkyl substances (PFAS). The FDA scientists performed a thorough evaluation of publicly available animal and human exposure data on 6:2 FTOH, a type of fluorotelomer alcohol commonly used as a raw material to make grease- and water-proof paper and cardboard for food contact applications (Rice, 2015).

The FDA scientists identified three metabolites, namely the PFHxA mentioned above, 5:3 fluorotelomer carboxylic acid (5:3 A) and per-fluoroheptanoic acid (PFHpA) that could be used as markers of 6:2 FTOH exposure. For each metabolite, they also provided internal exposure estimates. As a result of their analysis, Kabadi and colleagues identified 5:3 A as an important biomarker for the potential biopersistence of 6:2 FTOH because 1) 5:3 A had the highest internal exposure and the slowest elimination by the body; and 2) 5:3 A's elimination was

reduced when exposure to 6:2 FTOH increased.

Following the reasoning presented by Luz and Anderson, any short-chain PFAS used in fluorotelomer-based products would be assumed to be as safe as PFHxA, including 6:2 FTOH. The authors, however, did not attempt to discuss the discordance between their conclusion and FDA's scientists' finding that 6:2 FTOH metabolite 5:3 A is an important biomarker for the potential biopersistence of 6:2 fluorotelomer alcohol.

The discrepancy between Luz et al. and Anderson et al. and FDA's scientists' analysis clearly demonstrate that we are far from understanding the pharmacokinetics and risks posed by short-chain PFAS to human and environmental health. This is partly due to inadequate safety study designs lacking a pharmacokinetics component, biopersistence assessment and developmental exposures. It also demonstrates that even though there are structural similarities between short chain PFAS, wide-range assumptions about similar risks are unwarranted.

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Fixing the Oversight of Chemicals Added to Our Food

Findings and Recommendations of Pew's Assessment of the U.S. Food Additives Program

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Overview

The American diet is dramatically different today compared with what it was when Congress enacted the Food Additives Amendment of 1958. Our food supply is more diverse and more processed and tends to be produced farther from where it is consumed. Chemicals used to process, package, store, and transport food more easily, as well as the compounds used to flavor, color or preserve it, are consumed by hundreds of millions of people every day. Ensuring that these additives are safe is a core function of the U.S. Food and Drug Administration under a law that, despite these tremendous changes to our diet, has remained largely unchanged for more than five decades.

From 2010 to 2013, The Pew Charitable Trusts conducted a comprehensive assessment of FDA's food additives regulatory program. Our analysis focused on how the program functions rather than weighing in on the ongoing controversies over the safety of specific chemicals. Relying on a transparent process that engaged stakeholders, we examined food additive issues in partnership with the food industry, the public interest community, and government. We held five expert workshops and published six reports in peer-reviewed journals. This report summarizes our findings and provides recommendations to address the problems we identified.

With more than 10,000 additives allowed in food, our research found the FDA regulatory system is plagued with systemic problems that prevent the agency from ensuring their use is safe. If one of these chemicals was causing health problems short of immediate serious injury, it is unlikely that FDA would detect the problem unless the food industry alerted the agency. When new research raises doubts about the safety of an additive that is already on the market, FDA's limited resources and authorities leave the agency heavily dependent on industry's voluntary cooperation with its requests and on public education. In practice, FDA may have to prove actual harm before it can restrict use of an additive in the food supply—even though Congress mandated that no additive is allowed in food unless there is a reasonable certainty that the intended use would not result in harm to consumers.

The cause of this breakdown in our food safety regulatory process is an outdated law with two significant problems. First, the law contains an exemption intended for common food ingredients that manufacturers have used to go to market without agency review if they determine that the additive use is "generally recognized as safe," or GRAS, in regulatory parlance. FDA has interpreted the law as imposing no obligation on firms to tell the agency of any GRAS decisions. As a result, companies have determined that an estimated 1,000 chemicals are generally recognized as safe and used them without notifying the agency. The firms usually use their own employees, consultants or experts that they select and pay to make the safety decision with no disclosure or apparent efforts to minimize the inherent conflicts of interest.

Voluntary GRAS notifications submitted by the food industry to the agency for review indicate that over the past decade, almost all new chemicals added directly to food have gone through this GRAS exemption rather than the formal approval process intended by Congress. The loophole essentially swallowed the law, hindering the agency's efforts to upgrade its science, because if FDA asks tougher questions, then firms may be less likely to voluntarily inform it of their GRAS decisions. In an increasingly global marketplace where additives and food are imported into the United States, the exemption presents a situation that undermines public confidence in the safety of food and raises significant questions about whether FDA has the ability to fulfill its statutory mission to protect public health by ensuring that all food additives are safe.

Secondly, the law does not give FDA the authority it needs to efficiently obtain the information necessary to identify chemicals of concern that are already on the market; set priorities to reassess these chemicals; and then complete a review of their safety. Moreover, the agency has not been given the resources it needs to effectively implement the original 1958 law. As a result, FDA has not reevaluated the safety of many chemicals originally

approved decades ago, generally rechecking safety only when requested by a company to do so, or when presented with allegations of serious adverse health effects.

One recent congressional remedy for food safety problems, the FDA Food Safety Modernization Act of 2011, required food manufacturers to produce a written plan to minimize hazards in food, including those created by additives, and have it in place by July 2012. The agency is behind schedule implementing this rule. In any case, the law falls short of what is needed, especially compared with modern tools that other agencies use to address problems with chemicals in consumer products.

What FDA says today about the safety of additives

“ It’s perhaps a time to look at what the legal framework looks like and what opportunities there are now to ask and answer questions in new ways because of advances in science and technology.

—FDA Commissioner Margaret Hamburg, (Reuters, May 2013)

“ We’re not driven by a sense that there is a pressing public health emergency. But there are decisions being made based on data that we don’t have access to, and that creates a question about the basis on which those decisions are made.

—FDA Deputy Commissioner for Foods Michael Taylor, (Associated Press, March 2013)

“ FDA plans to issue guidance to industry on meeting the GRAS criteria established under the Act.

—FDA spokeswoman Theresa Eisenman, (USA Today, August 2013)

Our evaluation confirms the 2010 findings of the U.S. Government Accountability Office that FDA cannot ensure the safety of new and existing GRAS additives. But our report also identifies additional problems plaguing the disjointed food safety regulatory system, in which outdated science generally continues to be the basis of the assessment and decision-making process. To remedy the problems, we recommend that Congress update the Food Additives Amendment of 1958 to ensure that FDA:

- Approves the first use of all new chemicals added to food.
- Reviews new uses or changes to existing uses of previously approved additives.
- Streamlines its decision-making process so it is timely and efficient.
- Upgrades its science to determine safety.
- Uses the scientific tools and has access to the data it needs to set priorities to reassess the safety of chemicals already allowed in food and take action.

In the meantime, the agency should use its existing authority to limit the GRAS exemption, modernize its science, and review the safety of older chemicals. Until it does, the safety of additives to food largely depends on the motivation and competence of food manufacturers, rather than on the agency with the responsibility—but not the authority or resources—to protect the food supply from chemical additives.

About the U.S. food additive regulatory program

Chemical additives are a fundamental part of our modern food supply. They provide flavor, enhance taste, appearance, and nutrient value, and prevent spoilage.¹ They are also used in food preparation and packaging materials. Their use enables consumers to have access to the food they want when they want it. But additives can also be controversial.²

The Food Additives Amendment of 1958,³ passed by Congress and signed by President Dwight D. Eisenhower, designed a system to handle 800 additives⁴—far fewer than the 10,000 allowed today.⁵ Most new chemical additives were supposed to go through a formal process of agency review that would be triggered when a company submitted a food additive petition.⁶ The petition process requires FDA to notify the public; provide an opportunity for comment; and, if the agency deems the chemical's intended use to be safe, issue a regulation allowing the use.⁷ The law provided an exemption for common food ingredients, such as oil and vinegar,⁸ when their use is "generally recognized as safe," or GRAS. When a chemical's use is designated as GRAS, the formal public notice and comment rulemaking process is not required.⁹

Meaning of "safe"

"Safe" for food additives is defined to mean "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use."¹⁰ Congress set this high standard in 1958 because it wanted to encourage innovation while ensuring public confidence that the chemicals added to food would not have harmful effects years later.¹¹ The benefits of an additive are not a factor in determining whether it is safe.¹²

The GRAS exemption on its face sounds very straightforward. For an additive to qualify, its use must be safe, and that safety must be generally recognized by scientists knowledgeable about the safety of substances added to food.¹³ But the food industry and FDA over the years have come to interpret the law as allowing additive manufacturers to determine that a chemical's use is safe without notifying the agency.¹⁴

Initially, the GRAS exemption was used by the flavor industry for its products¹⁵ and by manufacturers of additives that were in common use before 1958.¹⁶ Many of the 10,000 additives were authorized by FDA or the food industry by the end of the 1960s.¹⁷

In 1969, because of safety concerns, President Richard M. Nixon ordered the agency to reassess the safety of additives and review all its prior decisions.¹⁸ In 1982, an FDA-convened expert panel called the Select Committee on GRAS Substances completed its review of approximately 400 GRAS substances. The panel also laid out a rigorous approach to evaluating a chemical's safety and suggested improvements to the agency's process.¹⁹ (See Box on page 4 for a timeline of food safety policies related to FDA.)

In the 1980s, the agency laid out a comprehensive Priority-Based Assessment of Food Additives program to reevaluate its previous decisions.²⁰ This program set priorities but did not simplify the process the agency followed to reverse additive decisions due to new science or other concerns. This formal rulemaking process provided manufacturers with a right to an administrative hearing in most circumstances. As a result, only a handful of additives were ever reassessed, and citizen petitions calling for restriction have often not been resolved.²¹

Food additives safety timeline

1938	Congress passes Federal Food Drug and Cosmetic Act of 1938. ²²
1958	Congress passes the Food Additives Amendment of 1958. ²³
1969	President Nixon orders a review of FDA's additive decisions. ²⁴
1973	FDA revises food additive and GRAS regulations. ²⁵
1982	Select Committee on GRAS Substances completes its review. ²⁶
1982	FDA issues guidance (known as Redbook) based on comprehensive assessment of program. ²⁷
1982	FDA launches its Priority-Based Assessment of Food Additives program. ²⁸
1997	FDA launches voluntary GRAS notification program. ²⁹
2000	FDA launches food contact substance notification program. ³⁰
2010	Government Accountability Office issues report finding flaws with GRAS program. ³¹
2011	Congress passes the FDA Food Safety Modernization Act of 2011. ³²

With limited resources and an increasingly complicated rulemaking process, FDA had an overwhelming backlog of unresolved reviews by the early 1990s.³³ In response, in 1997 it began accepting voluntary notifications from additive manufacturers claiming that their chemicals are GRAS, which the agency would informally review.³⁴ The goal of companies submitting these notices is to persuade the agency to issue “no question letters.”³⁵ In some cases, these are subsequently cited as evidence of FDA clearance, although the agency maintains that the letters are informal and do not constitute approval.³⁶ Today, virtually all new chemical additives added directly to food go through the GRAS exemption: This loophole has effectively swallowed the law.³⁷

In 2010, the chairs of two congressional panels with jurisdiction over food safety, Senator Tom Harkin (D-IA) and Representative Rosa DeLauro (D-CT), asked the Government Accountability Office to scrutinize FDA's GRAS program. Later that year, the nonpartisan investigative arm of Congress concluded that:

- “FDA's oversight process does not help ensure the safety of all new GRAS determinations.”
- “FDA is not systematically ensuring the continued safety of current GRAS substances.”³⁸

GAO made a series of six recommendations,³⁹ but FDA has made significant progress on only one of them, by issuing draft guidance on nanoengineered particles in 2012.⁴⁰ As of October 2013, the agency has made little progress on the others except to request comment on several in 2010.⁴¹

In 2011, Congress passed the FDA Food Safety Modernization Act to address long-standing concerns, primarily involving pathogens.⁴² The law directs the agency to promulgate a series of regulations to prevent unsafe food from entering the market and gives it more authority to act if problems are found. One of these regulations, requiring food manufacturers to conduct a formal hazards analysis and have written risk-based preventive controls to minimize these hazards, was supposed to be finalized by July 2012. These rules have yet to be finalized, however, with only a proposal issued for comment in January 2013. When the regulations are completed and in effect, industry will have to evaluate in accordance with the rules its processes to ensure that no unapproved food additives are used in its products.⁴³

Overall, Pew estimates that more than 10,000 chemicals are permitted to be used in human food, about half

as direct additives and the balance in packaging or other food contact materials.⁴⁴ The number is not in itself a problem. Rather, it is a reflection of the diversity of the food supply and the ingenuity of industry. It also hints at the challenges facing FDA in ensuring that these chemical additives are safe.

Pew determined that FDA has not reviewed the safety of about 3,000 of the 10,000 additives allowed in food.⁴⁵ An estimated 1,000 of these 3,000 are self-affirmed as GRAS by additive manufacturers without notice to or review by the agency, with the balance affirmed as GRAS flavors by an expert panel convened by the flavor industry trade association.⁴⁶ FDA monitors but does not review these flavor industry decisions.

Pew's approach

In 2010, Pew launched its food additives project to:

- Evaluate the federal regulatory program designed to ensure that chemicals added to food are safe, including an examination of how it responds to advances in scientific understanding of chemical safety and changing uses of chemicals in food.
- Identify and assess viable, evidence-based, expert-vetted policy solutions if flaws are found in the regulatory program.
- Educate policymakers and key stakeholders, including industry, public interest groups, and medical associations, about the project's findings.⁴⁷

To accomplish these objectives, Pew hired a team of scientists and lawyers to conduct the review, assembled expert advisers to guide our work, arranged for the American Academy of Pediatrics to provide critical review, and committed to a transparent process that engaged stakeholders and published our findings in peer-reviewed scientific journals.

Pew spent more than two years conducting research. As part of this research, we wrote an article that provided a comprehensive analysis of the U.S. food additive regulatory program, including its history and recent trends, which was published in a peer-reviewed journal of the Institute of Food Technologists, the professional society of food scientists.⁴⁸ Recognizing the global marketplace for additives, we commissioned an industry consulting firm and a professor of international food science to compare food additive laws in other developed countries. We also held two workshops focused on the science used to make safety decisions. These workshops were and co-sponsored by the journal *Nature* and the Institute of Food Technologists, with FDA participating in them and assisting in their design. More than 70 experts from industry, academia, government agencies, and public interest organizations participated in each event.⁴⁹ We published the proceedings of each of these workshops in the Institute of Food Technologists' journal.⁵⁰

In 2012, Pew shifted from research to analysis of policy options. We held a workshop with multiple stakeholders, again in collaboration with *Nature* and the Institute of Food Technologists and with continued participation from FDA, to develop and critique potential recommendations proposed by participants. We also supported further research into three critical issues: nanoparticles, endocrine disruptors (substances that impair our hormones), and use of cell-based tests to identify chemical hazards (known as Tox21). To support this research, we held an additional workshop, supported three others, and funded an industry-affiliated think tank that convened a multidisciplinary team to evaluate methods of measuring exposure to nanoengineered particles in food.

With this foundation in place, in 2013 we identified three core issues and published our analysis in three peer-review journal articles. These issues are:

- Conflicts of interest that arise when an additive's manufacturer selects the scientist who makes the GRAS safety decision.
- Data gaps in toxicity testing for additives that have been previously approved by FDA.
- FDA's reliance on outdated science to assess the safety of chemical additives.

Finally, we hosted a fifth workshop to address potential conflicts of interest in more depth and submitted proposed guidance to FDA to help it resolve the issue and implement one of the Government Accountability Office's recommendations on this problem. (See Appendix 1 for a list of expert advisers, Appendix 2 for a list

of the peer-reviewed journal articles, and Appendix 3 for brief descriptions of each workshop that Pew's food additive project organized or supported.)

Pew's findings

Our analysis focused on the overall regulatory system that is expected to ensure the safety of more than 10,000 chemical additives,⁵¹ rather than on concerns raised about specific substances. We evaluated FDA's ability to fulfill the mission of its food additive regulatory program to protect public health from chemicals intentionally added to food or food packaging. We did not evaluate whether specific chemicals or groups of substances, such as salt, trans fat, caffeine, bisphenol A (which is used to line the inside of cans), or artificial colors or flavorings, cause actual harm to the public. We also did not consider contaminants found in food from natural sources or because of pollution, because those are not intentionally added and are regulated under a different set of health and safety standards.

Our research found that the FDA regulatory system is plagued with systemic problems that prevent the agency from ensuring the use of food additives is safe. If one of these chemicals were causing health problems short of immediate serious injury it is unlikely that FDA would detect the problems unless the food industry alerted it. This is particularly true if the health consequences of ingesting the additive take years or decades to become manifest after the food is eaten.⁵² If the agency did identify a problem, it would still face challenges proving harm. Proof of harm was not the safety standard laid out by Congress in 1958. Under the law, a chemical may be used in food if competent scientists are reasonably certain that the use will cause no harm over a lifetime. In short, the question is whether it will cause no harm, rather than whether harm can be proven.

Under the law, FDA is supposed to make a determination only after it has considered the cumulative effects from similar chemicals and has information ensuring an adequate margin of safety.⁵³ But it is essentially impossible for the agency to connect an additive to a health problem when it has:

- Not been notified about an estimated 1,000 chemicals⁵⁴ currently allowed in food.
- Not been informed of actual usage for all chemicals.⁵⁵
- Not been alerted to studies that suggest previously unknown potential health effects.⁵⁶

In contrast, Congress in 1976 gave the U.S. Environmental Protection Agency greater, albeit still limited, authority to get more of the information it needed to make safety decisions for virtually all chemicals that are used in consumer products not regulated by FDA. In 1996, Congress gave EPA additional authority to protect the public from pesticide residues that may be in food.⁵⁷ (See Box 4.)

Despite these fundamental limitations and ongoing resource challenges, FDA has:

- Pursued implementation of its many responsibilities under the FDA Food Safety Modernization Act, especially the hazard analysis and preventive control requirements that should improve food additive safety.⁶⁵
- Partnered with EPA and the National Institutes of Health on the federal Tox21 project, which set the stage to move chemical safety work into the 21st century.
- Launched the Advancing Regulatory Science Initiative,⁶⁶ in response to concerns raised by its Science Board, to help FDA develop tools, standards, and approaches to assess the products it regulates.
- Secured voluntary industry commitments to restrict use of existing additives when concerns have arisen.⁶⁷
- Developed methods to estimate exposure to chemicals that are proposed for use in food.⁶⁸

- Supported its food additive scientists, helping some of them to become recognized experts among their peers in the international community.⁶⁹

EPA v. FDA authority for chemical health and safety

Almost 20 years after Congress set up the regulatory program for food additives, it enacted the Toxic Substances Control Act of 1976 for use of nearly all chemical substances not regulated by FDA, whether toxic or not.⁵⁸ Although experts from Environmental Protection Agency,⁵⁹ the chemical industry,⁶⁰ and non-profit organizations⁶¹ have called for strengthening this law, it does give EPA significantly more authority than FDA to obtain certain information needed to assess the safety of chemicals. About half of the additives to food (more than 4,500) are also regulated by EPA under this law. Specifically:

- EPA must be notified at least 90 days before the manufacture of a chemical and be given an opportunity to veto it. In contrast, according to the agency's interpretation of the law, manufacturers are not required to notify FDA when a chemical's use is determined to be GRAS.
- Manufacturers, importers, and processors must notify EPA every five years about the uses of chemicals and their amounts. In contrast, FDA lacks clear authority to gather this information, which is critical to estimating exposure.
- EPA must be notified of unpublished health and safety studies (including sampling results) indicating a substantial risk. There is no similar requirement for FDA.
- EPA can require testing by rule for new and existing chemicals. FDA's authority to require such testing has been questioned.⁶²

In 1996, Congress went further, setting up a truly modern system to ensure the safety of pesticides used on food.⁶³ Manufacturers must report more information more often to EPA, and the pesticide's safety must be periodically reviewed by the agency under safety standards that are generally more rigorous than those for additives. Moreover, EPA has long had the authority to issue a "data call-in," requiring pesticide makers to test and provide other data for their products, through issuance of a simple order.⁶⁴

In summary, Pew's analysis documented that while the FDA has made efforts to improve oversight a number of serious problems with the food additive regulatory system that have led us to conclude that the Food Additives Amendment of 1958 is not working as Congress intended. Specifically, we found:

- **Conflicts of interest.** Food manufacturers make GRAS safety decisions without FDA's knowledge despite conflicts of interest among those making the determinations. The GRAS loophole as currently used is inconsistent with Congress' plan and the practices of other developed countries.
- **Lack of information.** FDA lacks even basic information needed to assess the safety of thousands of chemicals that have been cleared for use in food. As a result, the agency reevaluates the safety of only a relative handful of existing additives.
- **Outdated science.** FDA uses outdated science to evaluate additive safety. It relies on a process that does not ensure independent scientific input and is often not transparent, particularly for food contact substances.
- **Missed safety deadlines.** The agency has fallen behind the FDA Food Safety Modernization Act rulemaking deadlines. Until those rules are in place, the agency has limited means to identify compliance problems.

Each of these findings is explored in more detail below.

Conflicts of interest

Pew estimates that food manufacturers have designated 1,000 chemicals as “Generally Recognized as Safe” without FDA’s knowledge. This total does not include more than 100 chemicals that were reviewed by the agency for the first time through its voluntary GRAS notification program. It also does not include industry GRAS safety decisions involving existing additives that expand the allowed uses to different foods, allow increased concentrations in food, or accommodate different manufacturing processes or purities.

As noted above, Congress required the food industry to use a petition process to obtain FDA review and approval for safety decisions on additives. Only if there was “consensus” among scientists that the use was generally recognized as safe could a chemical avoid the petition route and be declared GRAS. From 2003 to 2012, however, only 23 food additive petitions were submitted. A handful of these were for changes to existing agency approvals, not new chemicals. In contrast, during this same time, food manufacturers submitted 332 GRAS notifications for more than 100 chemicals to FDA seeking letters from the agency saying it had “no questions” about the safety decision. This total does not include the safety decisions made by manufacturers that they chose not to provide to the agency.

The GRAS exemption has become the loophole that has swallowed the law. It is an anomaly: No other developed country allows new chemicals to be added to a food product without government approval.

Of the 451 GRAS notifications voluntarily submitted to FDA for review from 1997 to 2012, Pew found that financial conflicts of interest in these decisions are ubiquitous. Our findings relied on a conflict-of-interest framework developed by the Institute of Medicine in 2009. There is no basis to assume that the decisions withheld from agency review are any better. This lack of independent review raises concerns about the integrity of the process and the safety of the food supply, particularly when the manufacturer does not notify FDA.

The GRAS exemption has implications beyond the safety of a specific additive. It hinders the agency’s efforts to modernize its science, because if FDA asks tougher questions, then firms may be less likely to voluntarily inform it.⁷⁰ It also raises the issue of whether an additive can be recognized as safe while its identity and uses are kept secret.

Our analysis confirms the GAO’s conclusion that “FDA’s oversight process does not help ensure the safety of all new GRAS determinations.”⁷¹ In an increasingly global marketplace where additives and food are imported into the United States, this loophole presents a situation that undermines public confidence in the safety of food and raises questions about FDA’s ability to ensure the protection of public health. Until conflicts of interest are minimized and safety decisions are subject to FDA review, the safety of food additives will largely depend on the integrity and competence of food manufacturers.

Lack of information

Our investigation found that most additives are not tested for safety in accordance with FDA’s limited testing recommendations.⁷² Agency guidelines, for example, say that chemicals intentionally added to food should be fed to laboratory animals to identify potential harmful effects, but we found that in the majority of cases,

chemicals directly added to food did not undergo this very basic test. The data gaps are not significantly better for the chemicals reviewed by the agency under its voluntary notification program, even when the agency had no questions.

In instances where FDA has recommended reproductive toxicity tests on additives, such studies do not appear to have been done in the vast majority of cases.⁷³ And when health and safety studies indicate possible problems, food companies are not obligated to notify the agency except in very limited circumstances.⁷⁴

FDA also lacks clear authority to order companies to test the safety of chemicals they add to food. So even if the agency wanted to require additional testing, it is not clear that companies would be required to comply with such requests.⁷⁵ Further, companies are not required to regularly report the amount of a chemical added to food, making it difficult for FDA to assess exposure or identify troubling use trends.⁷⁶

FDA's lack of authority to get the information it needs stands in stark contrast to the Environmental Protection Agency. Although its authority is still limited, EPA has access to more information on pesticides and on chemicals that go into consumer products not regulated by FDA than that agency has on chemicals used in food. Congress gave EPA the ability to get information on pesticides and to make decisions on individual chemicals in a streamlined fashion that reduces the administrative burden without limiting transparency. This differential treatment of chemicals, which often are regulated simultaneously by both agencies, makes little sense.

As a result of these limits, thousands of chemical additives approved before 1980 have not been reassessed for safety.⁷⁷ With a lack of resources, no mandate from Congress, and an unusually difficult rulemaking process, FDA takes a passive approach to reviewing the safety of existing chemicals. Its failure to set science-based priorities for reassessment wastes resources, leads to litigation, undermines public confidence, and may result in firms selling unsafe food.⁷⁸ Our analysis confirms the GAO's conclusion that "FDA is not systematically ensuring the continued safety of current GRAS substances"⁷⁹ but also finds that it applies to most additives other than GRAS substances as well.

Outdated science

Much of the science that FDA uses to review the safety of chemicals added to food has not been significantly updated for decades.⁸⁰ Using the 1982 report by its Select Committee on GRAS Substances as a baseline, we identified areas of concern where the issues raised more than 30 years ago remain unresolved and relevant today. They include:

- **Behavioral effects.** FDA has not aggressively pursued the development of test methodologies for the impact of additives on behavior. It has not incorporated into its guidance methods that EPA and other developed country members of the Organization for Economic Cooperation and Development adopted years ago.
- **Endocrine systems.** FDA has not taken a leadership role in the development and validation of new technologies to identify and evaluate additives for potential endocrine disruption to hormones. Unlike EPA, it has not adopted or made use of validated screening tests and predictive models.
- **Subpopulations.** FDA has not systematically considered exposures of additives to sensitive populations except for infants. For hypersensitivity, it has not developed guidelines to screen or test for potential dangers or offered an effective system for consumers to report health problems.
- **Thresholds of alleged toxicological insignificance.** FDA has adopted inadequate thresholds of exposure in rules and guidance below which industry is not expected to develop toxicity data when evaluating the safety of a chemical.

- **Absorption, distribution, metabolism, and excretion data.** FDA's guidance allows industry to make safety decisions without the detailed data necessary to understand how the human body handles and eliminates chemicals that may be in food.
- **Reassessment and consistency across substances.** FDA has not developed a system to prioritize its review of previous safety decisions. Instead, it relies on a case-by-case approach. In addition, it does not appear to closely coordinate its hazard or exposure assessment with EPA when a chemical is regulated by both agencies.
- **Weight of evidence.** FDA maintains that it closely scrutinizes all available studies. But its analysis is often based on professional judgment without using the available methods to compare various studies in a more rigorous, transparent, and reproducible manner.⁸¹

In addition, the program Congress imposed on FDA in 1997 to review voluntary notifications for food contact substances lacks transparency. Until the agency takes final action on a notice, the public is unaware of the decision, and the notices are not publicly available. This process limits participation by academics, competitors, public interest organizations, and the public in additive safety reviews.⁸² As a result, the agency's decisions generally do not benefit from outside expertise.⁸³

Missing safety deadlines

As noted, under a provision in the FDA Food Safety Modernization Act of 2011, industry will have to evaluate its processes to ensure that no unapproved food additives are used in its products. Yet FDA has fallen behind in finalizing those rules, which were supposed to take effect by July 2012 but were not even issued in draft form until January 2013. Until the law's regulations are in place, FDA lacks an effective system to ensure compliance with food additive regulations, and food firms do not feel obligated to have internal management standards in place to prevent violations.⁸⁴ In the meantime, FDA relies on tips and complaints from competitors, voluntary reports from manufacturers, or the infrequent inspections it conducts to identify compliance problems with its regulations for additives to food.⁸⁵

Pew's recommendations

The systemic problems plaguing the food additive regulatory program prevent FDA from ensuring the safety of all chemicals added to our food as Congress has intended, but there is no need to start over. Rather, it is better to adopt administrative and legislative solutions so that the Food and Drug Administration can more effectively ensure that new and existing uses of chemical additives in food are safe.

We recommend that FDA take immediate action on its own to narrow the “generally recognized as safe” exemption to what Congress originally intended so that it is no longer a loophole and that it modernize its food additive science. We believe Congress should provide FDA with the funding and authority it needs and ensure that the agency takes these actions. Legislative oversight and direction are essential to build and maintain stakeholder support.

For additives already on the market, the situation is different. FDA lacks the clear authority to get the information it needs to identify problems, set priorities, and, when necessary, efficiently restrict the use of these additives to ensure safety. With about half of the additives already regulated by the Environmental Protection Agency under the Toxic Substances Control Act, and with many additives also regulated as pesticides, Congress needs to look at what is working at both agencies and devise an integrated chemical safety program that allows each agency to fulfill its essential responsibilities in a coordinated manner to minimize duplication of effort, recordkeeping, and the regulatory reporting burden on industry.

To accomplish these objectives, we make the following recommendations:

- Close the GRAS loophole.
- Modernize FDA's food additive science.
- Ensure that existing chemical additives are safe.
- Establish a fee-based funding program to pay for the review process.

Each recommendation is examined in more detail below.

Close the GRAS loophole

Congress should amend the Food Additives Amendment of 1958 so that FDA approves the use of all new chemicals added to food and reviews significant changes to the use of previously approved additives by implementing a more streamlined and efficient decision-making process

The food industry (and, to some extent, the agency itself) relies on the GRAS exemption because it believes that the food additive petition process that Congress adopted in 1958 is too burdensome and time-consuming, requiring that FDA use extensive formal rulemaking procedures. It prefers the GRAS notification program because it is informal and, as currently constructed, is voluntary. Manufacturers have the flexibility to seek FDA review when they want the legitimacy provided by that review and have the option to keep their innovations secret from competitors, even if the FDA and the public are excluded.

Yet as discussed above in our findings section and documented in our paper in the *Journal of the American Medical Association-Internal Medicine*,⁸⁶ the GRAS program has serious problems, especially with regard to conflicts of interest, that must be addressed in order for the public to have confidence in the safety of foods. We recommend that Congress require FDA to review and, if appropriate, approve the first food use of a new

chemical. The GRAS notification and the food contact substance notification program should be limited to changes in existing uses or to additional uses only after FDA has approved the chemical's use in food.

We recognize that concerns have been raised about the burden of the current food additive petition process. This is why we recommend that Congress establish a modernized, streamlined FDA approval process that the agency can effectively and efficiently administer; allows meaningful public input; meets industry's legitimate needs for timeliness and predictability; and, most importantly, restores public confidence that chemical additives are safe. Congress should consider as potential models existing programs that review and approve medical devices, drugs, and pesticides used on food.

To ensure that the notification programs are transparent and credible, Congress should allow FDA to revise the food contact substance notification program so it is more transparent. The notices, with confidential business information removed, should be publicly available on its website before the agency takes final action. Its decision letter to the company should also be posted on its website. This approach would be similar to what is done for GRAS notifications. In both programs, the public and stakeholders should have an opportunity to comment in an informal process before the agency takes final action.

Until Congress changes the law, FDA should revise how it implements the GRAS program to minimize conflicts of interest and to ensure that an additive's use is truly generally recognized as safe by the scientific community

General recognition of additive safety requires consensus in the scientific community. There can be no such consensus if the chemical's use is unknown to the scientific community and to FDA. The experts charged with assessing whether a scientific consensus exists should not have a relationship with the company that makes and sells the chemical additive. In addition, the experts must fairly represent the diversity of the scientific community.

Congress made clear that, in cases where there is no general recognition of safety, FDA should make the decision through the food additive petition process, which requires public notice and comment followed by an FDA rule. As an interim step, FDA should use its existing authority to establish clear guidance that an evaluation by an expert with a conflict of interest will not be effective:

- Until the agency has reviewed it and agreed upon its safety.
- Unless the expert making the decision would be eligible to serve on an agency advisory committee considering the issue.

Modernize FDA's food additive science

Congress should ensure that FDA uses the latest scientific methods to assess additive safety

Consistency is important in science, but FDA's approach to safety assessment is significantly different from those used by EPA and other agencies. FDA has the authority to upgrade its regulatory science and is committed to doing that through its Advancing Regulatory Science Initiative, but that initiative primarily focuses on areas other than chemical additives to food. Some of the differences in the way EPA and FDA assess additive safety stem from FDA's being subject to an outdated law while the laws for other chemicals regulated by EPA are more recent.

To overcome these safety assessment problems, Congress should provide FDA with directions to modernize its program so that it evaluates a wider array of important health effects and improves its ability to ensure that public health is protected. It should consider the standards used in the Food Quality Protection Act of 1996,

especially the margins of safety needed for vulnerable populations such as children and pregnant woman and the evaluation of chemicals for potential endocrine disruption.

FDA should modernize the regulatory science it uses to evaluate the safety of chemical additives

FDA should upgrade the science used to evaluate the safety of additives through its ongoing Advancing Regulatory Science Initiative. As a critical first step, the agency should seek advice from an independent scientific advisory body to guide its modernization efforts. It should also continue and enhance its evaluation of the Tox21 program, which shows significant promise in setting priorities. The evaluation should consider two aspects:

- **Upgrade the science:** FDA should define what constitutes harm and test for potential endocrine disruption, behavior effects, and developmental neurotoxicity at all life stages, including, when appropriate, additional safety factors for children and pregnant women.
- **Improve the process:** FDA should more clearly separate the evaluation of science from management decisions, minimize conflicts of interest and bias from industry evaluations, provide a clear process to assemble and evaluate the evidence, and harmonize its analysis to be consistent with other agencies, especially EPA.

The FDA should adopt and implement a science-based program to systematically review existing chemicals

FDA's current approach of reacting to citizen petitions, industry notifications, and media reports regarding additives already on the market is ineffective. Citizen petitions languish, and the agency stretches its limited resources, shifting from one additive to another without necessarily resolving the underlying scientific challenges.

The agency needs to rejuvenate its system to set priorities using modern scientific tools. We recognize that its Chemical Evaluation and Risk Estimation System is designed to accomplish this goal, but the details are unclear. Specifically, it is not clear that the system incorporates the information developed from Tox21 or that it will be rigorously validated through a transparent process that engages stakeholders. Both are essential.

The agency's top priorities should be widely used additives, those for which it lacks data, and those that are the source of public health concerns. Additives that do not merit immediate review include those recently reviewed and accepted by the European Union or other international organizations, or those that FDA moves to a lower priority based on the available evidence after some form of public input. Based on these priorities, the agency should establish a schedule to reassess chemicals in light of its resources. Additives that are designated as low-priority could be moved up based on new science or changing uses.

Although FDA may not immediately have the resources or tools to fully implement the plan, Congress is unlikely to give it what it needs without a plan in place. Industry and the public may withhold support if they lack confidence in its likelihood of success.

Ensure that existing chemical additives are safe

Congress should update the law to give the agency the ability to obtain the information it needs to set priorities and reassess the safety of existing additives

To effectively manage 10,000 additives, FDA needs to efficiently estimate consumer exposure, be alerted by industry to health and safety studies, and require testing. With about half the additives already regulated by EPA, we recommend that Congress strengthen and amend the Toxic Substances Control Act so food manufacturing

companies routinely report to EPA via existing programs the information about the use of those additives also regulated by that law and notify FDA through EPA when it believes there is a substantial risk posed by an additive that was previously unknown.

In addition, Congress should provide clear authority for FDA to issue orders requiring the food industry to conduct testing and submit safety and use data to the agency, as EPA is authorized to do for pesticides used on food.

The law should be updated to require FDA to conduct a retrospective assessment of previously cleared chemicals through a transparent public process that sets priorities based upon available information

Because 10,000 chemicals are already allowed in food, we acknowledge that it is not practical to conduct a thorough safety evaluation of all of them under current constraints. If FDA had the authority to get the information it needs and coupled it with modern scientific tools to set priorities, then reviews could be done more quickly and efficiently—especially if food manufacturers cooperated in the analysis.

The task is daunting and would take time, but the increasing complexity of our food supply chain makes it necessary so that consumers can have confidence in it. We recommend that Congress and the agency set a specific timetable for designing and completing a review cycle, as was done for pesticide food tolerances under the Food Quality Protection Act of 1996.

Until Congress updates the law, FDA needs to request missing information from other agencies and industry

Until Congress gives FDA the additional data collection authority and streamlined decision-making process it needs, we recommend that the agency obtain data from EPA and from the European Commission, which has undertaken a similar effort for chemicals added to food and other consumer products. The agency should also request that industry provide it with all relevant health and safety studies and exposure information.

Establish a fee-based funding program

Congress needs to establish a fee-based program similar to that used for the pharmaceutical and pesticide industries to pay for FDA's review and implementation of the food additives program. Although fees are not popular with manufacturers, FDA otherwise will not be able to make the investment it needs to ensure that food additives are safe and to restore public confidence in the safety of these additives. The agency has sufficient experience with fees to make independent science-based decisions in a timely and effective manner.

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Appendix 1

Expert academic advisers

The following individuals served as expert academic advisers. They provided guidance to Pew throughout the project, often commenting on drafts of articles and moderating sessions of workshops. While invaluable to this report, these advisers are not responsible for our analysis, findings, or recommendations.

P. Vincent Hegarty, Ph.D., *Founding Director and Professor Emeritus, Institute for Food Laws and Regulations, Michigan State University*

Joseph Hotchkiss, Ph.D., *Director and Professor, School of Packaging, Michigan State University*

D. Gail McCarver, M.D., *Professor, Pediatrics and Pharmacology, Co-director, Clinical Pharmacology, Pharmacogenetics and Teratology, Children's Hospital of Wisconsin, Medical College of Wisconsin*

J. Routt Reigart, M.D., *Professor Emeritus, Department of Pediatrics, Medical University of South Carolina*

Stephen M. Roberts, Ph.D., *Director, Center for Environmental & Human Toxicology, University of Florida*

I. Glenn Sipes, Ph.D., *Professor of Pharmacology, Chair, Department of Pharmacology, University of Arizona*

John G. Vandenberg, Ph.D., *Professor Emeritus, Department of Biology, North Carolina State University*

Tracey J. Woodruff, Ph.D., MPH, *Professor and Director, Program on Reproductive Health and the Environment, Institute for Health Policy Studies, University of California, San Francisco*

R. Thomas Zoeller, Ph.D., *Professor, Biology Department, University of Massachusetts Amherst*

Appendix 2

Peer-reviewed articles published by Pew staff on food additives

(in reverse chronological order)

Neltner, T. G., N. R. Kulkarni, H. M. Alger, M. V. Maffini, E. D. Bongard, N. D. Fortin, and E. D. Olson, "Navigating the U.S. Food Additive Regulatory Program," *Comprehensive Reviews in Food Science and Food Safety* (2011)10:342-368, <http://onlinelibrary.wiley.com/doi/10.1111/j.1541-4337.2011.00166.x/abstract>.

Maffini, M. V., H. M. Alger, E. D. Bongard, and T. G. Neltner, "Enhancing FDA's Evaluation of Science to Ensure Chemicals Added to Human Food Are Safe: Workshop Proceedings," *Comprehensive Reviews in Food Science and Food Safety* (2011)10: 321-341, <http://onlinelibrary.wiley.com/doi/10.1111/j.1541-4337.2011.00165.x/abstract>.

Alger, H. M., M. V. Maffini, N. R. Kulkarni, E. D. Bongard, and T. Neltner, "Perspectives on How FDA Assesses Exposure to Food Additives When Evaluating Their Safety: Workshop Proceedings," *Comprehensive Reviews in Food Science and Food Safety* (2013) 12: 90-119, <http://onlinelibrary.wiley.com/doi/10.1111/j.1541-4337.2012.00216.x/abstract>.

Maffini, M. V., H. M. Alger, E. D. Olson, and T. G. Neltner, "Looking Back to Look Forward: A Review of FDA's Food Additives Safety Assessment and Recommendations for Modernizing Its Program," *Comprehensive Reviews in Food Science and Food Safety* (2013) 12: 439-453, <http://onlinelibrary.wiley.com/doi/10.1111/1541-4337.12020/abstract>.

Neltner, T.G., H. M. Alger, J.T. O'Reilly, S. Krinsky, L.A. Bero, M. V. Maffini, "Conflicts of Interest in Approvals of Additives to Food Determined to Be Generally Recognized as Safe: Out of Balance," *Journal of American Medical Association - Internal Medicine*. Published online Aug. 7, 2013, <http://archinte.jamanetwork.com/article.aspx?articleid=1725123>. DOI:10.1001/jamaintermid.2013.10559.

Neltner, T. G, H.M. Alger, J.E. Leonard, M.V. Maffini, "Data Gaps in Toxicity Testing of Chemicals Allowed in Food in the United States," *Reproductive Toxicology* (Accepted 2013), DOI:10.1016/j.reprotox.2013.07.023.

Peer-reviewed articles funded or supported but not authored by Pew

Magnuson, B., I. Munro, P. Abbot, N. Baldwin, R. Lopez-Garcia, K. Ly, L. McGirr, A. Roberts, and S. Socolovsky "Review of the regulation and safety assessment of food substances in various countries and jurisdictions," *Food Additives & Contaminants: Part A*, published online June 20, 2013, <http://dx.doi.org/10.1080/19440049.2013.795293>.

Beausoleil, C., J.-N. Ormsby, A. Gies, U. Hass, J. J. Heindel, M. L. Holmer, P. J. Nielsen, S. Munn, G. Schoenfelder "Low Dose Effects and Non-monotonic Dose Responses for Endocrine Active Chemicals: Science to Practice Workshop: Workshop Summary, *Chemosphere*, accepted June 13, 2013.)

A series of articles developed by the "NanoRelease Food Additive" project lead by the International Life Sciences Institute Research Foundation will publish a series of five articles and a State of the Science report on methods to measure the release of nanoengineered particles from food. A summary of these articles will be submitted to one or more of the following peer-reviewed journals in 2013 and 2014: *Nanotoxicology*; *Regulatory Toxicology and Pharmacology*; *Comprehensive Reviews in Food Science and Food Safety*; and *Nature Nanotechnology*.

Appendix 3

Stakeholder events

Pew-led with co-sponsorship of the journal *Nature* and the Institute of Food Technologists

(in reverse chronological order)

“Enhancing FDA’s Evaluation of Science to Ensure Chemicals Added to Human Food are Safe,” April 5-6, 2011, at Pew’s Washington, DC, conference center

- Pre-workshop webinar on March 29, 2011
- Report for participants distributed on March 29, 2011
- Proceedings published in Oct. 2011

“Perspectives on FDA’s Exposure Assessment to Ensure Substances Added to Human Food are Safe,” Nov. 17-18, 2011, at Pew’s conference center

- Pre-workshop webinar on Oct. 19, 2011
- Report for participants distributed on Nov. 10, 2011
- Proceedings published in Dec. 2012

“Workshop on Enhancing FDA’s Food Additives Program to Ensure the Safety of Substances Added to Food,” April 19, 2012 at Pew’s conference center

- Policy suggestions distributed to participants on April 12, 2012

“Workshop on Non-Monotonic Dose Responses: Relevance and Implications for Food,” April 20, 2012, at Pew’s conference center

“Workshop on Potential Conflicts of Interest in GRAS Additive Decisions,” August 7, 2013, at Pew’s conference center

- Draft guidance distributed to participants on July 23, 2013

Other significant food additive-related workshops organized or supported by Pew

“Food Additives Workshop,” Dec. 13, 2010, in Washington, DC, convened by the Grocery Manufacturers Association to learn about Pew’s project.

“International Law for Chemicals Added to Food: Different Approaches to Protecting Public Health,” June 13, 2011, in New Orleans, LA, convened by Pew as a session at the annual meeting of the Institute of Food Technologists.

“Navigating the U.S. Food Additives Regulatory Program,” May 22, 2012, as a webinar convened by Pew for the Institute of Food Technologists.

“Low Dose Effects and Non-monotonic Dose Responses for Endocrine Active Chemicals: Science to Practice Workshop,” Sept. 12-14, 2012, in Berlin, convened by the European Commission and National Institute of Environmental Health Sciences with facilitation and technical support provided by Pew.

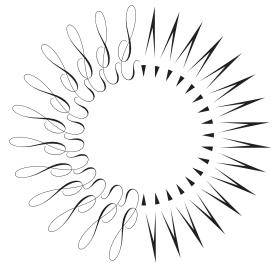
“Workshop on Measurement Methods for the Release of Engineered Nanomaterials from Food and Absorption by the Body,” Dec. 11-12, 2012, at Pew’s conference center convened by the International Life Sciences Institute Research Foundation as part of the Pew co-funded NanoRelease Food Additive Project.

“Chemical Testing in the 21st Century: Opportunities and Challenges,” Jan. 23-24, 2013, at Pew’s conference center convened by the Environmental Defense Fund.

“Environmental Health and Food,” May 6, 2013, at a session of the annual meeting of Academic Pediatrics Association.

“The Whole Package: Regulating Chemicals in the Food Supply,” May 21, 2013, as a webinar for the Sustainable Agriculture & Food Systems Funders Network.

Pew’s food additive staff also delivered at least a dozen additional presentations as part of other events for industry, scientific, or public interest organizations.



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Appendix 5



The elephant in the room: potential biopersistence of short-chain PFAS

By [Tom Neltner](#) / Published: February 20, 2019

Maricel Maffini, Ph.D., Consultant and [Tom Neltner, J.D.](#), Chemicals Policy Director

In January 2018, US Food and Drug Administration (FDA) scientists published a [peer-reviewed journal article](#) stating a commonly used raw material to make greaseproof paper is likely to persist in the human body. FDA scientists' sophisticated analysis and remarkable conclusion raises questions about the broad assumption that short-chain perfluorinated alkyl substances (PFAS), as a class, did not accumulate.

Strangely, [two recent](#) reviews funded by the [FluoroCouncil](#), ignored FDA scientists' study even though it was published ten months before the industry group submitted their analysis for peer-review. The peer reviewers appear to have missed the omission as well. As a result, the industry evaluations continue to perpetuate the flawed assumptions, concluding that perfluorohexanoic acid (PFHxA) and related short-chain PFAS “present negligible human health risk” and that this substance alone is a suitable marker for the “safety of fluorotelomer replacement chemistry.”

In this blog, we discuss the differences between the studies and the implications of the discordance between FDA's and industry's conclusions for the safety assessment of short-chain PFAS.

What do we know about short-chain PFAS?

With the phase-out of long-chain PFAS to make water- and grease-proof materials, companies shifted to short-chain fluorotelomer-based chemistry.^[1] These new raw materials are used to build polymers and include chemicals that contain six fully-fluorinated carbon groups with additional non-fluorinated carbons. These molecules are usually known as C6 and a common starting material for polymers is a 6:2 fluorotelomer alcohol (6:2 FTOH) that has six fully-fluorinated carbons and two non-fluorinated carbons with an alcohol on the non-fluorinated end.

Industry expected that these C6 compounds, among them 6:2 FTOH and its main manufacturing impurity perfluorohexanoic acid (PFHxA), would: 1) be less toxic than long-chain PFAS such as 8:2 FTOH, PFOA and PFOS; and 2) not accumulate in the body.

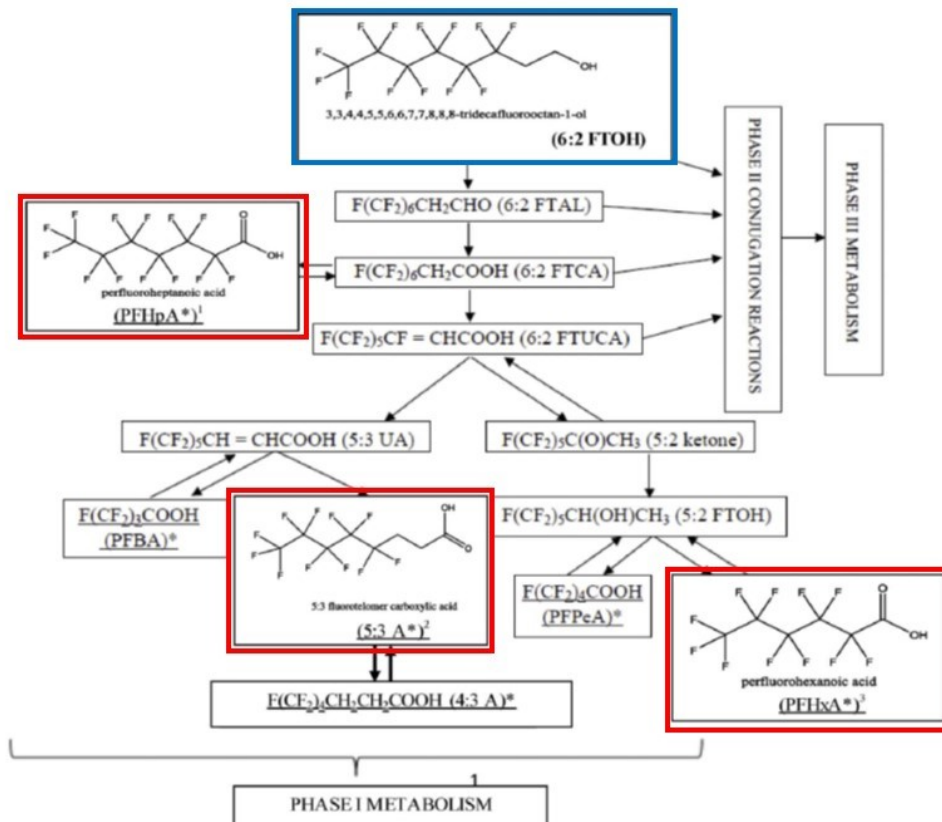
However, these expectations do not hold up under scrutiny. A [2015 study](#) by an FDA scientist concluded that “significant data gaps remain” about the toxicity of the 6:2 FTOH, and in the [2018 study](#), the agency scientists raised the potential for biopersistence.

Significance of FDA's conclusion about potential biopersistence of C6 fluorotelomer alcohol

FDA scientists' thorough evaluation of publicly available^[2] animal and human exposure data on 6:2 FTOH provided important insight into the

metabolites, namely the PFHxA mentioned above, 5:3 fluorotelomer carboxylic acid (5:3 A) and perfluoroheptanoic acid (PFHpA) that could be used as markers of 6:2 FTOH exposure. For each metabolite, they also provided internal exposure estimates. The figure below shows 6:2 FTOH (in blue box) and how the body converts it to the three metabolites (in red boxes).

Proposed scheme for metabolism of 6:2 FTOH. Adapted from Kabadi et al. (2018)



As a result of their analysis, **FDA scientists identified 5:3 A as an important biomarker for the potential biopersistence of 6:2 FTOH** because:

- 5:3 A had the highest internal exposure and the slowest elimination by the body; and

- 5:3 A's elimination was reduced when exposure to 6:2 FTOH increased.

FDA's scientists also concluded there are sex-based differences in the elimination of the other two metabolites, PFHxA and PFHpA, in animal studies. Although human data was only available in men, the difference observed in animals could mean that men and women may have different internal exposures and, therefore, experience different toxicity.

FluoroCouncil-funded reviews reached a different conclusion

In January 2019, two reviews ([HERE](#) and [HERE](#)) funded by the FluoroCouncil were published concluding that:

- PFHxA “is less hazardous to human health than PFOA”;
- “PFHxA and related fluorotelomer precursors currently appear to present negligible human health risk to the general population”; and
- PFHxA is not expected to bioaccumulate due to its “rapid and nearly complete elimination” from the body.

These reviews evaluated the toxicology, exposure and biomonitoring data available for PFHxA. The analysis included the estimation of a toxicity reference dose and drinking water and residential groundwater screening levels. The overall conclusion was that “PFHxA levels currently present in the environment are well below levels that may present a concern for human health.”

The main difference between these reviews and the study by FDA scientists is that the industry-funded scientists focused exclusively on PFHxA. Their goal was to review the literature relevant to risk assessment to answer questions regarding “potential human health risks associated with exposure to fluorotelomer-based products” using PFHxA as a reference chemical for the entire short-chain PFAS class.

The two industry-funded reviews reported that PFHxA [has been measured](#) in water, soil, household dust, human serum, plasma, whole blood, urine, breast milk, and food with various frequencies. And that the substance is [environmentally persistent](#), mobile and may accumulate in the leaves and fruits of plants. The reviews also reference a [2013 publication](#) estimating that the mean half-life in humans is 32 days. In other words, it may take a month on average for half the amount present in the body to be eliminated.

Although the industry-funded reviews narrowly focused on a single chemical, the authors extended their conclusion to the entire fluorotelomer-based chemical process when they say that PFHxA is a “suitable marker for the safety of fluorotelomer replacement chemistry used today.” That is quite a bold statement that was not fully explained.

Following their reasoning, any other short-chain PFAS used in fluorotelomer-based products would be assumed to be as safe as PFHxA, including 6:2 FTOH. That assumption, however, appears to be flawed based on FDA scientists’ study showing that 6:2 FTOH metabolite 5:3 A is an important biomarker for the potential biopersistence of 6:2 fluorotelomer alcohol.

Conclusion

The study by FDA scientists has the potential to be a game changer in the safety assessment of short-chain PFAS. Based on their conclusions, safety studies must:

- Assess how the body breaks down these chemicals and how fast they are eliminated; and
- Be redesigned to account for biopersistence by including long-term exposures and exposures during development.

A decade ago, industry led us to believe that the new technology replacing toxic long-chain PFAS would be “more favorable” to human health and the environment. As a result, FDA has been approving short-chain fluorotelomer chemicals to make polymers for use in contact with food [without information](#) on the potential biopersistence of the chemicals themselves or their metabolites.

As we have noted in [previous blogs](#), it is time to start making decisions on chemicals’ safety based on scientific evidence – not on assumptions. For PFAS, FDA needs to reassess the safety and environmental impacts of these chemicals for use as food contact substances. Until that review is complete, companies should avoid using products treated with the chemicals.

[1] For more information see Buck et al. 2011. [Perfluoroalkyl and Polyfluoroalkyl Substances in the Environment: Terminology, Classification, and Origins](#). Integrated Environmental Assessment and Management — Volume 7, Number 4—pp. 513–541.

[2] Except for Nilsson et al. (2012), all the publications were by DuPont

[al.](#) (2011). [Himmelstein et al.](#) (2012).



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