U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

October 1, 2019

Devon Wm. Hill
Keller & Heckman LLP
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Washington, DC 20001
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RE: Pre-Notification Consultation (PNC) 2422

Dear Mr. Hill:

This correspondence is in regard to FCN numbers 820, 827, 888, 933, 1044, 1360, and 1451, which you submitted on behalf of Daikin America, Inc. (Daikin). These FCNs became effective on July 31, 2008, September 9, 2008, June 18, 2009, December 30, 2009, February 16, 2011, February 21, 2014, and September 4, 2014 respectively. FCN 820 is for the food contact substance (FCS) "2-Propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester, polymer with α-(1-oxo-2-propen-1-yl)-ω-hydroxypoly(oxy-1,2-ethanediyl)." FCNs 827 and 888 are for the FCS "2-propenoic acid, 2-hydroxyethyl ester, polymer with α-(1-oxo-2-propen-1-yl)-ω-hydroxypoly(oxy-1,2-ethanediyl), α-(1-oxo-2-propen-1-yl)-ω-[(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 (CAS Reg. No. 1012783-70-8)." FCN 933 is for the FCS "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 (CAS Reg. No. 1158951-86-0).")." FCN 1044 is for the use of the FCS "2-propenoic acid, 2-methyl-, 2-hydroxyethyl ester polymer with 1-ethyenyl-2-pyrrolidinone, 2-propenoic acid and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate sodium salt (CAS Reg. No. 1206450-10-3)." FCNs 1360 and 1451 are for the FCS "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)." The subject FCS in FCNs 820, 827, 888, 933, 1044, 1360, and 1451are intended for use as grease-proofing agents to be applied to paper and paperboard for use in contact with food. Due to the chemical structure of these FCSs, the Food and Drug Administration (FDA) considers them to belong to a class of chemicals termed "short-chain per- or polyfluorinated substances" (short-chain PFAS)[1].

FDA routinely monitors developments in scientific research and information to ensure that our safety assessments of regulated food contact substances remain adequate within the context of currently available scientific data. FDA has recently become aware of toxicological data that is relevant to short-chain (SC) PFAS as a class. FDA's review of these newly available toxicological data has revealed safety concerns for SC-PFAS which are applicable to the food contact use authorized under FCNs 820, 827, 888, 933, 1044, 1360, and 1451. The intent of this letter is to outline FDA's safety concerns for SC-PFAS based on our review of these toxicological data and provide a framework for future discussions with you regarding our safety concerns associated with FCNs 820, 827, 888, 933, 1044, 1360, and 1451.

Background

[1] "Short-chain PFAS" refers to PFAS with seven or fewer carbons in an alkyl chain (n-1 carbons are perfluorinated).

Recently available toxicological data on 2-(perfluorohexyl)ethyl alcohol (CAS Reg. No. 647-42-7) (6:2 fluorotelomer alcohol (FTOH)), one of the impurities listed for the FCS in FCNs 820, 827, 888, 933, 1044, 1360, and 1451, reveals concerns for biopersistence of a key metabolite, 2H, 2H, 3H, H-perfluorooctanoic acid (5:3 acid) (CAS Reg. No. 914637-49-3). Our review of newly available toxicological data provides evidence that the 5:3 acid, a key metabolite of the 6:2 FTOH, is biopersistent in rodents; 6:2 FTOH may also be carcinogenic in the livers of rodents, based on data from repeated-dosing oral toxicity studies conducted with 6:2 FTOH in mice and rats. Our review also identifies concerns for immunotoxicity and postnatal toxicity for the 6:2 FTOH and, by extension, for the SC-PFAS monomers and the low molecular weight oligomers (LMWO) which are constituents or impurities of short-chain PFAS FCS. None of these concerns are addressed by the current dataset provided in support of FCNs 820, 827, 888, 933, 1044, 1360, and 1451. The following studies are considered the minimum dataset needed to address the safety concerns and data gaps identified above: toxicokinetics/pharmacokinetics (TK/PK) studies in rodents, a two-year carcinogenicity bioassay in mice, and an extended one-generation reproductive toxicity study in mice conducted with the 6:2 FTOH. For more detailed information of our toxicology review, please see Enclosure 1.

Conclusion

FDA's Office of Food Additive Safety (OFAS) requests that Daikin come to discuss these safety concerns with us no later than October 25, 2019. The purpose of this meeting is to facilitate a timely resolution of these and any other issues that may influence the safety determination for the intended use of the FCSs subject to FCNs 820, 827, 888, 933, 1044, 1360, and 1451.

If you have any further questions concerning this matter, please do not hesitate to contact us.

Sincerely,

Dennis M. Keefe -S

Digitally signed by Dennis M. Keefe -S
Date: 2019.10.01 16:49:48 -04'00'

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

Enclosure (1)

Enclosure 1: Toxicology Review and Summary of Scientific Questions on SC-PFAS

FDA's initial review[2] of FCNs 820, 827, 888, 933, 1044, 1360, and 1451 concluded that the exposures to the PFAS impurities deriving from the use were supported by the then-available toxicity data based on:

- No concern for genotoxicity from reviews of an extensive array of genotoxicity studies conducted with the 6:2 fluorotelomer methacrylate (6:2 FTMAC) and the 6:2 FTOH that had been submitted as part of similar FCNs;
- Lack of concern for biopersistence, based on PK data from studies conducted in rats with perfluorohexanoic acid (PFHxA); and
- Adequate margins of exposure between the respective estimated daily intakes for PFHxA and 6:2 FTOH and no observed effect levels (NOELs) or lowest observed effect levels (LOELs) from OECD 422, 90-day oral toxicity, and one-generation reproductive toxicity studies conducted in rats with PFHxA or its sodium salt and OECD 422, 90-day oral toxicity, one-generation reproductive toxicity, and teratology studies conducted in rats with 6:2 FTOH that had been reviewed for similar FCNs.

Basis for Initiation of Postmarket Reevaluation of SC-PFAS FCSs

In December of 2015, FDA identified a publication (Russell *et al*., 2015)[3] documenting accumulation of organic fluorine in the serum of rats administered 6:2 FTOH by gavage for 90 days. This published result informed FDA as to potential biopersistence of these compounds and raised potential safety concerns about the effective FCNs for SC-PFAS generally. To address these issues, OFAS initiated a reassessment of the available data supporting the safe use of SC-PFAS FCSs. In January 2018, FDA became aware of unpublished toxicological and toxicokinetic (TK) studies conducted on 6:2 FTOH, SC-PFAS monomers, PFHxA, and the 5:3 acid, which is a metabolite of the 6:2 FTOH. OFAS has reviewed the additional toxicology studies and our review is summarized below.

Biopersistence Affects Data Needs for Safety Evaluation

Safety evaluation of a compound for food contact use considers lifelong exposure of the U.S. population to the migrant in the diet. Typically, a cumulative estimated daily intake (CEDI) is calculated that takes into account exposure from all approved uses of the food contact substance. This CEDI is then compared to a safety threshold. A CEDI is commonly used in place of an internal dose estimate by assuming ADME[4] results in a relatively quick period to internal steady state levels. Biopersistence violates this assumption and method by causing the internal dose to increase over time with chronic dietary intake. In the case of biopersistence, TK and long-term toxicity data are necessary to take into account the increase in internal dose and evaluate toxicity from chronic dietary intake.

FDA's Toxicology Guidance[5] assumes that the ADME of a compound results in a relatively quick period to internal steady state levels and provides guidance regarding the toxicological dataset needed to support a given exposure based upon this assumption. However, since available data pertinent to both long-chain and short-chain PFAS compounds demonstrate that many of these compounds biopersist in human and animal tissue, PFAS compounds appear to be exceptions to the FDA Toxicology Guidance.[5] In addition to

[2] FCN 820 Toxicology Review Memorandum, P. Rice to M. Hepp, July 14, 2008. FCN 827 Toxicology Review Memorandum, P. Rice to P. Honigfort, August 12, 2008. FCN 888 Memorandum to the File, P. Honigfort, May 27, 2009. FCN 933 Toxicology Review Memorandum, W. Roth to K. Randolph, December 8, 2009. FCN 1044 Toxicology Review Memorandum, P. Rice to M. Hepp, January 13, 2011. FCN 1360 Toxicology Review Memorandum, D. Levy to E. Furukawa, January 13, 2014. FCN 1451 Toxicology Review Memoranum, T.-F. Cheng to A. Chang, July 24, 2014.

[3] Russell, M.H. et. al., Chemosphere, 120 (2015), 328-335.

[4] Absorption, distribution, metabolism, excretion (ADME)

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-preparation-food-contact-notifications-food-contact-substances-toxicology

biopersistence, several members of this class of compounds have demonstrated carcinogenic activity in rodents, and potent developmental and immunological toxicity in animal models and humans. PFAS as a class are generally negative for activity in traditional genotoxicity tests and act primarily through non-genotoxic mechanisms of action: FDA's assessment of the endpoint of carcinogenicity for PFAS in general focused on data indicative of ability to cause peroxisome proliferation and xenobiotic-metabolism enzyme induction in the liver, which appear to be key mechanisms of action for tumor induction for PFAS compounds (Rice/Honigfort, July 27, 2015, RE: FAP 4B4809).[6] At low exposures FDA's Toxicology guidance to industry[5] only recommends conducting genotoxicity studies and does not recommend testing to evaluate systemic toxicity until dietary concentrations reach 50 ppb or higher. Due to biopersistence, the internal dose of a PFAS compound may reach a level at which systemic toxicity occurs even though the dietary exposure of the compound is < 50 ppb, indicating that FDA's Toxicology Guidance[5] does not sufficiently address the toxicological concerns that the FDA may have for PFAS compounds. As toxic potency is directly proportional to systemic half-life, a compound's TK properties, particularly the time to systemic steady-state, are key to predicting its toxicological profile. Reproductive/developmental toxicity, particularly toxicity during early postnatal development, is a sensitive endpoint for PFAS toxicity and must also be considered. Given that the 5:3 acid metabolite of the 6:2 FTOH, and by extension the SC-PFAS monomers and the LMWO SC-PFAS, have been found to be biopersistent in rodents, FDA considers the endpoints of carcinogenicity, reproductive/developmental, and systemic toxicity to be relevant to the assessment of migrating substances into food from the authorized uses SC-PFAS FCSs at less than 50 ppb. Additional data may also be needed, depending upon the results of the TK and toxicity studies.

Available dataset for SC-PFAS

The conclusions of FDA's reanalysis may be summarized as follows:

- The 5:3 acid, a significant metabolite of the 6:2 FTOH, is clearly biopersistent in the liver, fat, and serum of rodents and possibly also in human tissues. Further TK studies in rodents, hepatocytes, and kidney cells are needed to derive critical TK parameters necessary for calculating systemic steady-state body burdens for 6:2 FTOH and its metabolites in humans and animal models;
- Short-term studies identify the liver, teeth, and kidney and potentially the immune system as target organs for the 6:2 FTOH and, by extension, the SC-PFAS monomers and the LMWO SC-PFAS. Target organs for PFHxA include the liver, kidney, and, potentially, the immune system. Due to the biopersistence of the 5:3 acid, longer-term repeated dose studies of at least one-year in duration are necessary to potentially derive reliable points of departure for quantitative risk assessment. Specialized studies examining functional and physiological endpoints for the immune system are recommended to fully-characterize the effects of the 6:2 FTOH on the immune system;
- Toxic effects of the 6:2 FTOH on reproduction include decreased gestation indices and numbers of pups born and, in mice, impaired lactation phenotype. Prenatal developmental effects include ossification delays and wavy ribs; postnatal effects include decreased bodyweight gain and, in mice, increased postnatal mortality and delayed developmental indices. Due to the biopersistent nature of the 5:3 acid and the high potency of PFAS compounds generally as toxicants during the postnatal period, FDA recommends conduct of an extended one-generation reproductive toxicity study (EOGRTS, OECD 443) in mice, the more sensitive species, with the 6:2 FTOH to characterize the effects of postnatal exposure on development of the immune system, nervous system, and reproductive tract; and
- No evidence of neoplastic activity was noted for PFHxA in an oral bioassay conducted in rats. In contrast, proliferative lesions suggestive of neoplastic potential were noted in the livers of mice and rats administered 6:2 FTOH for 90 days. As the SC-PFAS monomers and 6:2 FTOH were negative for activity in the standard genotoxicity test battery, the observed liver lesions represent a nongenotoxic mode of action, likely unrelated to PPAR-alpha activation. These results suggest that 6:2 FTOH may be a hepatocarcinogen in both rodents and humans. To fully-characterize the

[6] See Ref. 4 to FDA's Final Rule, 81 FR 5 (Jan. 4, 2016).

carcinogenic potential of the 6:2 FTOH, FDA recommends conduct of a two-year bioassay in mice, the more sensitive species, with the 6:2 FTOH.

In the absence of the above-recommended studies, FDA does not have adequate information to evaluate the endpoints of carcinogenicity or systemic toxicity for the current CEDI to the 6:2 FTOH, as the reviewed genotoxicity studies are not predictive of carcinogenic potential in the current context and the 28-90-day repeated dose studies are of inadequate duration to model chronic exposure to the 6:2 FTOH. As such, the current toxicological dataset for the 6:2 FTOH and SC-PFAS monomers is inadequate to support the calculated CEDIs to these compounds. We also conclude that, contrary to FDA's previous assessments of SC-PFAS FCSs and the conclusions of a recently-published assessment of PFHxA,[7] the toxicological dataset for PFHxA cannot be used to support the CEDIs for the 6:2 FTOH, SC-PFAS monomers, and LMWO SC-PFAS. This conclusion is based on the clear quantitative and qualitative differences in effects on the livers and kidneys between rats administered the 6:2 FTOH versus rats administered PFHxA/NaPFHx in the OECD 422 and 90-day oral toxicity studies, as well as the fact that the 5:3 acid metabolite of the 6:2 FTOH is biopersistent in rats, while PFHxA is rapidly eliminated. FDA considers the overall toxicological profile of the 6:2 FTOH to be significantly more concerning than that of PFHxA. As such, use of points of departure from toxicological studies conducted with PFHxA in the human health risk assessment of 6:2 FTOH exposure may significantly underestimate the risk to human health and may fail to capture apical effects that may be relevant to human health.

CONCLUSIONS

FDA has completed our toxicological re-assessment of SC-PFASs incorporating the cumulative dietary exposures to 6:2 FTOH, SC-PFAS monomers, and LMWO SC-PFAS deriving from currently-authorized uses of SC-PFAS grease-proofing agents under the FCN program. We conclude that the 6:2 FTOH is biopersistent and possibly carcinogenic in rodents and likely to be so in humans. The re-assessment also identifies concerns for immunotoxicity and postnatal toxicity for the 6:2 FTOH and, by extension, for the SC-PFAS monomers and the LMWO SC-PFAS. None of these concerns are addressed by the current dataset provided in support of FCNs FDA's initial review[8] of FCNs 820, 827, 888, 933, 1044, 1360, and 1451. The following studies are considered the minimum dataset needed to address the safety concerns and data gaps identified above: toxicokinetics/pharmacokinetics (TK/PK) studies in rodents, a two-year carcinogenicity bioassay in mice, and an extended one-generation reproductive toxicity study in mice conducted with the 6:2 FTOH.

[7] Luz, A.L., Anderson, J.K., Goodrum, P., and Durda, J. (2019) Perfluorohexanoic acid toxicity, part I: Development of a chronic human health toxicity value for use in risk assessment. *Regul. Toxicol. Pharmacol*., **103**: 41-55. "Response to "Overgeneralization by Anderson et al. and Luz et al. regarding safety of fluorotelomer-base chemistry", Anderson, J.K., Luz, A.L., and Goodrun, P.; 2019; *Regul. Toxicol. Pharmacol* , doi: 10.1016/j.yrtph2019.03.015.

[8] FCN 820 Toxicology Review Memorandum, P. Rice to M. Hepp, July 14, 2008. FCN 827 Toxicology Review Memorandum, P. Rice to P. Honigfort, August 12, 2008. FCN 888 Memorandum to the File, P. Honigfort, May 27, 2009. FCN 933 Toxicology Review Memorandum, W. Roth to K. Randolph, December 8, 2009. FCN 1044 Toxicology Review Memorandum, P. Rice to M. Hepp, January 13, 2011. FCN 1360 Toxicology Review Memorandum, D. Levy to E. Furukawa, January 13, 2014. FCN 1451 Toxicology Review Memoranum, T.-F. Cheng to A. Chang, July 24, 2014.

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January 17, 2020

Via Electronic and U.S. Mail

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Center for Safety and Applied Nutrition
U.S. Food and Drug Administration
5001 Campus Drive,
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CONTAINS CONFIDENTIAL BUSINESS INFORMATION

Re: Daikin America, Inc.; Follow-up to December 9, 2019 letter

Dear Dr. Keefe:

On behalf of our client, Daikin America, Inc. (Daikin), the purpose of this letter is to provide our proposed phase-out period for effective Food Contact Notification (FCN) Nos. 820, 827, 888, 933, 1944, 1360, and 1451 for C6 fluorotelomer chemistries used in the production of food-contact paper and paperboard ("C6 compounds" or "C6 products") (Attachment A). This letter also provides the scientific support (Attachment B) and regulatory precedent (Attachment C) for our proposal. Note that in developing this proposal, we have worked cooperatively with AGC Chemicals Americas, Inc. ("AGC"), and Archroma Management LLC ("Archroma") in an effort to provide FDA with a unified framework for this process.

As committed to in our December 9, 2019 letter, Daikin is willing to work cooperatively with FDA and to consider a voluntary market withdrawal of the C6 products, as long as it is tied to a mutually agreeable phase-out period which will help ensure a smooth transition to suitable alternatives and help prevent potentially harmful market disruptions for consumers and the supply chain. The enclosed data and information package provides proper justification for the proposed phase-out plan. We believe Daikin's proposed voluntary phase-out period is commensurate with a scientific-based assessment of the risk to public health, especially given that consumer exposure to C6 compounds is very low. The phase-out period achieves the desired transition from C6 compounds as food contact substances in a manner that shows continuous progress with low risk to consumers. Daikin does not challenge the relevance of the new data on bioaccumulation of these compounds. The available data shows no imminent public health risk that would necessitate a precipitous market withdrawal. Further, regulatory precedent set by FDA and EPA are consistent with a methodical, risk-based approach.

1. Proposed Phase-Out Plan

In response to FDA's stated goal of eliminating the use of C6 fluorotelomer chemistries in the production of food-contact paper and paperboard in the United States (U.S.), we propose a (b) (4) of product sold into food-contact applications in the United States, according to the terms outlined in Attachment A and set forth below.

(b) (4)

We strongly believe this proposal is the simplest, most effective means to accomplish FDA's goal of reducing dietary exposure while ensuring an orderly market transition for end-use manufacturers and consumers.

This market-based approach will allow a natural selection process to take place, where the easier-to-transition packaging products will disappear first and the last-remaining products will be those that are more difficult to transition to replacement products. This approach will also convey benefits along the supply chain, ensuring that small businesses lacking the financial capability to readily undertake the time-consuming and costly steps to transition to alternate technology (*e.g.*, qualifying new products, installing new equipment, *etc.*) will not be disproportionately impacted by FDA's stated goal of eliminating the use of C6 fluorotelomer products in food-contact applications in the U.S. This plan also allows for a unified industry-wide approach in a manner consistent with anti-trust laws.

2. Scientific Justification

Daikin engaged the third-party expert consultant group, Exponent, Inc., to conduct an independent expert review of the toxicological evidence available (See Attachment B). The purpose of the review was to assess the level of risk to consumers, if any, that would be presented if the requested 5-year phase-out of these compounds were granted. To be clear, this report does not assess whether these C6 compounds would meet the premarket standard of review for food contact substance materials. Rather, the sole purpose of the report is to assess any risk to consumers during the proposed 5-year phase-out period.

Key conclusions from the report include:

- "The new animal studies on bioaccumulation are suggestive in nature, but are not sufficient to make any final safety assessment of these compounds."
- "FDA has not identified an imminent health or safety concern, particularly considering the conservatisms built into the exposure and hazard assessment procedures, that would require immediate withdrawal as opposed to an appropriate phase out approach."
- "[A] comprehensive peer reviewed safety/risk assessment shows a low risk to the public were the compounds allowed to remain available during a 5 year phase-out period."

These conclusions are reinforced by the fact that a Margin of Exposure (MOE) of 6850 exists between the subchronic 6:2 FTOH No Observed Adverse Effect Level (NOAEL) and the Cumulative Estimated Dietary Intake (CEDI); this MOE is above FDA's recommended MOE of 2000 for subchronic data.

Accordingly, Daikin believes this independent expert report provides a strong scientific basis for FDA to grant industry's request for a 5-year phase-out period, (b) (4) (b) (4) 5 years. Once again, Daikin does not assert that the new data on bioaccumulation are not relevant to transitioning away from these C6 compounds for use in food packaging, just that the demonstrated risk to the public is low during such transition period and that a reasonable transition period is justified in order to avoid market disruption. We firmly believe it is clear that the available data does not demonstrate an imminent public health risk necessitating a precipitous market withdrawal.

3. Regulatory Precedent

Federal regulatory precedents from FDA and the Environmental Protection Agency (EPA) include examples ranging from precipitous to extended withdrawal periods for food additives (including both direct and indirect additives), which together demonstrate a pattern of risk-based approaches to phase-out periods. (See Attachment C). We propose that the same risk-based approach should be applied to the C6 compounds.

We believe the closest precedent is the Agency's phase-out of partially hydrogenated oils (PHOs), which spanned seven years, beginning in 2013 with a tentative determination that PHO should no longer be regarded as GRAS, and ending in 2020/2021. One of the key factors affecting the PHO timeline was the practical need for food manufacturers to reformulate their products with suitable alternatives. C6 users face a similar challenge. Moreover, PHOs were direct food additives with far greater human exposure and impact on human health than exists with the C6 compounds, which are indirect food additives and pose much lower human exposure levels, resulting in significantly lower risk to human health.

We also would like FDA to consider the EPA PFOA Stewardship Program ("Stewardship Program") as a suitable precedent for the present C6 phase-out. As explained in more detail in Attachment C, the Stewardship Program brought major industry players together in a voluntary agreement to incrementally cut, and ultimately eliminate, PFOA use and emissions over a period of 9+ years. Through an agreed-upon annual reporting system, industry and EPA reached the goal of total elimination of emissions and presence in product content by 2015. Using the essential characteristics of the Stewardship Program, Daikin's proposed phase-out period would transition C6 fluorotelomer chemistries in the production of food-contact paper and paperboard off the U.S. market steadily over only 5 years.

We believe that following either the FDA precedent with PHOs or the EPA precedent with the Stewardship Program would be a "win-win-win" situation where government, industry, and consumers can all benefit. The FDA would benefit from a unified industry-wide commitment for a continuous reduction over 5 years with clear accountability. Industry would benefit from an orderly and predictable process and consumers would benefit from a steady reduction in exposure to these C6 compounds. Importantly, any potential risk to consumers during this phase-out period would be low, based on an independent scientific assessment.

* * * *

We look forward to cooperatively and voluntarily working with the Agency, as outlined above. In addition to our proposed phase-out plan, Daikin is open to discussing additional research opportunities with the Agency, if FDA would find that helpful.

Should you have any further questions regarding this matter or how we propose to move forward, please do not hesitate to contact us. We would be pleased to meet with the FDA staff, either separately or together with the other two affected companies, as the Agency may find useful.

Cordially yours,

Devon Wm. Hill

Attachments:

A: Proposed Phase-Out
B: Scientific Support
C: Regulatory Precedent

cc: Paul Honigfort, Ph.D.
Sharon Koh-Fallet, Ph.D.
Joseph Levitt

Attachment A – Proposed Phase-Out

Attachment A.1: Proposed Phase-Out of C6 Fluorotelomer-Containing Food Contact Substance Products

Attachment A.2: Rationale for a Market-Based Approach to Exiting the U.S. Food-Contact Market

Attachment A.3: Overview of End-Use Applications for Paper and Paperboard Packaging Containing C6 Fluorotelomer Products

Attachment A.1

Proposed Phase-Out of C6 Fluorotelomer-Containing Food Contact Substance Products

Proposed Phase-Out of C6 Fluorotelomer-Containing Food Contact Substance Products

PRIVILEGED AND CONFIDENTIAL

In response to FDA's stated goal of eliminating the use of C6 fluorotelomer chemistries in the production of food-contact paper and paperboard in the United States (U.S.), we propose the following terms to achieve an orderly withdrawal of our C6 products from the U.S. market.

(b) (4)

[redacted]

Our rationale and justifications for the extended phase-out proposed here are addressed in a separate attachment to this submission.

Attachment A.2

Rationale for a Market-Based Approach to Exiting the U.S. Food-Contact Market

Phase-Out of C6 Fluorotelomer-Containing Food Contact Substance Products

Rationale for a Market-Based Approach to Exiting the U.S. Food-Contact Market

PRIVILEGED AND CONFIDENTIAL

Since our December 5, 2019 meeting with the Food and Drug Administration (FDA), and our December 9, 2019 letter regarding the same, we have been working diligently to develop a phase-out proposal for our C6 fluorotelomer products that takes into account the timelines (b) (4) to avoid adverse market impacts. While we initially had anticipated that an orderly market exit would be best achieved by a phase-out (b) (4), we now strongly believe that a withdrawal plan based on (b) (4) of product sold into food-contact applications in the United States is the simplest and most effective means to accomplish FDA's goal of reducing dietary exposure while ensuring an orderly market transition for end-use manufacturers and consumers. (b) (4) better accountability, (b) (4) avoidance of antitrust liability, consistency and alignment between companies, simplicity, enhanced predictability, and reduced market disruptions for companies, particularly small businesses, and consumers. These important advantages are discussed in detail below.

1. Better Accountability

(b) (4)

(b) (4)

This approach will also convey benefits (b) (4) [redacted] FDA's stated goal of eliminating the use of C6 fluorotelomer products in food-contact applications in the U.S.

3. Avoidance of Antitrust Liability

We are committed to ensuring compliance with all applicable antitrust laws. We have consulted with knowledgeable antitrust counsel and learned that discussions among competitors aimed at addressing FDA concerns are generally immune from antitrust challenge under the Noerr–Pennington doctrine. (b) (4) [redacted] Our current proposal will achieve FDA's stated goal while avoiding any antitrust implications for the affected companies.

4. Consistency and Alignment

In developing our current proposal, it became apparent to us that the affected companies participate in different market segments and use differing and sometimes overlapping terminology to describe the different application types that utilize C6 fluorotelomer products. (b) (4) [redacted]

5. Simplicity

We recognize that FDA will need to communicate any withdrawal plan for the C6 products internally, as well as externally, and to justify and explain to interested parties how the market exit strategy is effectively reducing dietary exposure to the C6 products. (b) (4) [redacted] will have a ready means to communicate quantitative progress.

6. Enhanced Predictability

Our market-based proposal will result in enhanced predictability for all parties. (b) (4) [redacted] we discovered that it will be difficult to (b) (4) [redacted] the phase-out period. This, in turn, will make it challenging for FDA to show how it is quantitatively improving safety by removing the C6 technology from specific applications, and to explain these reductions both internally within the Agency and externally. A market-based approach, however, provides all parties with a clear

understanding of how the market withdrawal will be achieved from (b) (4) [redacted]

Furthermore, (b) (4) [redacted] his approach will also send a clear a signal to the value chain that downstream users urgently need to identify and implement suitable replacements, while concurrently allowing for the market to respond to this urgency in an orderly, non-chaotic way.

7. Reduced Market Disruptions for Companies and Consumers

(b) (4) [redacted]

Once companies are able to identify a suitable alternative, there remains a lengthy lead time and multi-step process to transition to replacement technology that will impact many players in the supply chain. For example, considerable time is needed for packaging manufacturing companies to fully qualify new technology, identify and install new equipment, and confirm printing for the new material. Likewise, food companies face similar hurdles to transition to alternative packaging, including qualifying the new technology and designing and installing new equipment to handle and fill the new packaging material. The qualifying process for food companies is not insignificant. It can take 6 months to 1 year to schedule and perform test kitchen evaluations and then a further 18 months to execute a staged roll-out of the new

packaging to introduce it at the national level. The transition burdens will be particularly difficult for small business companies that might be affected.

As illustrated above, there are many competing factors for affected companies to consider, and numerous hurdles that will need to be overcome, as a result of any phase-out of the C6 fluorotelomer chemistries in food-contact paper and paperboard. Consequently, precipitous market withdrawal of the C6 fluorotelomer chemistries will inevitably lead to significant market disruptions. In addition to the C6 manufacturers, numerous companies along the supply chain, particularly small businesses, as well as consumers, will be negatively impacted by market disruptions resulting from premature withdrawal of the C6 technologies. The potential consequences include unavailability of certain food products on store shelves and in quick service restaurants, employee lay-offs, and significant financial repercussions for companies.

Attachment A.3

Overview of End-Use Applications for Paper and Paperboard Packaging Containing C6 Fluorotelomer Products

The following attachment is CONFIDENTIAL and has been removed in its entirety from the redacted version of this filing.

Overview of End-Use Applications for Paper and Paperboard Packaging Containing C6 Fluorotelomer Products

Privileged and Confidential

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[redacted]

CONFIDENTIAL

CONFIDENTIAL

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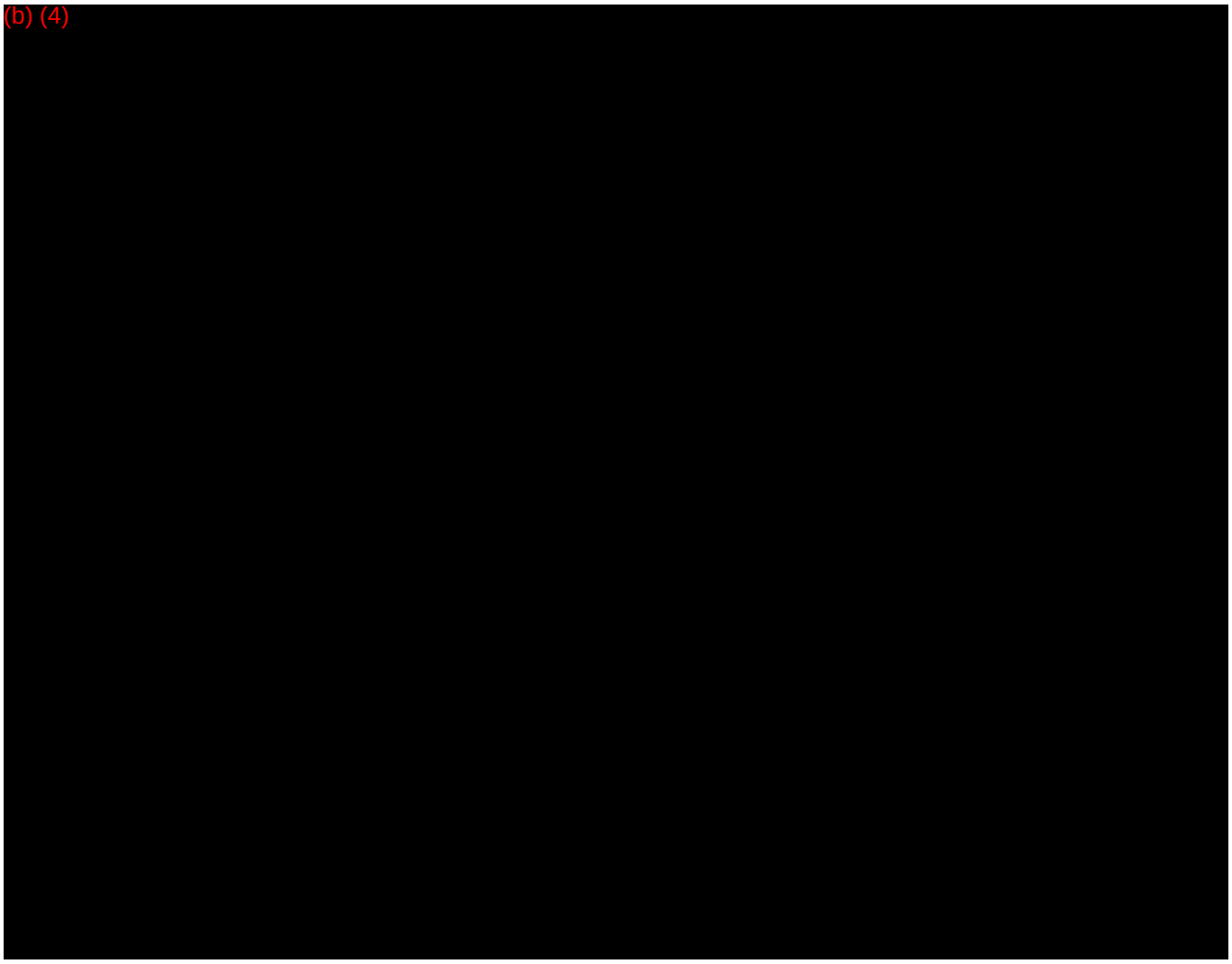

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Attachment B – Scientific Justification

Exponent Report: C6-PFAS Safety/Risk Assessment

Exponent®

TO:	Joseph Levitt, Hogan Lovells US LLP, Counsel to Daikin-America, Inc.
FROM:	Michael Bolger, Ph.D., DABT, Exponent, Inc.
DATE:	January 14, 2020
PROJECT:	(b) (4)
SUBJECT:	C6-PFAS Safety/Risk Assessment

BACKGROUND

The Center for Food Safety and Applied Nutrition (CFSAN)/ US Food and Drug Administration (FDA) has conducted a review as to whether the use of C6 perfluoroalkyl moieties (C6- PFAS) and the current Cumulative Estimated Daily Intake (CEDIs) for the low molecular weight oligomers (LMWO) C6- PFAS and C6-PFAS monomeric components and impurities, including 6:2 fluorotelomer alcohol (6:2 FTOH), and perfluorohexanoic acid (PFHxA)) migrating from the use of these compounds as grease proofing agents, are adequately supported by the available data; specifically;

- Whether data gaps still exist in the toxicological dataset for these compounds; and
- What studies would be needed to fill any identified gaps.

The Toxicology Group 1, Division of Food Contact Substances (DFCS), in the Office of Food Additive Safety conducted a comprehensive overview of new data from rodent studies showing preferential accumulation of the 6:2 FTOH 5:3-Acid metabolite in fatty tissues and concluded that it precluded the ability to base a safety determination on the basis of the extended serum half-life for the 5:3-Acid metabolite of 6:2 FTOH . The toxicological information cited is indirect in that the study was done on a metabolite and not on the parent compound, LMWO C6- PFAS.

The review conducted by DFCS concluded that because in its opinion the toxicological dataset is inadequate that a safety/risk assessment cannot be performed according to the application of safety/uncertainty factors (SFs/UFs) to a Lowest Observed Effect Level (LOEL)/No Observed Effect Level (NOEL) derived from an appropriate toxicological study. The main argument made by DFCS to support this conclusion is that the currently available short term/subchronic/chronic studies are too short

in duration in light of the potential biopersistence of LMWO C6 PFAS and that another chronic study is required in order to address these issues. While chronic rodent studies have been performed DFCS concluded that a chronic study in mice of at least one year in duration is required to address potential systemic effects. On the basis of this conclusion a Margin of Exposure (MOE) or Margin of Safety (MOS) for C6 PFAS was not developed in support of their conclusion that the available toxicity dataset is insufficient to support the CEDI resulting from authorized uses of C6 PFAS.

The DFCS also concluded that certain studies are required in order to answer specific questions regarding biopersistence, chronic systemic toxicity, carcinogenicity and reproductive/developmental effects of LMWO C6 PFAS. The required studies include the following; toxicokinetics/pharmacokinetics (TK/PK) studies in rodents, a chronic study in mice of at least one year in duration to address potential systemic effects, a two-year carcinogenicity bioassay in mice, and an extended one-generation reproductive toxicity study in mice conducted with the 6:2 FTOH.

DFCS does not assert that current evidence indicates that any of these outcomes do occur, but rather that the current studies which supported the original submission and approval of the use of these compounds in food packaging are now inadequate. Again, this conclusion is solely predicated on several rodent studies which suggest the potential for biopersistence for 6:2 FTOH and by analogy to C6 PFAS. This is not evidence of an imminent hazard to human health, but rather that the current toxicological database is not adequate to satisfy the pre-market approval process. This latter issue is not the same as or equivalent to an assertion of and clear evidence of an imminent hazard to human health.

SAFETY/RISK ASSESSMENT CONSIDERATIONS

While the new animal data on bioaccumulation are informative, they are by no means dispositive of the safety of the C6 PFAS compounds. It is clear at this point in time that the available toxicological information does provide preliminary suggestive evidence of the bioaccumulative/persistence potential of 6:2 FTOH and by implication of LMWO C6- PFAS based on several rodent studies. This in turn may or may not indicate the potential of adverse effects, and the evidence is far from conclusive or clear enough to draw any definitive conclusions regarding potential hazard. Biopersistence potential, of and by itself, is not sufficient evidence to determine whether any particular adverse health outcome may or may not occur. Biopersistence merely indicates that a certain reservoir of a chemical of concern maybe stored in the body and in the case of C6 PFAS because of their lipophilicity in fatty tissue. Storage in such tissue means that the chemical will not exert a biological response while in storage. Once released the chemical may at that point exert a biological response but there are many important factors that have to be taken into account in order to assess any potential hazard. These critical factors include the turnover rate in the

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fatty tissue, what steady state systemic dose levels are realized and how rapid is the metabolism and excretion of the parent compound and/or its metabolites. Presently no information is available that can provide answers to these critical questions. If C6 PFAS are slowly released from the fatty tissue and then rapidly metabolized and excreted then the potential hazard would be considered minimal.

The nominal application of SF/UFs in the hazard/safety/risk assessment paradigm is comprised of the following components.

- a factor of 10 to extrapolate from subchronic to chronic exposure;
- a factor of 10 to extrapolate from a Lowest Observed Adverse Effect Level (LOAEL) to a No Observed Adverse Effect Level (NOAEL). Other national and international health authorities such as European Food Safety Authority (EFSA), and Joint Expert Committee on Food Additives of the World Health Organization and Food and Agriculture Organization and the U.S. Environmental Protection Agency (EPA) use the lower limit of a Benchmark Dose (BMDL), rather than a LOAEL/NOAEL, as the Point of Departure (POD) for safety/risk assessment in lieu of an additional safety factor to derive a MOE or MOS;
- a factor of 10 for interspecies variability (extrapolation from experimental animals to humans);
- a factor of 10 for intraspecies variability (interindividual human variability).

It should be emphasized that several of these factors do take into account biological differences in an issue like biopersistence between species and individuals. This safety/risk assessment paradigm is inherently conservative so that unknown issues like biopersistence are accounted for.

In a very recent extensive review and toxicological/hazard/safety/risk assessment (that was published as two articles in the peer reviewed scientific literature (Luz et al., 2019; Andersen et al., 2019), it was concluded that sufficient data exists to conclude that perfluorohexanoic acid (PFHxA) is not carcinogenic, is not a selective reproductive or developmental toxicant, and does not disrupt endocrine activity. PFHxA is a short-chain, six-carbon perfluoroalkyl acid (PFAA) and is a primary impurity, degradant, and metabolite associated with the short-chain fluorotelomer-based chemicals used today. The authors also concluded that the effects caused by PFHxA exposure are largely limited to potential kidney effects, are mild and/or reversible, and occur at much higher doses than observed with the longer chain C8 PFAS (perfluorooctanoic acid (PFOA)). A chronic Reference Dose (RfD) for PFHxA of 0.25 mg/kg-day was calculated using benchmark dose modeling (BMD) of kidney effects (renal papillary necrosis) found in a chronic rat bioassay. PFHxA and C:6 FTOH are both C6 telomer compounds, with PFHxA

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having a rather robust toxicity data set applicable to this class of compounds. Dismissing the PFHxA toxicity data out of hand because of limited data on differences in hepatic and renal effects between PFHxA and 6:2 FTOH in one species, is premature and does not support a conclusion that reliance on PFHxA may underestimate risk. Such a conclusion is entirely speculative and therefore to ignore such information is not scientifically justified.

BMD software (BMDS) (USEPA version 2.7) was utilized to model dose response for the female kidney histopathological effects (papillary necrosis and tubular degeneration), in accordance with guidance for dichotomous endpoints (USEPA, 2012). The benchmark response (BMR) for extra risk was set at 10% of the control mean and default program parameters were used. The p-value to determine test acceptance or rejection was set at 0.1. Model fit was assessed considering the following; p-value for goodness-of-fit, Akaike information criterion (AIC) value, scaled residuals near the range of the BMD and visual inspection of the dose-response curves in the low-dose range. All available models for noncancer dichotomous data within the BMDS (Gamma, Logistic, Probit, Weibull) were run to aid in selecting a model that best fit the data. While the female papillary necrosis or tubular degeneration data did not provide robust data for BMD modeling as statistically significant responses only occurred in the highest exposure group, both data sets were amenable to modeling. Benchmark dose limits (BMDLs) of successful models for each data set were all within a factor of 3. Of the models with adequate fit to the data based on visual inspection, the one with the lowest AIC, lowest BMDL, and passing statistical fit to the data was the LogProbit Model of the papillary necrosis. This lowest $BMDL_{10}$ of 90.4 mg/kg/day for papillary necrosis was selected as the Point of Departure (POD).

The following are the considerations that entailed each of the SF/UFs used with the POD to derive a RfD.

- A SF/UF of 10 was selected to account for the differences in human sensitivity.
- A SF/UF of 3 was used account for the toxicodynamic differences in equivalent dose between animals and humans. Toxicokinetic differences were accounted for in the conversion of the POD to a RfD.
- A SF/UF of 1 was selected to account for subchronic to chronic study exposure because the study (Klaunig et al., 2015) selected for the derivation of the RfD was chronic in duration.
- A SF/UF value of 1 was used since a BMDL was used to derive the POD, and not a LOAEL.
- A SF/UF value of 3 was used for database quality which included systemic toxicity, reproduction and developmental, and cancer evaluations. The database included subchronic or chronic systemic toxicity in two species, a two-generation reproductive toxicity study, and developmental toxicity studies in two species (USEPA, 2002). The SF/UF of 3 was selected to account for the

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lack of an additional chronic toxicity study in a second species, absence of developmental toxicity data in a second species, lack of a two-generation reproductive toxicity study, and to account for additional data gaps that may affect the determination of the critical effect, POD and the RfD, including specifically immune system and thyroid hormone data.

Using these individual SF/UFs the total SF/UF was rounded to 100 and applied to the POD of 90.4 mg/kg-day to derive a RfD of PFHxA of 0.25 mg/kg-day (rounded to two significant figures). This RfD is approximately 340-fold higher (MOS) than the CEDI for 6:2 FTOH equivalents of 44 µg/p/day,[1] and a MOE of 123,835 exists between the $BMDL_{10}$ of 90.4 mg/kg-day (POD for RfD calculation) and the CEDI for 6:2 FTOH. These MOS and MOE were derived according to the following calculations.

6:2 FTOH CEDI

44 µg/p/day ÷ 60 kg bw = 0.73 µg/k/day

0.73 µg/kg/day ÷ 1000 = 7.3×10^{-4} mg/kg/day

PFHxA MOS/MOE

MOS (RfD/CEDI) = 0.25 mg/kg/day ÷ 7.3×10^{-4} mg/kg/day = 342

MOE (POD/CEDI) = 90.4 mg/kg/day ÷ 7.3×10^{-4} mg/kg/day = 123,835

Furthermore, this RfD 0.25 mg/kg/-day is four orders of magnitude greater than the RfD calculated by the U.S. EPA for the longer chain C8 PFAS which was derived on the basis of developmental toxicity (reduced ossification of the proximal phalanges (forelimb and hind limb) and accelerated puberty in male pups (Lau et al. (2006).

[1] FDA employed two approaches for calculating CEDI — one taking into account exposure from Chemours' FCNs and one without. Since we understand from news reports that Chemours no longer markets their C6 PFAS in interstate commerce, we have considered the CEDI value that does not take into account the Chemours' FCNs. The CEDI value represents exposure to 6:2 FTOH equivalents, which takes into account direct exposure to 6:2 FTOH as an impurity, as well as exposure to 6:2 FTOH that may result from hydrolysis of C6 side-chains of C6 PFAS monomers and C6 PFAS low molecular weight oligomers (LMWOs).

The occurrence and frequency of detection of PFHxA in food is reported to be low level (Rice, 2015). For example, in a study conducted in France levels of PFHxA were less than 1 ng/g in all of the food types sampled, with the highest reported levels in 'sweet and savory biscuits and bars' (0.915 ng/g), pastry and cakes (0.791 ng/g), and dairy-based desserts (0.583 ng/g) (Rice, 2015). EFSA (EFSA, 2016) tested a number of foods and detected PFHxA in 0.9% of samples. In addition, the FDA has conducted a fair amount of work on the analysis of levels of PFAS in food in specific surveys as well as part of its Total Diet Study (FDA, 2019). The results of this survey work indicate that most foods not grown or produced in specific geographic areas contaminated with PFAS do not have detectable levels of PFAS. Overall these results indicate that the occurrence and levels of PFHxA in food is low and that consumption of food that has come into contact with paper treated with short-chain PFAS-based polymeric products is not expected to be a major route of exposure to PFHxA.

In regard to 6:2 FTOH a 90-day subchronic study (Serex et al 2014) was conducted in rats which were administered 0, 5, 25, 125 and 250 mg/kg bw/day via gavage. Mortality was observed in the two highest doses groups starting at 3 weeks into the study. On the basis of hematological and hepatic effects the authors concluded that a NOAEL was identified at a dose level of 5 mg/kg bw/day. A BMD analysis was also performed on the most sensitive adverse effects noted (hepatic cell hyperplasia, pancreatic acinar apoptosis and teeth ossification). The lowest $BMDL_{10}$ was 18 mg/kg bw/day and was associated with liver hyperplasia. The authors observed that the lowest $BMDL_{10}$ was greater than the NOAEL and concluded that the NOAEL could serve as a POD for safety/risk assessment purposes. A similar conclusion was reached by Anderson et el., 2019 in their extensive review. In order to derive a RfD a total SF/UF of 1000 is deemed to be appropriate. The total SF/UF is comprised of the following SF/UFs to account for various issues of uncertainty:

- A SF/UF of 10 was selected to account for the differences in human sensitivity.
- A SF/UF of 10 was used account for the toxicokinetic/toxicodynamic differences between animals and humans.
- A SF/UF of 10 was selected to account for the use of a subchronic to derive a chronic RfD.

The resulting RfD for 6:2 FTOH is 0.005 mg/kg bw/day. This RfD is approximately 7-fold higher (MOS ~ 7) than the CEDI for 6:2 FTOH (44 µg/p/day), and a MOE of 6850 exists between the NOAEL of 5 mg/kg-day and the CEDI for 6:2 FTOH. Furthermore, a MOE of 24,657 exists between the $BMDL_{10}$ of 18 mg/kg-day for 6:2 FTOH and the CEDI for 6:2 FTOH. These MOEs were derived according to the following calculations.

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6:2 FTOH : CEDI

44 µg/p/day ÷ 60 kg bw = 0.73 µg/kg-day

0.73 µg/kg-day ÷ 1000 = 7.3 x 10^{-4} mg/kg-day

6:2 FTOH MOS/MOE

MOS (RfD/CEDI) = 0.005 mg/kg/day ÷ 7.3 x 10^{-4} mg/kg/day = 6.8

MOE derived from NOAEL of 5 mg/kg/day

MOE (NOAEL/CEDI) = 5 mg/kg-day ÷ 7.3 x 10^{-4} mg/kg/day = 6850

MOE derived from $BMDL_{10}$ of 18 mg/kg/day

MOE (BMDL/CEDI) = 18 mg/kg/day ÷ 7.3 x 10^{-4} mg/kg/day = 24,657

DFCS (Rice, 2011) concluded that the 90-day rat study with 6:2 FTOH, "did not reach a NOEL for toxicity in females, based on findings of increased thyroid weight parameters during recovery in all treatment groups; the LOEL for the study was the lowest dose tested of 5 mg/kg bw/day." This is a matter of professional judgement; however, it should be noted that the peer reviewed publication (Serex et al 2014) states that thyroid weight in female rats was statistically significantly higher than that of the control three months after cessation of dosing in the 25, 125, and 250 mg/kg/day groups. However, there was no significant difference noted for this parameter in the 5 mg/kg/day dose group when compared to the concurrent control.

Biomonitoring surveys demonstrate that PFHxA is infrequently detected in human serum and urine, and when detected, PFHxA levels tend to be low, often at or below the limit of quantification (LOQ) or the limit of detection (LOD). In recent work conducted by the US Centers for Disease Control and Prevention (CDC) PFHxA was not detected in preliminary evaluations of the general U.S. adult population. The low detection levels and rates of detection of PFHxA in human serum and urine indicate that human exposure to PFHxA may be of negligible concern. The low detection rate in serum could very well be due to the rapid serum elimination kinetics of PFHxA. Furthermore, since PFHxA appears to be infrequently detected in urine suggests that human exposure to PFHxA, when it occurs, is not of sufficient magnitude, frequency, and/or duration to be retained in serum or to accumulate in tissues. The data

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available to date demonstrate that there continues to be a low detection frequency and magnitude of PFHxA throughout the general global population and that PFHxA does not bioaccumulate over time and that there is no new evidence linking biopersistence noted in the several rodent studies to findings in humans. Any attempt to draw such a conclusion would be highly speculative, and it would be "quite a jump" to reach such a conclusion.

Several recent exposure assessments indicate exposures are low, including those conducted by FDA/CFSAN. In its most recent assessment, FDA/CFSAN developed a CEDI for 6:2 FTOH equivalents of 92 µg/person/day from all effective FCNs (from 6:2 FTOH as an impurity and as a hydrolysis product from LMWO C6- PFAS and C6- PFAS monomer).[2] It should be noted that the CEDI presented as a 6:2 FTOH equivalent is conservative and likely an overestimate as it included (in addition to 6:2 FTOH) LMWO and monomers in the exposure estimate and assumed that all of the LMWO C6-PFAS and C6-PFAS monomers will be completely hydrolyzed *in vivo* into 6:2 FTOH. Furthermore, the exposure assessment assumed 100% migration of the residual impurity to food. In addition, we understand from materials you provided that the EDI from the Chemours FCN should not be included in the CEDI as it is not in the market. Thus, the CEDI for 6:2 FTOH equivalents should be 44 µg/person/day as earlier derived by the Agency.[3]

The comparisons of the two thresholds for safety/risk for a 60 kg adult of 15 mg per day (or 15,000 µg/day) for PFHxA (RfD of 0.25 mg/kg bw/day) and 0.3 mg per day (or 300 µg/day) for 6:2 FTOH (RfD of 0.005 mg/kg bw/day) to the CEDIs of 92 µg/person/day or 44 µg/person/day indicates that the exposure levels are below the threshold safety levels of concern. In addition, human biomonitoring surveys show that exposures are quite low with PFHxA infrequently detected in human serum and urine. Exogenous compounds, stored in tissues may not produce a biological response, and accumulation in fat tissue is not indicative of an immediate health hazard. Compounds sequestered in fat are typically released slowly, so that any 5:3 acid accumulated in fat, if and when released, is expected to be rapidly metabolized through a Phase 1 metabolic process (Kabadi et al 2018) and subsequently excreted.

CONCLUSIONS

While the information presented in FDA's toxicological review is well presented overall it is circumstantial and far from conclusive as to the potential safety/risk issues pertinent to 6:2 FTOH and particularly LMWO C6 PFAS. The new animal studies on bioaccumulation are suggestive in nature, but

[2] FDA-CFSAN/DFCS Chemistry Review Memo, J.R Cooper, October 22, 2019
[3] FDA-CFSAN/DFCS Chemistry Review Memo, J.R Cooper, May 31, 2019

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are not sufficient to make any final safety/risk assessment of these compounds. While certain gaps may preclude a safety determination for a new food-contact material, FDA has not identified an imminent health or safety concern, particularly considering the conservatisms built into the exposure and hazard assessment procedures that would require immediate withdrawal as opposed to an appropriate phase out approach. No definitive and unequivocal evidence from appropriately conducted toxicology studies, either in laboratory animals or humans, are presented that would support a conclusion of an imminent hazard to human health. The evidence that is provided is merely suggestive of possible adverse health effects. A MOE of 6850 exists between the subchronic 6:2 FTOH NOAEL of 5 mg/kg-day and the CEDI for 6:2 FTOH, and a MOE of 24,657 exists between the $BMDL_{10}$ of 18 mg/kg-day for 6:2 FTOH and the CEDI for 6:2 FTOH. FDA generally recommends using a safety factor of 1000 when NOAELs are derived from subchronic studies [intraspecies variability (10x); interspecies variability (10x), sub-chronic to chronic extrapolation (10x), *i.e.*, 1000].[4] An additional factor of 2 is sometimes recommended to account for uncertainty regarding whether or not the most sensitive species has been assessed (data available in only one species). The fact that the MOE from the subchronic study of 6850 is greater than the FDA recommended MOE of 2000, suggests no immediate danger to public health. This conclusion is further supported by the larger MOE derived on the basis of the use of the $BMDL_{10}$ as the POD, which is the preferred method used by almost all national and international public health authorities. Indeed, a comprehensive peer reviewed safety/risk assessment shows a low risk to the public were the compounds allowed to remain available during a 5-year phase-out period.

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Attachment C – Regulatory Precedent

Precedent: FDA Authorized Phase-Out of Food Additives

Precedent: EPA's PFOA Stewardship Program

Precedent: FDA Authorized Phase-Out of Food Additives

Introduction

The Food and Drug Administration (FDA) has authorized phase-out periods for multiple food additives over the years. These phase-out periods have ranged from precipitous to gradual withdrawals, the timing of which depended on factors such as: the degree of exposure and public health risk to consumers, the immediacy of that risk, and the availability of suitable alternatives. Instances involving high levels of exposure, serious or immediate health risks to consumers, and/or readily-available suitable alternatives have resulted in precipitous withdrawals from the market – and appropriately so. In contrast, situations involving lower exposure, lower immediate health risk to consumers, and/or no readily available alternatives, have been resolved through more extended phase-out periods – taking place over a period of years, instead of months.

Examples representative of either end of this spectrum contextualize our phase-out proposal for C6 fluorotelomer chemistries used in the production of food-contact paper and paperboard ("C6 compounds" or "C6 products"). Both examples detailed below concern direct food additives, and generally these present the highest level of exposure risk as compared to food contact substances. At one end of the spectrum is the three-month phase out of cyclamates, an artificial sweetener, in 1969. At the other end is the seven-year phase-out of partially hydrogenated oils (PHOs), ending in 2020/2021. The current effort to phase out C6 compounds, which are indirect food additives, aligns much more closely with FDA's phase-out of PHOs than with cyclamates. And even compared to PHO's, the C6 compounds have a much lower level of exposure and hence lower potential risk to consumers, illustrating that our phase-out proposal for C6 compounds is commensurate with the risk presented and consistent with this FDA precedent.

1. Cyclamates

In late 1969, FDA revoked the Generally Recognized as Safe (GRAS) status of cyclamates, an artificial sweetener, and ordered the product off shelves by early 1970, a mere three months after the announcement was published in the Federal Register. 1/ Importantly, the action was based on evidence of carcinogenicity in laboratory animals, which triggered the so-called Delaney Clause, which prohibits the marketing of any food additive found to cause cancer in man or laboratory animals. Thus, for cyclamates, there was both a significant and immediate health risk to consumers, and consumer exposure was high because the product was a direct additive used as a sweetener in high volume products, such as carbonated beverages. Further, a suitable alternative was readily available. In sharp contrast to cyclamates, the current C6 example should not trigger such a precipitous market withdrawal because the C6 compounds have a much lower exposure level, do not present as serious or immediate a risk to consumers, and no technically nor commercially feasible alternatives are readily available. 2/ Importantly, as indirect additives, the C6 compounds have a very low level of exposure (measured in parts per *billion* (ppb)), so the risk to consumers is dramatically lower than with a direct food additive such as cyclamates.

2. PHOs

The more recent case of PHO phase-out provides a much better point of comparison. The Agency's phase out of PHOs began in 2013 with FDA's initial determination that PHO should no longer be

1/ 34 Fed. Reg. 17063 (Oct. 21, 1969).
2/ Also, from a legal standpoint, the C6 example also does not trigger the statute's Delaney Clause as did cyclamates.

regarded as GRAS. 3/ Public comment on the tentative determination was open for several months, and the Agency's Final Notice revoking PHOs' GRAS status was published in 2015. 4/ The Final Notice set a compliance date in 2018. Accordingly, the manufacturers had almost five years (2013-2018/2019) from the initial GRAS determination to the initial compliance date plus an additional year and a half for sell-through in the marketplace (until 2020/2021) for a total of about 7 years (2013-2020/2021). 5/

It is important to note that, as a direct food additive widely used in the food supply, the human exposure levels for PHOs were much higher than for the C6 compounds, which as noted are indirect additives. Indeed, the health risks from PHOs were based on the fact that PHOs were a primary dietary source of artificial trans fat, which is tied to higher cholesterol and with it an increased risk of heart disease, the leading cause of death in men and women in the U.S. Thus, there is a huge difference in exposure between PHOs and C6 compounds, with PHOs being measured in the parts per *million* and C6 levels being estimated in the parts per *billion.*

In spite of the much higher level of risk for PHOs, two key factors affecting the PHO timeline were the practical need for food manufacturers to reformulate their products with suitable alternatives and to sell-through the remaining product manufactured with PHO. Packaging companies and food companies that use C6-treated products face similar challenges in qualifying new technology, identifying and installing new equipment, and selling through existing product. 6/ Moreover, C6 manufacturers face the same challenge of developing suitable alternatives for their products that meet customer needs. Thus, if a 7-year phase-out was appropriate for the PHOs, then the 5-year proposed phase-out for C6 compounds is even more reasonable and appropriate.

Conclusion

The proposed 5-year phase-out of C6 compounds is much more appropriately aligned with the 7-year PHO phase-out than the more precipitous phase-out of cyclamates, for a number of reasons.

Compared to cyclamates, C6 compounds present a much lower level of exposure and less serious/immediate risk to human health (and do not trigger the Delaney Clause). Further, there are no readily available alternatives to C6 that are technically or commercially feasible. So the circumstances necessitating a precipitous phase-out are simply not present with the C6 compounds.

The similarities between PHOs and C6 compounds are much greater, in that both involved use in a wide range of products where substantial time was/is needed to reformulate with alternatives. Even

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3/ 78 Fed. Reg. 67169 (Nov. 8, 2013).
4/ 80 Fed. Reg. 34650 (Jun. 17, 2015).
5/ FDA Constituent Update, "FDA Extends Compliance Date for Certain Uses of Partially Hydrogenated Oils in Food; Denies Petition for Certain Uses of PHOs" (May 18, 2018), *available at* https://www.fda.gov/food/cfsan-constituent-updates/fda-extends-compliance-date-certain-uses-partially-hydrogenated-oils-food-denies-petition-certain.
6/ One could also look to the FDA precedent with C8 compounds which were also indirect additives used in food contact substances for grease proofing uses. There, FDA and industry had an extended dialogue over multiple years before those products were voluntarily withdrawn. However, at that time companies were able to transition quickly into the C6 category of compounds, whereas a similar transitional product is not available for companies to turn to today. Instead, such alternatives need to be developed, and that is the primary reason why a more extended phase-out period is necessary. As noted, the longer phase out for C6 compounds is supported by an independent safety assessment.

so, the risk presented by PHOs as direct food additives was substantially higher from an exposure standpoint as compared to the C6 compounds, which are indirect additives. Moreover, users of the C6 technology face the added challenge of finding suitable alternatives that do not presently exist for most applications. Therefore, if 7 years for the phase-out of PHOs (a direct food additive) is acceptable, then a 5-year phase-out for C6 compounds (only an indirect food additive), is even more reasonable and appropriate, especially since the risk to consumers during the proposed phase-out period is much lower. 7/

7/ FDA should also examine the precedent in the EPA Stewardship Program, described in an accompanying attachment.

Precedent: EPA PFOA Stewardship Program

Introduction

The U.S. Environmental Protection Agency ("EPA") worked with industry members to investigate and phase out certain man-made chemicals, including PFOA (perfluorooctanoic acid), beginning in the early 2000s. The EPA investigation and phase-out plan culminated in the establishment of the EPA PFOA Stewardship Program ("Stewardship Program") in 2006, a voluntary initiative which ended in 2015 when all eight of the participating companies met the goal of total PFOA phase-out. In total, industry worked cooperatively with EPA for over 9 years under the Stewardship Program to phase out PFOA in its various forms.

Even though PFOA presents a greater toxicological concern, the current effort by the Food and Drug Administration (FDA) to phase-out C6 fluorotelomer chemistries used in the production of food-contact paper and paperboard ("C6 compounds" or "C6 products") can be modeled on the successes of the EPA Stewardship Program, as both programs involve phase out of fluorotelomer chemicals. The three affected C6 manufacturers, including Daikin America, Inc. ("Daikin"), are proposing to phase out C6 products covered by food contact substance notifications over a period of 5 years (b) (4) which overall is significantly shorter than the 9+ year EPA program and for products with much lower potential toxicity concerns.

EPA-Industry Program to Phase Out PFOA

After three years of discussions with industry, which began in 2003, EPA launched the PFOA Stewardship Program in January 2006. The details of the Stewardship Program were developed by industry[1] and informally presented to the participating manufacturers by EPA.[2] Shortly thereafter, EPA sent formal invitations to join the program to the proposed participants.[3]

EPA invited eight major companies that used PFOA[4] to participate in the Stewardship Program. All 8 companies, including Daikin, formally committed to joining. The terms of the Stewardship Program, as set out in EPA's invitation letter, included two phases of reductions. In phase one, companies would eliminate a majority of PFOA from facility emissions and product content over a four-year period (2006 to 2010). In phase two, companies would work over an additional five years to completely eliminate PFOA in both emissions and product content (2010 to 2015).

The participating companies and EPA worked together to establish scientifically credible analytical and laboratory methods for the program, as well as confidential and non-confidential reporting forms.

1/ Letter to Susan B. Hazen, Principal Deputy Assistant Administrator, USEPA, OPPTS, from Takashi Tozuka, Manager, PFOA Project," Regulations.gov docket entry EPA-HQ-OPPT-2006-0621-0003.

2/ EPA Summary of Perfluorooctanoic (PFOA) Stewardship Program Meeting, Regulations.gov docket entry EPA-HQ-OPPT-2006-0621-0003.

3/ Letter to senior executives of 3M/Dyneon; Arkema, Inc.; Asahi Glass Co., Ltd.; Ciba Specialty Chemicals Corporation US; Clariant International; Daikin America Inc.; EI DuPont de Nemours and Company; and Solvay Solexis, Inc., from Stephan L. Johnson, Administrator, USEPA, Regulations.gov docket entry EPA-HQ-OPPT-2006-0621-0002.

4/ The eight participating companies are: 3M/Dyneon; Arkema, Inc.; Asahi Glass Co., Ltd.; Ciba Specialty Chemicals Corporation US; Clariant International; Daikin America Inc.; EI DuPont de Nemours and Company; and Solvay Solexis, Inc. *See*, EPA Risk Management for Per- and Polyfluoroalkyl substances (PFAS) under TSCA, *available at* https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-and-polyfluoroalkyl-substances-pfass#tab-3.

In 2006, companies submitted baseline data using production data from the year 2000. The next year, companies began to submit to EPA annual reduction reports, which tracked actual emissions and product content, as well as their percent reductions in both categories. EPA publicly released annual summary tables tracking companies' progress toward meeting the target reduction and elimination goals set out in the Stewardship Program. All 8 participating companies met the Stewardship Program goals by 2015, with several (including Daikin) meeting them ahead of schedule.

The Proposed C6 Phase-Out Can Build on the Successes of the PFOA Stewardship Program

The 3 leading C6 companies are proposing a phase-out plan based on the 9+ year phase-out under the EPA PFOA Stewardship Program, but condensing it to a 5-year transition period. The key features of the proposed C6 phase-out would borrow heavily from the Stewardship Program. For example, the program would be founded on written, voluntary agreements between government and industry, committing industry members to phasing out compounds (b) (4) [redacted] Additionally, it would establish a baseline year and use annual reports to measure progress.

Like the EPA Stewardship Program, the proposed C6 phase-out would be a voluntary program, designed to achieve regulatory success through industry-regulator cooperation. The benefits to consumers (b) (4) [redacted]. Any potential risk to consumers during this phase-out period would be low, as shown by an independent scientific assessment. The program would also provide transparency into FDA's oversight of industry's reduction efforts while creating additional accountability. It represents a desirable "win-win-win" situation where government, industry, and consumers can all benefit.