



Memorandum

Date: February 1, 2016

From: Division of Food Contact Notifications
Chemistry Review Team II
Abigail E. Miller, Ph.D.

Subject: **FCN 001601:** Center for Regulatory Services, Inc., on behalf of Daikin Industries, Ltd.; 2,3,3,4,4,5,5- heptafluoro-1-pentene polymer with ethene and 1,1,2,2-tetrafluoroethene as a processing aid in all food-contact polymers that may contact all food types under Conditions of Use A-H. Submission dated 9/9/15 (initial), 11/6/15 (substantive amendment), 11/10/15 (amendment), and 11/20/15 (amendment).

To: Division of Food Contact Notifications
Regulatory Review Team I
Attention: A. Chang, Ph.D.

The Center for Regulatory Services, Inc., on behalf of Daikin Industries, Ltd., submitted this food contact notification (FCN) for the use of a food contact substance (FCS), 2,3,3,4,4,5,5-heptafluoro-1-pentene (HFP) polymer with ethene and 1,1,2,2-tetrafluoroethene (TFE), as a processing aid in all food-contact polymers. The maximum use level of the FCS is 2000 ppm in the finished food-contact polymer. The FCS may be used in contact with all food types and under Conditions of Use A through H. The FCS is not intended for use in contact with infant formula and breast milk.

Regulatory Background

(b) (4) The FCS is not regulated for use in contact with food nor the subject of any effective FCN. However, there are a number of effective FCNs for fluorinated polymers used as processing aids in all food-contact polymers used in contact with all food types under Conditions of Use A through H.

FCN 736 is effective for 1-propene, 1,1,2,3,3,3-hexafluoro-polymer with 1,1-difluoroethene (CAS Reg. No. 9011-17-0) modified with a halogenated ethylene as described in the food contact notification limited to 1000 ppm in the finished food-contact polymer.

FCNs 260 and 1121 are effective for the use of tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymers (CAS Reg. No. 25190-89-0) limited to 2000 ppm in the finished food-contact polymer.

FCNs 1255, 1448 and 1560 are effective for vinylidene fluoride-hexafluoropropene copolymer (CAS Reg. No. 9011-17-0) limited to 2000 ppm in the finished food-contact polymer.

The chemistry information is contained in Form 3480 and Attachments 1-10. No information was initially incorporated from FCN (b) (4) The notifier's response dated November 6, 2015

contains chemistry information in Attachment 2a and the response letter. The response letter also referenced the residual study for 2,3,3,4,4,5,5-heptafluoro-1-pentene that is Attachment 5 in FCN (b) (4)

Identity

Identity information is contained in Form 3480.II.A, the proposed inventory listing and Attachments 1 through 3.

Name: 2,3,3,4,4,5,5- heptafluoro-1-pentene polymer with ethene and 1,1,2,2-tetrafluoroethene

CAS Number: 94228-79-2

Trade Name: (b) (4)

Other Names: poly(1-pentene-2,3,3,4,4,5,5-heptafluoro-co-ethene-co-tetrafluoroethene);

1-Pentene, 2,3,3,4,4,5,5-heptafluoro-, polymer with ethene and tetrafluoroethene; ETFE

Molecular weight: not provided

LMWO: not provided

Structure: $-(CF_2CF_2)_a-(CH_2CH_2)_b-(CH_2CFCF_2CF_2CF_2H)_c-$

(b) (4)

The notifier provided in Attachment 1 the ranges of the amount of each monomer in both mole percent and weight percent for the FCS. There are three grades of the FCS: EP-521, EP-610 and EP-620. The notifier provided the amount of the monomers for each grade of the FCS in response to the deficiency letter f (b) (4) (b) (4). These are reported in Table 1, below. The amount of monomers used in EP-610 and EP-620 are the same; (b) (4). EP-521 has a different monomer ratio than the other two grades containing less HFP and TFE and more ethene than EP-610 and EP-620.

Table 1. Amount of each monomer in the FCS Polymer Grades (b) (4)

(b) (4)

The notifier provided a ^{19}F NMR spectrum and an IR spectrum of the FCS in Attachment 2; the peak assignments for both spectra are listed in Attachment 2a in the November 6, 2015 response letter. The spectra and peak assignments are consistent with the structure of the FCS.

Physical/Chemical Characteristics

The physical specifications (melt flow rate, melting point, and specific gravity) and results for three batches of each of the three grades of the FCS are reported in Attachment 3. EP-610 and EP-620 contain the same amount of monomers, (b) (4)

(b) (4). Therefore, it has a higher melt flow rate, which corresponds to a lower molecular weight than EP-620.

We have no questions about the identity of the FCS.

Manufacturing Process

The starting materials are listed in Form 3480.II.B, Table 1. Manufacturing information is contained in Attachment 4.

(b) (4)

[REDACTED]

We have no questions about the manufacturing process.

Impurities

Information about the impurities is contained in Attachments 5, 5a and (b) (4) Attachment 5. The residual levels for the impurities in the FCS are reported in Table 2 below.

Table 2. Residual Levels of the Impurities in the FCS		
Impurity	CASRN	Residual (ppb)
2,3,3,4,4,5,5-heptafluoro-1-pentene (HFP)	1547-26-8	102

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2,3,3,4,4,5,5-heptafluoro-1-pentene (HFP)

The notifier determined the residual level of 2,3,3,4,4,5,5-heptafluoro-1-pentene (HFP) in the FCS, as reported in Attachment 5 (b) (4) by high temperature headspace gas chromatography – mass spectrometry (GC-MS) using the method of standard addition. A 1.00 ± 0.05 g sample of FCS pellets was placed in a sealed vial and heated at 180°C for 60 min, which is well above the boiling point of HFP of $56\text{--}58^\circ\text{C}$, then injected into the GC-MS. The HFP was quantified using single ion monitoring (SIM) using the ion at m/z 95 and secondary ions at 196, 69 and 51. For standard addition, $100\ \mu\text{L}$ of standard solutions of HFP in dimethylacetamide (DMA) were added to 1.00 ± 0.05 g samples of the FCS pellets. The final quantities of each standard addition were 0.083, 0.16 and $0.33\ \mu\text{g}$ HFP. Three batches of the FCS were tested and all samples were prepared in triplicate. The amount of HFP in the FCS was calculated from the x-intercept of the standard addition calibration. The standard addition calibrations have R^2 of 0.996, 0.995, and 0.995.¹ The HFP was detected in all three batches of the FCS at average values of 50, 49 and 51 ppb. The notifier calculated the limit of detection (LOD) from the peak size in unfortified samples as 20 ppb, and we calculated the LOD of < 40 ppb based on $3\times$ the standard error of the procedure². Therefore, the residual level of the HFP measured in the FCS of 51 ppb is above the LOD. The notifier only identified the sample in the study as DA720 and not as one of the specific grades listed in the identity section, EP-610, EP-620 and EP-521. A sample of EP-

¹ We were unable to reproduce the R^2 values exactly due to minor difference in the concentrations likely from the notifier's spreadsheet rounding the input values to display only three significant figures. The least squares fit is correct and the variation in R^2 between our values and the notifier's values is in the third significant figure, therefore it does not have a significant effect on the concentration of the HFP in the FCS.

(b) (4)

610 was used in the extraction study to quantify the impurities (b) (4) and in the migration study for determining migration of the low molecular weight oligomers. Therefore, it is likely that the DA720 is EP-610. However, EP-521 has half the amount of HFP than EP-610 and EP-620. If EP-521 was used to determine residual HFP, it may underestimate the residue level of HFP by a factor of 2. To be conservative, we will estimate that the sample was EP-521 and multiply the result by a factor of 2, which will double the residual level of HFP to 102 ppb.

We have no questions about the impurities in the FCS.

Intended Use and Technical Effect

Information about the intended use is contained in Attachment 6 and information about the technical effect is contained in Attachment 7.

The intended use of the FCS is as a processing aid in the extrusion, blowing or injection molding of all polymers to form films, bottles, or molded articles for use as food packaging. The FCS is intended to be used at 2000 ppm for 30 minutes in the start-up stage of production and followed by 500 ppm for 168 hrs. The FCS will contact all food types under conditions of use A-H.

To address our question about the technical effect of the FCS in our deficiency letter for FCN (b) (4) the notifier updated Attachment 7. Attachment 7 in this FCN contains data supporting the use of the FCS up to 500 ppm to (1) decrease the pressure in the die (2) eliminate the melt fracture, (3) reduce the formation of die build up, and (4)³ reduce haze from die build up.

While you asked the notifier multiple times about the fate of the polymer from the start-up phase containing 2000 ppm FCS, they never provided a clear explanation about whether it ends up in the finished food contact article. As it is not clear the fate of the polymer containing 2000 ppm FCS from the start-up stage of production, we will use 2000 ppm of the FCS to calculate exposure since it is possible that food contact articles would be produced with 2000 ppm of the FCS. However, the technical effect data only supports the use of up to 500 ppm FCS. We accept this as sufficient because food contact articles containing the FCS will predominately contain 500 ppm of the FCS.

We have no questions about the intended use and technical effect of the FCS.

Stability

Stability information is contained in Attachment 8.

Attachment 8 contains a thermogravimetric analysis (TGA) of the FCS. It demonstrates that the FCS is stable up to 350 °C and degrades at 370 °C. The FCS is used as a processing aid in the extrusion, blowing or injection molding of polymers to form films, bottles, or molded articles for

³ The notifier provided sufficient data for the use of “reducing haze from die building up” but the data slide is mistitled as “reduce the formation of die build up” on page 4 in Attachment 7.

use as food packaging. The notifier claims this is typically done at less than 350 °C⁴.

We have no questions about the stability of the FCS.

Migration Studies & Exposure Estimates

Information about the migration studies and exposure estimates are contained in Attachments 5a, 9, and 10.

LMWO

The recommendations in our Chemistry Guidance for an FCS that is to be used in all polymers is to incorporate the FCS at its maximum use level into test plaques of low density polyethylene (LDPE) and conduct migration experiments on these test plaques using the appropriate conditions of use.. The notifier did not follow our Recommendations but, rather, conducted migration studies on the pure FCS using Condition of Use A. Typically, we would not accept these migration studies as the migration properties of PTFE polymers are significantly different than hydrocarbon based polymers. However, the mechanism of action of a fluoropolymer used as a processing aid in extrusion, molding, and blowing is that the fluoropolymer blooms to the surface of the base polymer so that the interfacial properties of the fluoropolymer prevent polymer building up in the die and hazing of the finished product.⁵ Because the FCS blooms to the surface, the FCS is essentially forming a coating on the surface of the base polymer. Therefore, migration of the low molecular weight oligomers (LMWO) and other impurities would best be represented by conducting migration experiments on the pure FCS rather than on a base polymer such as LDPE.

To determine the level of migration of the LMWO, the notifier measured the total nonvolatile extractives (TNEs) from the pure powdered FCS (EP-610) into the food simulants under simulated condition of use A (121°C for 2 hrs followed by 238 hrs at 40 °C) as described in Attachment 9 of the FCN. The food simulants used are 10% ethanol (EtOH) for aqueous and acidic foods, 50% EtOH for alcoholic foods and 95% EtOH for fatty foods. A 5 g sample of the FCS was placed in a sealed container with 100 mL of food simulant. The extracts were collected at 2, 24, 96 and 240 hrs and evaporated to dryness. The mass of the TNEs was determined gravimetrically; therefore, there is no calibration curve. The limit of detection (LOD) is the fluctuation from analytical operation of the balance of 0.5 mg, which corresponds to 100 mg

4 The extrusion, blow molding or injection molding of polymers must be done above or near the melting point of the base polymer but below the degradation or decomposition temperature. For example, polyethylene (LLDPE, LDPE, HDPE) melt around 120-140 °C, and polypropylene melts around 160 °C; PET melts around 250 °C but it degrades at 350 °C. The melt and decomposition temperatures are from the Kirk-Othmer *Encyclopedia of Chemical Technology* (1992), 4th edition entries for “Polyesters” by A. J. East, M. Golden, and S. Makhija, Vol. 19 pp609-652, “Polyethylene” by Y. V. Kissin Vol. 17, pp702-784, and “Polypropylene” by R. B. Lieberman Vol.17 pp784-819.

5 C. Dubrocq-Baritaud¹, E. Darque-Ceretti, B. Vergnes “Fluoropolymer processing aids in linear-low density polyethylene extrusion: How to improve their efficiency?” *Journal of Non-Newtonian Fluid Mechanics*, 208-209, June-July 2015, p42-53; C. Dubrocq-Baritaud¹, E. Darque-Ceretti, B. Vergnes “Multi-scale phenomena induced by fluoropolymer processing aids during the extrusion of linear-low density polyethylene”, *Journal of Non-Newtonian Fluid Mechanics*, 166, January 2011, p1-11

LMWO/kg FCS. All measurements were conducted in triplicate and the results summarized in Table 3, below.

Table 3. Migration of LMWO of the FCS	
Food Simulant	TNEs
10% ethanol	120 ppm
50% ethanol	< 100 ppm
95% ethanol	440 ppm

The notifier characterized the TNEs by IR spectroscopy and gel permeation chromatography (GPC). The TNEs in the 10 % EtOH was predominately inorganic whereas the TNEs in the 50 % and 95 % EtOH were oligomers. The notifier, while they did provide the GPC calibration, did not provide slice tables for the GPC measurements of the TNEs and only characterized the oligomers as above or below 1000 Da. However, since the FCS is a fluorinated substance a 1000 Da threshold is not sufficient for fluorinated LMWO⁶. Because we are unable to determine the quantity of LMWO from the GPC data, we will use the TNE value in our exposure estimates. This is a conservative estimation of the LMWO since the IR characterization demonstrates that some of the TNEs are inorganic substances.

The notifier's migration calculations in Attachment 10 are correct except they used the average residual levels, not the maximum residue levels when calculating the dietary concentrations (DCs) for the impurities. To calculate the exposure to the LMWO of the FCS, we utilized the migration results above and the following information: (1) a typical thickness of the food-contact article of 0.02 inches (= 0.5 mm) as provided by the notifier, (2) the typical density of a food-contact polymer of 1.5 g/cm³ as provided by the notifier, (3) the maximum level of the FCS in the food-contact polymer of 2000 ppm and (4) our standard assumption that 10 grams of food contacts each square inch of the polymer. Thus, the concentration in aqueous and acidic food (M_{10%EtOH}) of the LMWO of the FCS is:

$$M_{10\%EtOH} = 0.02 \text{ in} \times \frac{1.5 \text{ g polymer}}{1 \text{ cm}^3} \times \frac{(2.54 \text{ cm})^3}{1 \text{ in}^3} \times \frac{0.2 \text{ g FCS}}{100 \text{ g polymer}} \times \frac{120 \text{ } \mu\text{g LMWO}}{1 \text{ g FCS}} \times \frac{1 \text{ in}^2}{10 \text{ g food}} = 0.0118 \frac{\text{ } \mu\text{g LMWO}}{\text{g food}} = 11.8 \text{ ppb LMWO}$$

Similarly, the M_{50%EtOH} and M_{95%EtOH} were calculated to be 9.8 ppb and 43.3 ppb, respectively. Using a consumption factor (CF) of 0.4 for all polymers⁷ and a combined food-type distribution factor of 0.65 for aqueous and acidic foods, of 0.01 for alcoholic foods, and of 0.34 for fatty foods, the dietary concentration (DC) of the LMWO of the FCS from the proposed use of the FCS is:

6 Several previous chemistry memoranda contain discussions of the LMWO molecular-weight threshold for fluorinated polymers. In the chemistry memorandum for FCN 599 (K. Paquette to P. Honigfort, dated May 31, 2006) the threshold was 2400 Da, and in the chemistry memorandum the FCN 885 (S. Elyashiv-Barad to P. Honigfort, dated May 14, 2009) the threshold was 2000 Da. The chemistry memorandum for FCN 933 (S. Elyashiv-Barad to K. Randolph, dated December 1, 2009) contains a detailed discussion on determining the LMWO threshold of the FCS from a comparison of the solvent exclusion volume and molecular mass of the perfluorohexylethyl acrylate to its hydrocarbon equivalent to determine the scaling factor of 1.87.

7 The use of a CF of 0.4 excludes the use of the FCS in polymers used to coat metal and paper.

$$DC = 0.4 [(0.65 \times 11.8 \text{ ppb}) + (0.01 \times 9.8 \text{ ppb}) + (0.34 \times 43.3 \text{ ppb})]$$

$$DC = 0.4 = 0.4 \times 22.5 \text{ ppb} = 9 \text{ ppb LMWO}$$

Using our standard assumption that a person consumes 3000 g food/day, the estimated daily intake (EDI) of the LMWO is 27 µg LMWO/p/d.

Impurities

Exposure to the impurities is calculated assuming 100% migration of the impurities from the food contact article to food. The notifier's calculations in Attachment 5a are correct except they used the average residual levels, not the maximum residual levels when calculating the DCs for the impurities.⁸ To calculate the average migration, <M>, for the impurities we used the following information, as provided by the notifier: (1) a typical thickness of the food-contact article of 0.02 in (= 0.5 mm), (2) a typical density of a food-contact polymer of 1.5 g/cm³, (3) the maximum level of the FCS in the food-contact polymer of 2000 ppm, (4) the maximum residual level of the impurities in the FCS, and (5) our standard assumption that 10 grams of food contacts each square inch of food-contact polymer. Thus, the average migration, <M>, of (b) (4) from the proposed use of the FCS is:

$$< M > \frac{(b) (4)}{(4)} = 0.02 \text{ in} \times \frac{1.5 \text{ g polymer}}{1 \text{ cm}^3} \times \frac{(2.54 \text{ cm})^3}{1 \text{ in}^3} \times \frac{0.2 \text{ g FCS}}{100 \text{ g polymer}} \times \frac{5 \text{ µg } (b) (4)}{1 \text{ g FCS}} \times \frac{1 \text{ in}^2}{10 \text{ g food}} =$$

$$.00049 \frac{\text{µg } (b) (4)}{\text{g food}} = 0.49 \text{ ppb } (b) (4)$$

Using a CF of 0.4, the DC of (b) (4) from the propose use of the FCS is 0.4 x 0.49 ppb = 0.197 ppb. With a daily diet of 3000 g food/person/day, the estimated daily intake (EDI) of (b) (4) is 0.6 µg (b) (4) /p/d. The other impurities were calculated in the same manner, and their average migration, DCs and EDIs are listed below in Table 3.

Table 3. Exposure Estimates for the FCS and its Impurities			
Impurity	<M> (ppb)	DC (ppb)	EDI (µg/p/d)
LMWO	22.5	9	27
2,3,3,4,4,5,5-heptafluoro-1-pentene	0.010	0.004	0.012
(b) (4)	0.020	0.008	0.024
	0.010	0.004	0.012
	1.082	0.433	1.3
	0.492	0.197	0.6

We have no questions about the migration and exposure estimates for the FCS and its impurities.

Cumulative Exposures

2,3,3,4,4,5,5-heptafluoro-1-pentene is a new substance. We have no record of it used in any other FCNs or regulations. Therefore the EDI presented in Table 3 is its current cumulative estimated

⁸ It also does not include an exposure estimate for HFP. The notifier includes the DC for HFP, calculated from a residual level of 51 ppb, in their November 6th, 2015 response letter.

daily intake (CEDI).

(b) (4)

Notification Language

The notification language as written in the December 15, 2015 acknowledgement letter, while likely sufficient, has some ambiguity. We recommend using the limitation language in FCN 736 as a model because it clearly indicates that the limitations are for the FCS rather than the polymer containing the FCS. The limitation language in FCN 726 is "The FCS may be used at levels up to 1000ppm in the finished polymer...The FCS will be used in contact with all food types and under Conditions of Use A through H, as described in Table 2."

Conclusions

We have no questions.

Abigail E.
Miller -S

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Abigail E. Miller, Ph.D.

HFS-275 (R/F)

HFS-275:AEMiller: 240-402-1224:FCN001601_C_memo.doc:AEM:Draft 1/4/16, 1/29/16

Init: KArvidson: 2/1/2016

Final: AEM: 2/1/2016



Memorandum

Date: January 19, 2016

From: Division of Food Contact Notifications (DFCN)
Toxicology Group 2 (HFS-275)
Tsu-Fan Cheng, Ph.D.

Subject: Acceptance of the final three Technical Data Evaluation Reports (Task Order No. 2015-27; dated December 18, 2015) prepared by Toxicology and Hazard Assessment Group, Environmental Sciences Division, Oak Ridge National Laboratory (ORNL).

To: Administrative Files of FCN 1601

Genetic Toxicity Studies

The notifier for FCN 1601 submitted three genotoxicity studies: (1) Reverse mutation assay “Ames test” using *Salmonella typhimurium* and *Escherichia coli* / SPL Project No. (b) (4) (2) Chromosomal aberration test of 2,3,3,4,4,5,5-heptafluoro-1-pentene in cultured mammalian cells / Japan Bioassay Laboratory Study number (b) (4) and (3) Combination Study of Micronucleus Test and Comet Assay in Rats Treated with H2Pentene / LSI Medience Corporation Study No. (b) (4) The ORNL contract reviewers performed the primary review, and this reviewer performed the secondary review. The Technical Data Evaluation Reports (TDERs) of these reports are attached to this memorandum.

The test article, 2,3,3,4,4,5,5-heptafluoro-1-pentene (CASRN: 1547-26-8), is the monomer used in the production of the polymer that is the FCS for FCN 1601.¹ The three studies reviewed herein were received on November 6, 2015 as supplemental information in response to the deficiency letter dated October 23, 2015.

In the first bacterial reverse gene mutation assay (SPL Project No. (b) (4) *S. typhimurium* TA98, TA100, TA1535, and TA1537 and *E. coli* WP2(uvrA) were treated with H2Pentene (99.9% pure) in DMSO with or without metabolic activation (S9). This is a GLP study with both signed and dated GLP and QA statements. The assay constituted a preliminary cytotoxicity test, a range-finding test, a main study and a confirmatory study (pre-incubation method and only TA100 + S9). No cytotoxicity or precipitation of the test article was observed when cells were tested up to 5000 µg/plate. A dose-dependent increase in the number of TA100 revertant colonies at doses ≥ 500 µg/plate was constantly reported in all 4 experiments in the presence of S9. No increase in the number of revertant colonies was reported for any other tester strains. The positive

¹ FCN 1601: The use of 2,3,3,4,4,5,5-heptafluoro-1-pentene polymer with ethene and tetrafluoroethene for the property improvement in extrusion process of all polymers for food packaging, except for use in contact with infant formula and breast milk.

and negative concurrent controls produced colony counts that were within or very near the respective historical control values. Toxicology concurred with the contract reviewer that the test article, 2,3,3,4,4,5,5-heptafluoro-1-pentene, is mutagenic under the test conditions. In addition, the TDER also noted that due to high volatility of the test substance, the concentration that caused the positive response could not be confirmed.

In the second *in vitro* chromosomal aberration test, Chinese hamster lung (CHL) cells were exposed to H2Pentene (99.2% pure) in 1% carboxymethylcellulose (CMC) in the presence and absence of S9 metabolic activation. This is a GLP study with both signed and dated GLP and QA statements. The study consisted of a preliminary cytotoxicity/cytogenetic test and a main cytogenetic test. The positive control agents were mitomycin C (- S9) and benzo(a)pyrene (+ S9). The cells were exposed to the test article for 24 and 48 hours without S9, and 6 hours with or without S9. Colcemid was added to the treated cultures 2 hours before harvest. One hundred and two hundred metaphase cells were evaluated for aberrant chromosomes for the preliminary and the main tests, respectively. For both tests, a dose-dependent increase in the incidence of structural chromosomal aberrations at doses ≥ 0.1 mg/ml was observed in the presence of S9, but not in its absence. Polyploidy was not increased (\pm S9). The positive and negative controls yielded appropriate results. The ORNL reviewer mistakenly stated that the short-term (6 hours) treatment was conducted only in the presence of S9 and not in its absence. Toxicology considered this oversight does not affect the overall assessment of the study since no increase of structural or numerical aberration was reported for CHL cells treated with H2Pentene for 6 hours without S9. The contract reviewer concluded, and Toxicology concurred, that H2Pentene induced a dose-dependent increase in structural chromosomal aberrations in CHL cells under the test conditions (in the presence of S9). In addition, the TDER also noted that due to high volatility of the test substance, the concentration that caused the positive response could not be confirmed. Toxicology concurred.

In the third combination study of micronucleus test and comet assay in rats treated with H2Pentene, 5 – 7 male Crl:CD (SD) rats/dose were treated with H2Pentene (purity not given) in olive oil via oral gavage at nominal doses of 0, 250, 500, and 1000 mg/kg/day at 48, 24 and 3 hours before sacrifice. Analysis showed that the formulations were unstable, and the respective mean concentrations administered to the animals were 191-208, 375-467 and 719-859 mg/kg/day. Ethyl methanesulfonate (200 mg/kg) was the positive control for both assays, and was administered by gavage on the same schedule. Bone marrow cells were harvested from the right femur after sacrifice, and 2000 immature erythrocytes (IMEs) per dose, per rat, were evaluated for the presence of micronuclei. The liver, glandular stomach and kidneys were collected from the same animals, and single cell preparations were made by homogenization and evaluated for DNA damage via the Comet assay. Gross necropsy of the liver, glandular stomach and kidneys revealed no treatment-related findings.

H2Pentene did not increase the incidence of micronucleated immature erythrocytes (MNIME) at any test dose, and all test and control mean values were within the laboratory's historical negative control range. H2Pentene was cytotoxic to the bone marrow at all test doses, based on the significantly ($p < 0.05$) decreased immature: mature erythrocyte ratio. This suggests that bone

marrow cells were well exposed to H2Pentene during the test. The positive control induced a significant increase in micronucleated IMEs and was cytotoxic to the bone marrow.

The Comet assay using liver, glandular stomach and kidney cells showed no significant differences between control and H2Pentene-treated groups in the tail length, tail moment, or % tail DNA. Mean values for all Comet parameters were within or comparable to historical negative control ranges for the vehicle control and H2Pentene-treated groups. The fraction of hedgehog cells was $\leq 4.0\%$ in all test groups for all three organs, indicating a lack of severe cytotoxic effects on these tissues. The positive control values yielded appropriate results. Systemic absorption and distribution of the test article was indicated by clinical signs of toxicity and decreased body weight gain at 1000 mg/kg/day, and bone marrow toxicity at 250, 500, and 1000 mg/kg/day; gavage dosing ensured exposure of the glandular stomach.

Several deficiencies were identified for the study: (1) the test compound purity was not stated; (2) the preliminary study did not include treated females, and it is unknown whether females may be more susceptible to H2Pentene toxicity than males; and (3) the historical control data for the Comet assay using kidney cells were limited. These deficiencies were considered not to impact the conclusion of the study. The contract reviewer concluded and Toxicology concurred, that H2Pentene was not clastogenic and does not induce DNA damage indicative of being non-mutagenic and non-clastogenic under the *in vivo* test conditions.

These TDERS are acceptable as finals.

Tsu-fan
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Tsu-Fan Cheng, Ph.D.

(b) (5)



Memorandum

Date: February 02, 2016

From: Division of Food Contact Notifications (DFCN)
Toxicology Group 2 (HFS-275)
Tsu-Fan Cheng, Ph.D.

Subject: **Toxicology Memorandum for FCN 1601:** The use of 2,3,3,4,4,5,5-heptafluoro-1-pentene polymer with ethene and tetrafluoroethene (CAS Registry No. 94228-79-2) as a polymer additive for property improvement in extrusion process of all polymers for food packaging.

To: Regulatory Group 1, DFCN
ATTN: Huichen Chang, Ph.D. (HFS-275)

INTRODUCTION:

This Food Contact Notification (FCN) is submitted by Center for Regulatory Services, Inc., on behalf of Daikin Industries, Ltd., for the use of the Food Contact Substance (FCS), 2,3,3,4,4,5,5-heptafluoro-1-pentene polymer with ethene and tetrafluoroethene (CAS Registry No. 94228-79-2) as a polymer additive for property improvement in extrusion process of all polymers for food packaging. (b) (4). The notifier updated the exposure estimates for the current FCN and re-submitted the 3 genotoxicity studies already submitted (b) (4) to support the safe use of the FCS polymer. These 3 genotoxicity studies contain the same original data but with an amendment that updated the solubility of the testing article in acetone but did not provide information of why solubility would change from the (b) (4) to this current one. In addition, substantive supplemental information was received on 11/06/2015 which contained 3 genotoxicity studies that addressed the safety of the FCS monomer (2,3,3,4,4,5,5-heptafluoro-1-pentene). The FCS may be used in contact with all food types and under Conditions of Use A through H. The FCS is not intended for use in contact with infant formula and breast milk.

FOOD CONTACT SUBSTANCE (FCS):

CAS Name: 2,3,3,4,4,5,5-Heptafluoro-1-pentene polymer with ethene and tetrafluoroethene

CAS Number: 94228-79-2

Trade Name: (b) (4)

ESTIMATED EXPOSURE:

The following dietary concentrations (DCs) of the FCS low-molecular-weight-oligomer (LMWO) and impurities are provided in the Chemistry note (Miller/Chang, 02/01/2016). The estimated exposure for LMWO is based on migration studies, and the exposure estimates for impurities were based on 100% migration of the residual levels.

Chemical	CASRN	Dietary Concentration
FCS LMWO	94228-79-2	9 ppb
2,3,3,4,4,5,5-Heptafluoro-1-pentene	1547-26-8	4 ppb

(b) (4)

TOXICOLOGY:

This reviewer searched various databases (FARM, ChemIDplus, PAFA, CPDB, IRIS, IARC, NTP, etc.) using CAS No. and names of the constituents and impurities. The notifier submitted a Safety Narrative (SN) and a Comprehensive Toxicology Profile (CTP) for the FCS and its impurities in the Form 3480 to the FCN. Relevant toxicological data for the FCS and impurities are discussed below.

1. LMWO (CASRN: 94228-79-2; DC: 9 ppb)

The notifier submitted three *in vitro* genotoxicity studies that were already submitted for (b) (4) (withdrawn, 06/24/2015) to support the safe use of the FCS in the current submission. These studies used the LMWO fraction of the FCS (MW: 400 Da ~ 6000 Da) as the testing article. The studies are: (1) *in vitro* mammalian chromosomal aberration test of (b) (4) (2) mutagenic potential of (b) (4) in the mouse lymphoma TK assay, and (3) bacterial reverse mutation test of (b) (4). For the current submission, the notifier amended the solubility of the testing article in acetone in the *in vitro* chromosomal aberration test and the mouse lymphoma assay in response to questions we raised during the review (b) (4) (b) (4). The notifier updated the report from “suspend” to “> 100 g/L” but did not provide any supporting data that confirms the reported solubility of the test substance. The rest of the reports (data) are essentially the same as those submitted for (b) (4). The original studies have been primary reviewed by Oak Ridge National Laboratory (ORNL) contract reviewer and secondary reviewed by Toxicology (b) (4). Since no new data is provided in the current FCN, these studies are not reviewed again. The studies are summarized as follows:

- (1) *In vitro* mammalian chromosomal aberration test of (b) (4) (Study number: (b) (4))

This is a GLP-compliant study with both signed and dated GLP and QA statements.

(b) (4) (CASRN: 94228-79-2) was tested in a chromosomal aberration assay using CHL/IU (Chinese hamster lung fibroblasts) cells with a short-term (6 hr) treatment

(b) (4)

with or without the metabolic activation (S9), and continuous (24 and 48 hr) treatments without S9. Acetone was the vehicle control, and mitomycin C (-S9) and benzo(a)pyrene (+S9) were used as positive controls. Duplicate cultures were treated and 300 cells were counted for every dose tested. Two hours prior to harvest, colcemid was added to cultures to obtain metaphase cells. Both vehicle and positive controls produced expected results, and no statistically significant increase of cells with aberrant chromosomes was reported when treated with (b) (4). Acetone was used as the solvent but precipitation was observed at every dose tested. Toxicology considered that (b) (4) is not clastogenic in CHL/IU cells *in vitro*, but the confidence of this conclusion was decreased due to precipitation reported at every dose tested.

(2) Mutagenic potential of (b) (4) in the mouse lymphoma TK assay (Study number: (b) (4))

This is a GLP-compliant study with both signed and dated GLP and QA statements. The mutagenicity potential of (b) (4) (CASRN: 94228-79-2) was tested in the mouse lymphoma L5178Y cell TK assay. The assay was carried out in the 96-microwell plate with or without S9, and comprised of dose range-finding studies, short-term studies (3 hrs exposure +/- S9) and one long-term study (24 hrs exposure -S9). Methyl methanesulfonate (-S9) and cyclophosphamide (+S9) were the positive control agents. Acetone was the vehicle control. The test article was tested in the soluble form at several lower doses (before precipitation appeared) in both 3hr and 24 hr treatment without S9, precipitation was observed for every testing dose in the 3hr treatment with S9. No dose-related, statistically significant increase in mutation frequency was observed. Toxicology considered that (b) (4) did not induce mutations in the mouse lymphoma TK locus assay using L5178Y cells under the test conditions, but several deficiencies had decreased the confidence in this conclusion: (1) an insufficient number of six concentrations were tested per assay with single cultures, whereas Redbook 2000 guidelines call for at least 8 analyzable test concentrations with single cultures. (2) The lowest Relative Total Growth percentage (% RTG) in the 24-hour assay was 39%. Per Redbook 2000 guidelines, there should be at least one data point between 10 and 20% RTG unless the test material is clearly mutagenic. In addition, precipitation was observed at every dose tested when cells were exposed for 3 hours with S9.

(3) Bacterial reverse mutation test of (b) (4) (Study number: (b) (4))

This is a GLP-compliant study with both signed and dated GLP and QA statements. The mutagenicity potential of (b) (4) (CASRN: 94228-79-2) was tested in a bacterial reverse mutation test using pre-incubation method with or without S9. Four tester strains of *Salmonella typhimurium*, TA100, TA1535, TA98, TA 1537, and *E.coli* WP2uvrA were employed in the assay. A dose range-finding study was first conducted where precipitation was observed at 5000 µg/plate. Two independent assays were subsequently conducted from 156 ~ 5000 µg/plate where precipitation was observed at

2500 and 5000 µg/plate (+/- S9), and cytotoxicity was observed at 5000 µg/plate (-S9). All testing was done in triplicate and acetone was used as the solvent and vehicle control. All positive controls produced significant increase in the number of revertant colonies, and none of the testing dose produces statistically significant increase in the revertant colonies as compared to the vehicle control. 2-Aminoanthracene was used as the sole positive control agent in the presence of S9, which is considered as a deficiency according to Redbook 2000.² Toxicology considered that (b) (4) was not mutagenic under the test conditions.

A preliminary QSAR analysis was conducted by the QSAR Team in DFCN for the withdrawn (b) (4). The results indicated that the LMWO is not likely to be mutagenic or carcinogenic (Arvidson/Cheng, personal communication). No alerting structural feature can be identified from the LMWO, Toxicology has no safety concerns at the proposed exposure of 9 ppb.

2. **2,3,3,4,4,5,5-Heptafluoro-1-pentene (H2Pentene; CASRN: 1547-26-8; DC: 4 pptr)**

The notifier submitted three genotoxicity studies for this monomer as supplemental information on 11/06/2015. The studies are (1) Ames assay, (2) *in vitro* chromosomal aberration assay, and (3) Combination study of micronucleus test and comet assay in rats. These studies were primary reviewed by ORNL contract reviewer and secondary reviewed by Toxicology. The studies are summarized as follows:

(1) H2Pentene: Reverse Mutation Assay "Ames Test" using *Salmonella Typhimurium* And *Escherichia Coli* (SPL PROJECT NUMBER: (b) (4))

This is a GLP-compliant study with both signed and dated GLP and QA statements. *Salmonella typhimurium* tester strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2uvrA⁻ were treated with the test article up to five dose levels in triplicate, both with and without the addition of metabolic activation (S9). The study consisted of the range-finding experiment, a main experiment using the plate incorporation method, and the confirmatory experiment using the pre-incubation method. Dimethyl sulphoxide (DMSO) was used as the vehicle control. No cytotoxicity and precipitation was reported at the top dose of 5000 µg/plate.

The test article induced statistically significant ($p \leq 0.05$), dose-related and reproducible increases in the number of revertant colonies only in the tester strain TA100 with S9 at and above 500 µg/plate in both the range-finding and the main experiment using the plate incorporation method. To confirm this result, the third confirmatory experiment using the pre-incubation method was carried out using only the tester strain TA100 with S9 and a more closely spaced dose levels (0, 2000, 3000, 4000 and 5000 µg/plate). Statistically significant increases in the number of revertant colonies were again observed in the

²<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm078330.htm>

confirmatory test. Toxicology considered the testing article, H2Pentene, is mutagenic under the test conditions.

(2) Chromosomal Aberration Test of 2,3,3,4,4,5,5-Heptafluoro-1-Pentene in Cultured Mammalian Cells (Study Number (b) (4))

This is a GLP-compliant study with both signed and dated GLP and QA statements. 2,3,3,4,4,5,5-Heptafluoro-1-pentene was tested in a chromosomal aberration assay using Chinese hamster lung cells (CHL) with a short-term treatment (6 hrs) with and without metabolic activation (S9), or continuous treatments (24 or 48 hrs) without S9. 1% Solution of carboxymethyl cellulose (CMC) sodium salt was the vehicle control, and Mitomycin C and benzo(a)pyrene were used as the positive controls without and with metabolic activation, respectively.

200 cells were scored for aberrant chromosomes, and increased chromosomal aberrations were observed between 0.1 mg/ml and 0.4 mg/ml after 6 hours treatment in the presence of the S9. No induction of chromosomal aberration was observed in the absence of metabolic activation. Toxicology considered that the test article induced structural chromosomal aberrations in CHL cells under the test conditions.

(3) Combination Study of Micronucleus Test and Comet Assay in Rats Treated with H2Pentene (Study No.: (b) (4))

This is a GLP-compliant study with both signed and dated GLP and QA statements. Male Crl:CD(SD) rats were dosed via gastric tube at 0, 250, 500 or 1000 mg/kg bw/day at 48, 24 or 3 hr before sacrifice. Seven animals were allocated for the top group and 5 animals were allocated for the rest of the groups. Ethyl methanesulfonate (EMS) was used as the positive control agent and was administered by gavage at 200 mg/kg/day. Bone marrow cells were harvested from the right femur after sacrifice, and 2000 immature erythrocytes (IMEs) per dose, per rat, were evaluated for the presence of micronuclei. The liver, glandular stomach, and kidneys were collected from the same animals, and single cell preparations were made and evaluated for DNA damage via the Comet assay. Gross necropsy of the liver, glandular stomach, and kidneys revealed no treatment-related findings. H2Pentene did not increase the incidence of micronucleated immature erythrocytes (MNIME) at any test dose, and all test and control mean values were within the laboratory's historical negative control range. H2Pentene was cytotoxic to the bone marrow at all test doses, based on the significantly ($p < 0.05$) decreased immature: mature erythrocyte ratio. The positive control induced a significant increase in micronucleated IMEs, and was cytotoxic to the bone marrow.

The Comet assay using liver, glandular stomach, and kidney cells showed no significant differences between control and H2Pentene-treated groups in the tail length, tail moment, or % tail DNA. Mean values for all Comet parameters were within or comparable to historical negative control ranges for the vehicle control and H2Pentene-treated groups.

The fraction of hedgehog cells was $\leq 4.0\%$ in all test groups for all three organs, indicating a lack of severe cytotoxic effects on these tissues. The positive control values yielded appropriate results. Though the presence of the test article in the liver, glandular stomach and kidney was not shown analytically in the study, observation of clinical signs of toxicity (salivation, peritoneal soiling, and decreased locomotor activity), decreased body weight gain at 1000 mg/kg/day, and bone marrow toxicity at 250, 500, and 1000 mg/kg/day indicated that the test article was absorbed and distributed systemically. Gavage dosing ensured that the glandular stomach was exposed to the test material.

Toxicology concluded that the test article was neither clastogenic, nor had the potential for DNA damage, under the test conditions. The confidence of the results would be improved if (1) the test compound purity was stated; (2) the preliminary study had also tested females, and showed that they were not more susceptible to H2Pentene toxicity than males; and (3) more complete historical control data were provided for the Comet assay using kidney cells.

The *in vivo* micronucleus (MN) and Comet assays are recommended by EFSA in a genotoxicity testing strategies report as follow-up assays for compounds that are tested positive in the *in vitro* genotoxicity studies.³ The negative *in vivo* MN results alleviate the concern over that H2Pentene is an *in vivo* clastogen as suggested by the *in vitro* chromosomal aberration assay. The *in vivo* Comet assay has been suggested as a suitable test to investigate endpoints such as gene mutation and clastogenicity (but not aneugenicity) in several publically available literature reports. In addition, H2Pentene does not belong to the potent carcinogenic chemical classes (*e.g.*, *n*-nitroso compound, polycyclic amines) as listed in Cheeseman et al., (1999)⁴ and therefore it can be expected that at the exposure level below 0.5 ppb, the LCR for H2Pentene is not likely to exceed the one in a million risk level. At the estimated exposure of 4 ppb, negative results from the *in vivo* genotoxicity studies and no alerting structural feature, Toxicology has no safety concerns for the use of 2,3,3,4,4,5,5-heptafluoro-1-pentene (H2Pentene) as proposed.

3.

(b) (4)

(b) (4)

3 EFSA Scientific Committee; Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Journal 2011;9(9):2379. [69 pp.] doi:10.2903/j.efsa.2011.2379. Available online: www.efsa.europa.eu/efsajournal

4 Cheeseman MA, Machuga EJ, Bailey AB. (1999) A tiered approach to threshold of regulation. Food Chem Toxicol. 37(4):387-412.

5 <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@rn+@rel+80-56-8> (accessed April, 2015)

4.

(b) (4)



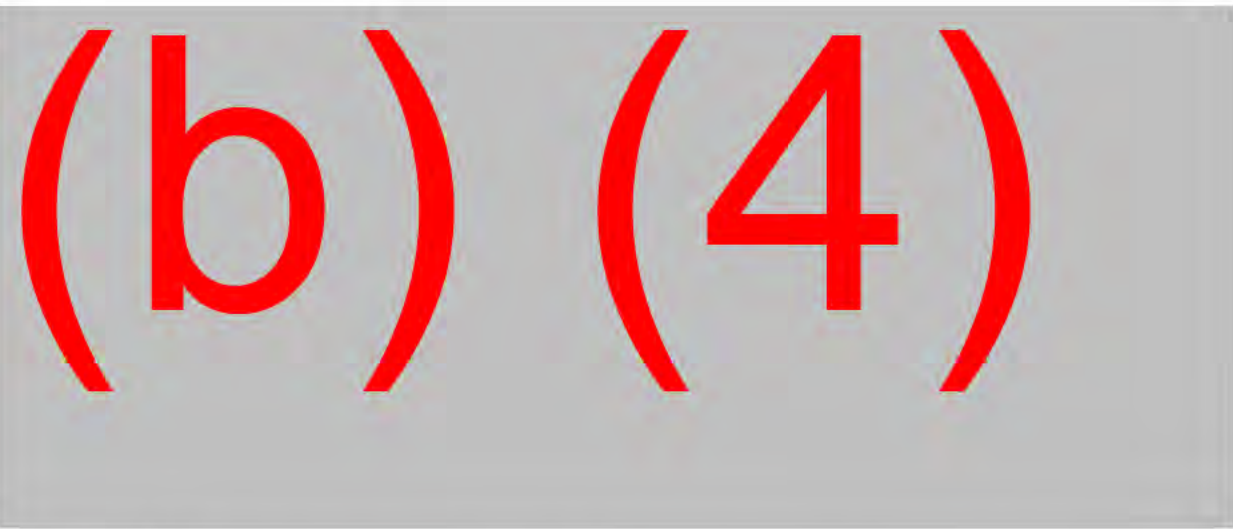
5.

(b) (4)



6.

(b) (4)



CONCLUSION

Center for Regulatory Services, Inc., on behalf of Daikin Industries, Ltd., submitted this FCN for the use of the FCS identified as 2,3,3,4,4,5,5-heptafluoro-1-pentene polymer with ethene and tetrafluoroethene (CAS Registry No. 94228-79-2) as a polymer additive for property improvement in extrusion process of all polymers for food packaging. Toxicology has no safety

6 Memorandum for FCN 321 by R. Chanderbhan dated June 13, 2003.

concerns regarding the proposed use of the FCS, based on the exposure estimates and the toxicological evaluation of the available data as indicated above.

Tsu-fan
Cheng -S

Digitally signed by Tsu-fan Cheng -S
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ou=HHS, ou=FDA, ou=People,
cn=Tsu-fan Cheng -S,
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Tsu-Fan Cheng, Ph.D.

(b) (5)



Memorandum

Date: December 16, 2015

From: Biologist, Environmental Review Team, Division of Biotechnology and GRAS Notice Review (HFS-255)

Subject: FCN 1601 (2,3,3,4,4,5,5-Heptafluoro-1-pentene polymer with ethene and tetrafluoroethene, CAS Reg. No. 94228-79-2) Categorical Exclusion Memorandum

Notifier: Center for Regulatory Services, Inc. on behalf of Daikin Industries, Ltd.

To: Anita Chang, Ph.D., Consumer Safety Officer, Division of Food Contact Notification (HFS-275)

Through: Suzanne Hill, Environmental Team Supervisor, Office of Food Additive Safety (HFS-255)

This memorandum explains how the Food and Drug Administration Center for Food Safety and Applied Nutrition (FDA CFSAN) has met the requirements under the National Environmental Policy Act (NEPA) for the food contact substance (FCS) notification 1601 (FCN 1601).

The FCS that is the subject of FCN 1601 is 2,3,3,4,4,5,5-Heptafluoro-1-pentene polymer with ethene and tetrafluoroethene (CAS Reg. No. 94228-79-2). The FCS is intended to be used for the property improvement in extrusion process of all polymers for food-packaging. Specifically, the FCS is intended to be used at levels up to 2000 ppm in all polymers that contact all food types under conditions of use A-H, as described in Tables 1 and 2.¹ The finished product is not for use in contact with infant formula and breast milk. Such uses are not included as part of the intended use of the substance in the FCN.

We reviewed the notifier's claim of categorical exclusion under 21 CFR 25.32(i) for FCN 1601 and concluded that the categorical exclusion is warranted. The claim of categorical exclusion cites the section, 21 CFR 25.32(i), under which the categorical exclusion is warranted, states compliance with the categorical exclusion criteria, and states that no extraordinary circumstances exist that require the submission of an environmental assessment (EA).

As a part of our review, we confirmed the criteria for a categorical exclusion under 21 CFR 25.32(i) were met, which include that the FCS will be used in finished food-packaging material, the use level is less than 5% by weight, and the FCS will remain with the food-packaging through use by the consumer. We also confirmed that to the best of our knowledge there are no extraordinary circumstances associated with the effective notification of FCN 1601 that would require the preparation of an EA under NEPA. In particular, we identified no extraordinary circumstance involving greenhouse gas emissions (as estimated emissions

¹ <http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/FoodTypesConditionsofUse/default.htm>

are below those that require quantitative disclosure as outlined in the Council on Environmental Quality's *Revised Draft Guidance for Greenhouse Gas Emissions and Climate Change Impacts*²).

Please let us know if there is any change in the identity or use of the FCS.

Sarah C. Winfield

cc: HFS-255 Winfield

File: FCN No. 1601

² The Council on Environmental Quality (2014), *Revised Draft Guidance for Greenhouse Gas Emissions and Climate Change Impacts*,
https://www.whitehouse.gov/sites/default/files/docs/nepa_revised_draft_ghg_guidance_searchable.pdf



Date: July 07, 2015

From: Kelly Randolph, D.V.M, M.P.H.

Subject: FCN 001560: Vinylidene fluoride-hexafluoropropene copolymer (CAS Reg. No 9011-17-0)

To: Administrative File, Food Contact Substance Notification (FCN) No. 001560

This memorandum is in reference to FCN 001560 received May 21, 2015, submitted on behalf of Arkema, Inc., in accordance with section 409(h) of the Federal Food, Drug, and Cosmetic Act (FFDCA)(21 U.S.C. 348(h)).

Technical Review Team

Consumer Safety Officer: Kelly Randolph, D.V.M, M.P.H.
Chemist: Daniel Chan, Ph.D.
Toxicologist: William Roth, Ph.D.
Environmental Scientist: Leah Proffitt

Background

GRAS Associates LLC, on behalf of Arkema, Inc., submitted this FCN for the use of a food contact substance (FCS) described as vinylidene fluoride-hexafluoropropene (VDF-HFP) copolymer (CAS Reg. No. 9011-17-0). The FCS, marketed under the name (b) (4) is intended for use as a processing aid for food-contact polymers at levels not ppm in all polymers with a maximum thickness of 10 mils in contact with all food types under conditions of use A-H. The FCS is not for use in contact with infant formula and breast milk and such use was not included as part of the intended use of the substance in the FCN.

Regulatory Status

VDF-HFP copolymers for food contact use are authorized under 21 CFR 177.1350 (Ethylene-vinyl acetate copolymers) and 177.1520 (Olefin polymers), and as the base elastomer under 177.2600 (Rubber articles intended for repeated use). These copolymers are also the subject of FCN 736. The most relevant authorizations are in FAP 9B4169 and FCN 1448.

(b) (4)

Chemistry

Identity

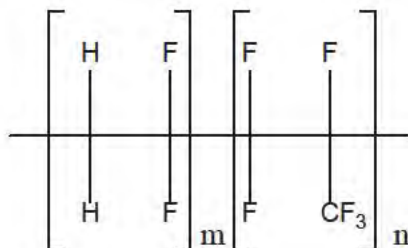
CAS Name: 1-Propene, 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene

CAS Number: 9011-17-0

Trade Name: (b) (4)

Other Names: Poly(vinylidene fluoride-hexafluoropropylene) copolymer
VDF/HFP copolymer

Structure:



Characterization: In attachment 2 of the submission, the notifier provided an ^1H -NMR, ^{19}F -NMR and an IR that adequately characterize the FCS. These were previously reviewed and accepted in our review of FCN 1448².

While the FCS is essentially identical to that described in FCN 1448, the notifier requests a change in the composition of the FCS from a maximum of 16% hexafluoropropene to a maximum of 19% hexafluoropropene.

Manufacture

The manufacturing process is the same as described in FCN 1448, which was reviewed previously¹. The notifier refers to two patents: (b) (4) to describe the manufacturing process. A synopsis of the process, including percentages of each reagent, is found in attachment 5. Certificates of analyses are provided for all reagents including the two monomers and the catalyst.

Intended Use/Technical Effect

Data to support the FCS use level and technical effect are listed in Attachments 20-21 of the submission. The FCS is intended for use as a processing aid for all polymers with a maximum thickness of 10 mils at a maximum level of 2000 ppm for all food types under conditions of use A-H. The FCS eliminates melt fracture (shark skin) and reduces gels. Additionally, it improves film transparency, smoothness and surface aspect, product appearance, and mechanical properties.

² See our summary memorandum on FCN 1448 dated 07-29-2014; M. Swain.

We have no questions on the use and technical effects of the FCS.

Stability

Aging data, color and property retention data (attachment 22) along with thermogravimetric analysis data from FAP 9B4169 indicate appropriate stability of resins containing the FCS. Initial thermal decomposition of the FCS described in FAP 9B4169, which is similar to the subject FCS, occurs above 375 °C in air. Attachment 22 is the same attachment that was provided in FCN 1448.

We have no questions regarding the stability of the FCS.

Migration and Consumer Exposure

As the manufacture of the FCS is essentially identical to that described in FCN 1448, except for a slight increase in hexafluoropropene incorporation from (b) (4) we expect that there would be little change in the properties of the FCS and its impurity profile from that described in FCN 1448. Additionally, GPC data shows the percentage of LMWO < (b) (4) Daltons in the FCS is lower than in the representative batch of polymer used in FCN 1448. Therefore, we would expect the exposure to the FCS and its impurities to be no greater than those calculated in FCN 1448.

In the summary memorandum on FCN 1448¹, we note that a consumption factor of (b) (4) should be used for these types of perfluorinated additives in place of the notifier's CF of (b) (4). As such, exposure to LMWO was recalculated to be 2.08 ppb. However, we note that the table of exposure estimates provided in the summary memorandum on FCN 1448 is incorrect in that it does not contain the exposure values recalculated by FDA using the (b) (4) consumption factor; it only reproduces the notifier's estimates. We have recalculated the exposure values to the FCS and its impurities using the appropriate consumption factor of (b) (4) and summarized those values in Table 1.

Table 1. Exposure estimates for the constituents/impurities of the FCS

Chemical/Common Name	CAS Reg. No.	DC /ppb	EDI/(µg/p/d)
LMWO < 2500 Daltons		2.08	6.24
Vinylidene fluoride	75-38-7	Essentially zero	
Hexafluoropropene	116-15-4	Essentially zero	
(b) (4)		0.006	0.018
		1.07	3.21
		0.36	1.08
		0.18	0.54
Fluoride	16984-48-8	0.001	0.003
(b) (4)			

Toxicology

Toxicity of FCS:

Previous reviews of this polymer in FAP 9B4169 and FCN 260 found no concern as oligomers of the FCS were negative in genetic toxicity studies and no information was found indicating other toxic or carcinogenic activity.

Constituents / Impurities

A list of expected migrating constituents and impurities was provided by the notifier. All of these chemicals are authorized for use in foods at levels well above the expected incremental dietary concentrations from the proposed use.

Toxicity Information Provided

The notifier included a safety narrative and Comprehensive Toxicology Profile for all constituents and impurities. All are authorized for multiple uses. (b) (4) ☐

(b) (4)

There are no safety concerns with this FCN.

Environmental

In the FCN submission, the notifier makes a claim of categorical exclusion under 21 CFR 25.32(i), non-coating use of the FCS. In this notification the maximum use level of the FCS in the finished food-contact article is 2000 ppm (0.2 wt%), which meets the use limit criterion of “not greater than 5 percent-by-weight” specified in the categorical exclusion.

The Environmental Review Team has reviewed the claim of categorical exclusion for the above referenced notification and has concluded that it is warranted. The notifier cites the section under which the categorical exclusion is applicable, states compliance with the criteria for the categorical exclusion, and states that no extraordinary circumstances exist that require the submission of an environmental assessment. Attached is a memorandum for categorical exclusion for this FCN (L.Proffitt to K. Randolph, 07/01/2015) (Attachment 1).

Environmental has no concerns regarding the notified use of this FCS.

Conclusion

FDA has evaluated data in the FCN 001560, and other relevant material. Based on this information, FDA has concluded that the proposed use of the food contact substance is acceptable subject to the following conditions:

Food Contact Substance (FCS)	Intended Use	Limitations/Specifications
Vinylidene fluoride-hexafluoropropene copolymer (CAS Reg. No. 9011-17-0)	As a processing aid for food contact polymers, except for use in contact with infant formula and breast milk (see Limitations/Specifications)	For use at levels not to exceed 2000 ppm in all polymers with a maximum thickness of 10 mils in contact with all food types (I-IX) under conditions of use A-H, as defined in Tables 1 and 2, respectively (see Attachment 1). The FCS is not for use in contact with infant formula and breast milk. Such use was not included as part of the intended use of the substance in the FCN.

Effective Date: This notification will become effective on September 18, 2015.

Kelly M. Randolph -A Digitally signed by Kelly M. Randolph, A
DN: cn=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People
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Date: 2015.07.07 08:48:55 -0400

Kelly Randolph, D.V.M, M.P.H.

Attachment(s): Categorical Exclusion Memorandum for FCN 1560 dated

cc: HFS-275 FCN 001560
 FileName: F001560summary memo
 R/D:HFS-275:KMRandolph 06/23/15
 INIT:ALipman:HFS-275:07/01/15
 DChan:HFS-275:06/25/15
 WRoth:HFS-275:06/23/15
 LProffitt:HFS-246:06/29/15



Date: July 29, 2014

From: Marla D. Swain, Ph.D.

Subject: FCN 001448: Vinylidene fluoride-hexafluoropropene copolymer (CAS Reg. No 9011-17-0)

To: Administrative File, Food Contact Substance Notification (FCN) No. 001448

This memorandum is in reference to FCN 001448 received April 30, 2014 submitted by GRAS Associates, LLC, on behalf of Arkema, Inc., in accordance with section 409(h) of the Federal Food, Drug, and Cosmetic Act (FFDCA)(21 U.S.C. 348(h)).

Technical Review Team

Consumer Safety Officer: Marla D. Swain, Ph.D.
Chemist: Michael C. VanDerveer, Ph.D.
Toxicologist: Adejoke Ogungbesan, Ph.D.
Environmental Scientist: Mariellen Pfeil

Background

GRAS Associates, LLC, on behalf of Arkema, Inc., submitted this FCN for the use of a food contact substance (FCS) described as vinylidene fluoride-hexafluoropropene (VDF-HFP) copolymer (CAS Reg. No. 9011-17-0). The FCS, marketed under the name (b) (4), is intended for use as a processing aid for food-contact polymers at levels not to exceed 2000 ppm in all polymers with a maximum thickness of 10 mils in contact with all food types under conditions of use A-H. The FCS is not for use in contact with infant formula and breast milk and such use was not included as part of the intended use of the substance in the FCN.

Regulatory Status

VDF-HFP copolymers for food contact use are authorized under 21 CFR 177.1350 (Ethylene-vinyl acetate copolymers) and 177.1520 (Olefin polymers), and as the base elastomer under 177.2600 (Rubber articles intended for repeated use). These copolymers are also the subject of FCN 736. The specifications for currently authorized VDF-HFP copolymers compared to those of the subject FCS are summarized in the table below:

Table 1. Specifications for currently authorized VDF-HFP copolymers with this FCS

Sample	Composition (ratio in percent weight)	Mn
Authorized uses	VDF: HFP (b) (4)	
FCN 1448	VDF:HFP (b) (4)	

This notification is also related to tetrafluoroethylene (TFE)-HFP-VDF copolymers that were the subject of FCN 260 and FCN 1121, submitted by Dyneon and 3M, respectively. FCN 260 (effective October 3, 2002) authorizes use of TFE-HFP-VDF copolymer as a processing additive at levels up to 2000 ppm in food-contact polyolefins in contact with all food types under Conditions of Use B-H. FCN 1121 (effective January 17, 2012) expanded the use of the TFE-HFP-VDF copolymer described in FCN 260 to all polymers (excluding paper and metal coatings), at levels not to exceed 2000 ppm in the finished polymer under Conditions of Use A-H.

While the FCS in this notification is similar to VDF-HFP copolymers described above, it is not identical to any previously reviewed copolymer in that it has a higher molecular weight. However, the intended use of the subject FCS is the same as the intended use in FCN 1255.

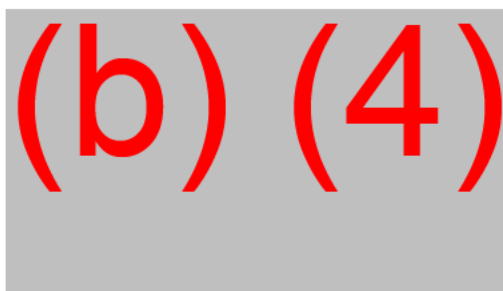
The notifier frequently references FAP 9B4169¹ throughout the FCN submission.

Chemistry

Identity

CAS Name:	1-Propene, 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene
CAS Reg. No.:	9011-17-0
Trade or Common Name:	(b) (4)
Other Chemical Name:	Poly(vinylidene fluoride-hexafluoropropylene) copolymer VDF/HFP copolymer
Molecular Weight:	Mw (b) (4) Da Mn (b) (4) (b) (4)

Structure:



In Attachment 2 of the submission, the notifier provided proton nuclear magnetic resonance (¹H-NMR), fluorine NMR (¹⁹F-NMR), and infrared spectral data that adequately characterize the FCS.

Manufacture

The notifier referred to FAP 9B4169 for details regarding the manufacturing process of the FCS. A description of the manufacturing process, including a list of components and certificates of analysis for the ingredients, was provided in Attachments 5-12. The notifier provided extensive data on impurities in Attachments 7 and 8.

¹ FAP 9B4169 was submitted by Pennwalt Corp., now known as Arkema, to allow for the use of a vinylidene fluoride-hexafluoropropylene copolymer, also known by the tradenames (b) (4), as a processing adjuvant at levels up to 10,000 ppm. Effective 5/13/13.

We have no questions on the manufacture and the impurity profile of the FCS.

Intended Use/Technical Effect

Data to support the FCS use level and technical effect are listed in Attachments 19-20 of the submission. The FCS is intended for use as a processing aid for all polymers with a maximum thickness of 10 mils at a maximum level of 2000 ppm for all food types under conditions of use A-H. The FCS is marketed as eliminating melt fracture (shark skin) and improving film transparency, smoothness and surface aspect, product appearance, mechanical properties and reduction of gels.

We have no questions on the use and intended technical effect the FCS.

Stability of the FCS

Aging data, color and property retention data (Attachment 21), along with thermogravimetric analysis data from FAP 9B4169, indicate appropriate stability of resins containing the FCS.

Migration Studies

Arkema used migration modeling of oligomers from (b) (4) resins in lieu of performing traditional migration studies (Attachment 22). In the current FCN, they state that they have evaluated the FCS resins for low-molecular-weight oligomers (LMWOs) (b) (4) Daltons. Generally, the LMWOs <1000 Daltons are considered in the safety evaluations of polymers. However, in the case of perfluoro-compounds the molecular size is smaller than polymers of similar molecular weight ranges. Since certain properties of the substances, such as spatial size and MW, are involved in transport/systemic absorption, increasing the MW cut-off to (b) (4) Daltons was considered a conservative but justified approach to the safety evaluation of these perfluoro-compounds. We concurred.

Arkema also determined migration values assuming 100% migration based on use level, oligomer level and thickness of packaging. The provided models, which varied depending on the resin, resulted in migration levels of approximately 50-100 ppb.

Exposure

With so many variations on the specific resin, use level and packaging thickness, exposure to the FCS is challenging to summarize. However, the basic dietary concentration (DC) estimate of the FCS is 42 ppb, compared with FCN 1255 where a consumption factor (CF) of (b) (4) was used² (Arkema has used a CF of (b) (4). For consistency, we will apply a CF (b) (4) which results in a DC close to 2 ppb (6 µg/p/d). Overall, the exposures to VDF and HFP monomers are expected to be “essentially zero.” The end of Attachment 22, Attachment 23 and Form 3480(II)(G)(3) contain some estimated daily intake calculations and information on impurity exposures.

Exposure estimates for the constituents and impurities of the FCS are presented in Table 1.

(b) (4)

Table 1. Exposure estimates for the constituents/impurities of the FCS

Chemical/Common Name	CAS Reg. No.	DC /ppb	EDI/(µg/p/d)
LMWO- <1000 daltons		41.6	124.8
Vinylidene fluoride	75-38-7	Essentially zero	
Hexafluoropropene	116-15-4	Essentially zero	

(b) (4)

(b) (4) is considered generally recognized as safe (GRAS) under (b) (4). The notifier indicated that most (b) (4) are GRAS.

Cumulative Estimated Daily Intake (CEDI)

The use of the FCS is substitutional for existing authorized processing aids and therefore would have no effect on current exposure values.

Toxicology

The notifier submitted a Safety Narrative (SN) and Comprehensive Toxicology Profile (CTP) for the FCS and its impurities in Attachments 24 and 25, respectively.

The Toxicology Reviewer conducted an updated database search (FARM, ChemIDplus, CERES, etc.) using CAS Reg. Nos. and names of the FCS and impurities. Unless indicated specifically, no new relevant information was located that can be used for this safety assessment.

FCS and FCS LMWO (DC of 41.6 ppb)

In the SN, the notifier indicated that the FCS is a copolymer of vinylidene fluoride (VDF) and hexafluoropropylene (HFP) and that the primary use of the copolymer will be as a polymer processing aid. The notifier stated that several FCNs of various copolymers containing these two monomers have been authorized for use by the Agency. They also indicated that Arkema currently manufactures and supplies product to manufacturers of food packaging materials complying with the listing for CAS Reg. No 9011-17-0 in 21 CFR 177.1520 (b) as authorized in FAP 9B4169 for Conditions of Use B-H. The notifier also stated that the proposed use of the FCS is not a new use and not expected to increase dietary exposure to the expected fluorocarbon oligomers. According to the notifier, the FCS is expected to compete for market share with similar fluoropolymers currently authorized by the Agency.

Monomers

In the CTP, the notifier indicated that vinylidene fluoride and hexafluoropropylene are the two monomers used in the manufacture of the copolymer and that there are no measureable residual monomers in the FCS. According to the notifier, the genetic toxicity information on these monomers was provided in effective FCN 000260.

In FCN 000260, the exposure to each of these monomers was stated as essentially zero and Toxicology (Twaroski/Gilliam, 10/01/2002) cited negative results of genetic toxicity studies with hexafluoropropylene (such as Ames, CHO/HGPRT³ and dominant lethal inhalation study in rats), positive results with hexafluoropropylene in a micronucleus assay and a chromosomal aberration assay under metabolic activation in CHO cells, respectively. Toxicology noted that hexafluoropropylene was not tested for carcinogenicity. Literature searches by this Toxicology Reviewer revealed mixed results of genetic toxicity studies⁴ with hexafluoropropylene.

Regarding vinylidene fluoride, in FCN 000260, Toxicology noted a carcinogenicity citation in FAP 9B4169 for a publication⁵ of long-term bioassays in rats which was reviewed by IARC and found to lack evidence of carcinogenicity. The negative carcinogenicity results were also reported in the CPDB⁶ dataset. Toxicology indicated that literature searches revealed several toxicity studies including mutagenicity (predominantly negative results) and subchronic toxicity studies in addition to an inhalation rat bioassay⁷ which was considered irrelevant since it was an inhalation study. The mixed results (positive and negative results) of the genetic toxicity studies and negative results of the inhalation carcinogenicity study were reported in the IUCLID⁸ dataset.

(b) (4)

³Chinese hamster ovary/hypoxanthine guanine pyrimidine ribonuclease thymidine (CHO/HGPRT).

⁴HSDB: The hydrochlorofluorocarbons, HCFC-225ca and HCFC-225cb, were not mutagenic in the Ames reverse mutation assay, or clastogenic in the chromosomal aberration assay with Chinese hamster lung cells. Neither induced unscheduled DNA synthesis in liver cells. Both of these agents were clastogenic in the chromosomal aberration assay with human lymphocytes.

⁵Maltoni C and Tovati D. First experimental evidence of the carcinogenic effects of vinylidene fluoride; long-term bioassays on Sprague-Dawley rats by oral administration. *Med Lav* 1979 Sep-Oct;70(5):363-368. This study was republished in 1982 in *Ann. N.Y. Acad. Sci.* 381:216 – 249.

⁶Carcinogenicity Potency DataBase (CPDB) accessible at:

<http://toxnet.nlm.nih.gov/cpdb/chempages/VINYLLIDENE%20FLUORIDE.html> (accessed July 2014).

⁷TSCAT: Chronic toxicity/carcinogenicity inhalation study of vinylidene fluoride vapour in rats (final report, Doc#: 86-920000883).

⁸IUCLID accessible at: <http://esis.jrc.ec.europa.eu/doc/IUCLID/datasheet/75387.pdf> (accessed July 2014).

(b) (4)

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(b) (4)

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(b) (4)

(b) (4)

(b) (4)

(b) (4)

International Uniform Chemical Information Database accessible at:
<http://esis.jrc.ec.europa.eu/doc/TUCLID/datasheet/151213.pdf> (accessed July 2014).

²⁰ National Toxicology Program (NTP) database accessible at:
http://tools.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.showStudiesForChemical&cas_no=151-21-3
(accessed July 2014).

(b) (4)

Since the proposed use of the FCS is substitutional for the currently authorized uses such that the cumulative exposure to the FCS and its impurities would not increase if the notification becomes effective, Toxicology has no concerns regarding the notified use of this FCS.

Environmental

In the FCN submission, the notifier makes a claim of categorical exclusion under 21 CFR 25.32(i), non-coating use of the FCS. In this notification the maximum use level of the FCS in the finished food-contact article is 2000 ppm (0.2 wt%) and the notifier asserts that 100% of the FCS remains with the final food-contact item.

The Environmental Review Team has reviewed the claim of categorical exclusion under 21 CFR 25.32(i) and has concluded that categorical exclusion is warranted. The claim cites the section under which the categorical exclusion is applicable, states compliance with the criteria for the categorical exclusion, and states that no extraordinary circumstances exist that require the submission of an environmental assessment. Attached is a memorandum for categorical exclusion for this FCN (M. Pfeil to M. Swain, 6/24/2014) (Attachment 1).

Conclusion

FDA has evaluated data in FCN 001455, and other relevant material. Based on this information, FDA has concluded that the proposed use of the food contact substance is acceptable, subject to the following conditions:

(b) (4)

Food Contact Substance (FCS)	Intended Use	Limitations/Specifications
Vinylidene fluoride-hexafluoropropene copolymer (CAS Reg. No. 9011-17-0)	As a processing aid for food contact polymers, except for use in contact with infant formula and breast milk (see Limitations/Specifications)	For use at levels not to exceed 2000 ppm in all polymers with a maximum thickness of 10 mils in contact with all food types (I-IX) under conditions of use A-H, as defined in Tables 1 and 2, respectively (see Attachment 1). The FCS is not for use in contact with infant formula and breast milk. Such use was not included as part of the intended use of the substance in the FCN.

Therefore, the agency does not object, under Section 409(h)(2)(b) of the Federal Food, Drug and Cosmetic Act, to the marketing of the FCS described above, manufactured by Arkema, Inc., as a processing aid for food contact polymers.

This notification will become effective on August 28, 2014.

Marla D. Swain, Ph.D.

Attachment(s): Categorical Exclusion Memorandum for FCN 1448 dated June 24, 2014

Attachment (1)

cc: HFS-275 FCN 001448

FileName: FCN 1448_Summary Memo

R/D: MSwain: HFS-275: 07/15/2014

INIT: ALipman: HFS-275: 07/28/2014

MVanDerveer: HFS-275: 07/21/2014

AOgungbesan: HFS-275: 07/24/2014

MPfeil: HFS-255: 07/25/2014

F/T:HFS-275:MSwain: 07/29/2014

**Memorandum**

Date: March 18, 2013

From: Division of Food Contact Notification
Chemistry Review Group II
Jeannie Jeong-Im, Ph.D.

Subject: **FCN 1255:** Intertek on behalf of 3M for the use of vinylidene fluoride and hexafluoride copolymers as a process aid in all polymers. Submissions dated 12/10/12 (initial) and 1/31/13 (amendment with chemistry).

To: Division of Food Contact Notifications
Regulatory Team II
Attn: Kenneth McAdams

Intertek has submitted FCN 1255 on behalf of 3M for the use of vinylidene fluoride (VDF, a.k.a. 1,1-difluoroethene, 60 wt.-% or 80 mole-%) and hexafluoropropene (HFP, 40 wt.-% or 20 mole-%) copolymer (CAS Reg. No. 9011-17-0) as a process aid at levels up to 2000 ppm in all polymers (excluding metal and paper coatings) in contact with all food types under Conditions of Use A-H.

HFP-VDF copolymers were the subject of FCN 736 and are currently regulated under §177.1350 (Ethylene-vinyl acetate copolymers) and §177.1520 (Olefin polymers), and as the base elastomer under §177.2600 (Rubber articles intended for repeated use). The specifications for each copolymer are summarized in Table 1.

Table 1. Specifications of HFP-VDF Copolymers

Sample	Composition of FCS (ratio in wt.-%)	Mooney Viscosity	Mn	Use
FCN 1255 (this FCN)	HFP/VDF (20:80 to 40:60)	(b) (4)	73,490- 81,550	2000 ppm in all polymers (excluding metal and paper coatings) under Conditions of Use A-H
FCN 736 ¹	HFP/VDF (40:60 to 42:58) and <0.5% bromodifluoroethylene	(b) (4)		1000 ppm in all polymers under Conditions of Use A- H

¹ Although the FCS contains the (b) (4), the majority of the FCS is structurally similar to other HFP/VDF copolymers. See FCN 736 (effective 10/26/07) was submitted by Ciba Expert Services (Ciba), on behalf of Dyneon (a 3M Company). See Chemistry memorandum dated 10/15/07 on FCN 736 (S. Elyashiv-Barad to V. Gilliam).

§177.1520 ²	HFP/VDF (36:64 to 50:50) ^a	≥28	64,000 - 78,000	2000 ppm in olefin polymers under Conditions of use B-H
§177.1520 ³	HFP/VDF (13:87 to 0:100)	-- ^b	-- ^c	10000 ppm in olefin polymers under Conditions of use B-H
§177.1350 ⁴	HFP/VDF (36:64 to 50:50) ^a	≥28	64,000 - 78,000	2000 ppm in ethylene-vinyl acetate copolymers
§177.2600 ⁵	HFP/VDF (30:70 to 5:95)	--	≥70,000	rubber articles intended for repeat use

^a The regulation states the VDF/HFP copolymer should have a fluorine content of 65-71% F, which corresponds to HFP content ranging from 36 to 50 wt.-%.

^b Specification list a melt viscosity of 12 to 27 kilopoise at a shear rate of 100 s⁻¹ at 232 °C.

^c The copolymer is not completely soluble in typical solvents; therefore, size exclusion chromatography and other solution techniques were unable to determine molecular weight.

This notification is also related to tetrafluoroethylene (TFE)-HFP-VDF copolymers that were subject of FCN 260 and FCN 1121. Dyneon's FCN 260 (effective October 3, 2002) is for use of TFE-HFP-VDF copolymers as a processing additive at levels up to 2000 ppm in food-contact polyolefins in contact with all food types under Conditions of Use B through H.⁶ FCN 1121 (effective 1/17/12) submitted by 3M expanded the use of the TFE-HFP-VDF copolymer described in FCN 260 to all polymers (excluding paper and metal coatings), at levels not to exceed 2000 ppm in the finished polymer under the Conditions of Use A-H.⁷

This notification is similar to the HFP/VDF copolymers described in Table 1, but the intended use is the same as FCN 1121.

Organization of the FCN

Chemistry information is contained in Form 3480, Part II, and in Attachments 1-13 as follows: 1) Identity of the FCS; 2) IR and NMR spectra of FCS; 3) Manufacturing Process; 4) GC/MS of Monomers; 5) GPC of Oligomers <2500 Daltons; 6) TGA spectra; 7) Migration and Exposure Calculations of FCS; 8) Size Exclusion Chromatography (SEC) Analysis of Total Non-Volatile Extractives (TNE); 9) Protocol for SEC Assay; 10) TNE Study; 11) Fluorine Assay of 95%

² Chemistry memorandum dated 12/4/85 on FAP6B3902 (M. Flood to V. Anand) and Chemistry memorandum dated 8/11/89 on FAP 9B4129 (L. Borodinsky to G. Robert-Baldo).

³ Memoranda on FAP9B4169 dated: 11/3/87 (L. Borodinsky to M.Mack); 12/20/89 (L. Borodinsky to R. White); and 1/23/90 (K. P. Misra to R. White)

⁴ Memorandum dated 8/11/89 on FAP9B4154 (L. Borodinsky to Indirect Additives Branch)

⁵ (a) Memorandum of Conference dated 9/25/67 on FAP5B1794 (A. Holtz to Randolph); and (b) Memorandum dated 10/3/67 on FAP 5B1794 (K.P. Misra and J. McLaughlin to PCB).

⁶ FCS contains TFE (52 ± 13 wt.-%), HFP (19 ± 3 wt.-%), and VDF (28 ± 13 wt.-%). See Chemistry memorandum dated 9/19/02 on FCN 260 (S. Elyashiv-Barad to V. Gilliam).

⁷ FCS contains TFE (52 ± 13 wt.-%), HFP (19 ± 3 wt.-%), and VDF (28 ± 13 wt.-%), which is the same as the FCS in FCN 260. See Chemistry memorandum dated 12/1/11 on FCN 1121 (R. Costantino to A. Chang).

EtOH Sample 1; 12) Fluorine Assay of 95% EtOH Sample 2; and 13) Fluorine Assay of 10% EtOH Samples. In response to our 1/22/13 deficiency letter, an amendment dated 1/31/13 was submitted containing new Attachments 1 that contains a revised copolymer manufacturing process.

Identity

CAS Reg Name: copolymer of vinylidene fluoride and hexafluoropropene

CAS Reg. No.: 9011-17-0

Trade Name: vinylidene fluoride-hexafluoropropene copolymer

Density = (b) (4)

Mooney Viscosity = (b) (4)

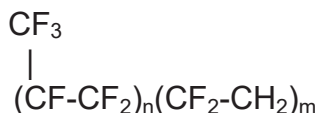
Fluorine Content = (b) (4)

Mw = 237,300 – 719,900

Mn = 73,490 – 81,550

LMWO <2500 = (b) (4)

Structure



The FCS is a random copolymer, with the values of m and n by weight and mole percent as follows:

By weight:	n = 40 weight %	m = 60 weight %
By mole:	n = 22 mol %	m = 78 mol %

The identity of the FCS was confirmed by FT-IR and ¹H- and ¹⁹F-NMR spectra in Attachment 2.

Intended Use

The FCS is intended for use as a process aid at levels up to 2000 ppm in all polymers (except metal and paper coatings).⁹ The FCS is intended to contact all food types under Conditions of Use A-H. The intended technical effect is to decrease surface defects and the cost associated with the manufacturing process, as well as improve the efficiency of the extrusion process.

Stability

Thermogravimetric analyses (TGA) spectra were provided on the FCS in Attachment 6. The FCS begins to degrade around 400 °C. Thus, the FCS is not expected to degrade under the expected Conditions of Use.

⁸ A graph relating the Mooney Viscosity to Mn provided in FAP 9B4129 (page 000078) and FAP6B3902 (page 000058) show that a Mooney viscosity of 25 has an Mn of 62,000, which is similar to the Mn of 64,000 of the regulated material under §177.1520 as a result of FAPs 9B4129 and 6B3902. Also, the Mn for this notification is 73,490 to 81,550. Therefore, a Mooney Viscosity of (b) (4) for FCN in this notification is acceptable.

⁹ In the 1/31/13 response letter, the notifier confirmed the (b) (4) intended use of the FCS similar to FCN 1121 and it is not intended to be used in paper and metal coatings.

Manufacturing

The manufacturing of the FCS was outlined in Attachment 3. A more detailed description in FAP6B3902 was referenced by the notifier. In FAP 6B3902 the notifier listed the use of (b) (4)

(b) (4)

(b) (4)

In the 1/31/13 response letter, the notifier confirmed that the manufacturing procedure in this notification and (b) (4) and provided a more detailed manufacturing description in Attachment 1. The batches range from (b) (4) gallons.

Table 2. Typical Batch Recipe for 2000 gallons of FCS

Reagent	CAS Reg. No.	Role	Amount (lbs)
(b) (4)			
VDF	75-38-7	monomer	(b) (4)
HFP	116-15-4	monomer	
water	7732-18-5	solvent	

(b) (4)

Impurities

(b) (4)

(b) (4)

which would be removed during the wash step. (b) (4) could be removed from the FCS during the drying step (b) (4). The only expected impurities from the FCS are the VDF and HFP monomers, as discussed below.

Monomers

In lieu of migration studies, the notifier analyzed three samples of the FCS by headspace GC/MS.

Due to the volatility of VDF (b.p. is -29 °C) and HFP (b.p. is -84 °C), this method would accurately determine the levels of the monomers in the FCS. Each sample was assayed in triplicate. Sealed vials containing samples were heated to 200 °C for 30 min before analysis of headspace.

VDF was not detected above the limit of quantitation (LOQ) of 0 (b) (4) ppm. The calibration curve shows good linearity and acceptable. The spiked amount was described as 0.025 mL, 0.05 mL, and high spike. The actual amounts are unclear. The spike recoveries were in the range of 101-115%. Since the boiling point of VDF is -29 °C and VDF was not detected above the LOQ, this validation is acceptable for this notification. Furthermore, any residual VDF in the FCS is expected to be removed during the drying step of the final food-contact article. Exposure to VDF monomer would be “essentially zero.”

HFP was detected in two samples at (b) (4) and one at (b) (4). The LOQ described as the lowest standard measured; however, the actual amount was not mentioned. Two calibration curves were provided with points that surround the two detected amounts of HFP. Recoveries for a 0.025 mL low spike was 71-229%, 0.05 mL low spike was 100-139%, and high spike was 109-113%. Although the analyses for HFP was not appropriately validated, the boiling point of HFP is -84 °C and is not expected to be in the final food contact article for the same reasons as VDF. Therefore, exposure to HFP is expected to be “essentially zero.”

Total Non-Volatile Extractives

Total Non-Volatile Extractives (TNE) are typically determined by an exhaustive extraction (i.e. Soxhlet extraction) of the FCS, which would represent the worst-case exposure to the FCS. In lieu of an exhaustive extraction, the notifier extracted four samples of “raw” FCS¹⁰ (approximately 11 g) with 10% EtOH and 95% EtOH using a (b) (4) as described in Attachment 10. (b) (4)

. The last extract for each of the analyses showed that minute amounts were still being extracted from the FCS. As such, this is not truly an exhaustive extraction. Considering that each FCS was extracted eight times for 2 h

¹⁰ In the 1/31/13 response letter, the notifier clarified that the extraction samples were pure FCS, which they referred to as “raw”. The samples did not contain other FDA compliant components (b) (4).

at 120 °C at 1500 psig and the majority of the migrants were extracted in the first few extractions, this method is sufficiently exhaustive to represent the TNE. After transfer and evaporating to dryness, the samples were weighed. The residues were dissolved in THF. The THF solution was removed from each sample and sent for SEC analyses (Attachment 8 & 9) and fluoride content (Attachment 11-13). The remaining non-THF soluble residues were dried and weighed. Most of the 10% EtOH extracts (35 mg) were not soluble in THF. The insoluble THF compounds from the 10% EtOH extraction are expected to be contaminants from the filter paper used during the extractions. Furthermore, the detected amount from samples were below the blank (52 mg). The residue from the 95% EtOH extracts completely dissolved in THF. Therefore, there is no significant exposure from the THF insoluble extracts. The total residual weights from the THF soluble extracts are summaries in Table 3. These values represent the total potential migration from the FCS, including monomers and LMWO.

Table 3. TNE Extraction of FCS

Sample	10% EtOH, THF Soluble (g)	95% EtOH, THF Soluble (g)
Blank	(b) (4)	
Sample 1		
Sample 2		

Fluorine Detection

The fluoride content of the THF soluble portions of the TNEs were analyzed by (b) (4) as described in Attachments 11-13. Fluorine was not detected above the limit of quantitation (LOQ) in the 10% EtOH extracts of (b) (4). Therefore, the 10% EtOH extracts does not appear to have any fluorinated compounds. Fluorine was detected in all the 95% EtOH extracts. The 95% EtOH extracts were submitted for LMWO determination.

Low Molecular Weight Oligomer (LMWO)

The THF soluble portion of the 95% EtOH TNEs was analyzed for LMWO < 2500. The SEC protocol was described in Attachment 9 and results of the analysis is provided in Attachment 8. The MW values were determined by calibrating the system against narrow molecular weight polystyrene standards. Most LMWO migration was seen in the first few extractions. A smaller amount was detected in extraction 8. Since all of the TNE 95% EtOH extracts contained fluorinated compounds, we assume the TNE below 2500 Daltons represents the LMWO for the FCS. The total LMWO extracted from 11.3 g of Sample 1 is 0 (b) (4) g, as summarized in Table 4. Therefore, the wt.-% of LMWO in sample 1 is (b) (4) / 11.3g x 100% = (b) (4) wt.-%.

Table 4. Amount of LMWO in Sample 1

Extraction #	TNE Amount (g)	Wt.-%<2500	LMWO (g)
1	(b) (4)		
2			
3			
4			
5			
6			
7			
8			
Sum			

The total LMWO extracted from 11.2 g of Sample 2 is (b) (4), as summarized in Table 5. Therefore, the wt.-% of LMWO in sample 2 is (b) (4) / 11.2 g x 100% = (b) (4) wt.-%.

Table 5. Amount of LMWO in Sample 2

Extraction #	Extracted Amount (g)	Wt.-%<2500	LMWO (g)
1	(b) (4)		
2			
3			
4			
5			
6			
7			
8			
Sum			

Therefore, the average LMWO <2500 is (b) (4) % of the FCS in 95% EtOH. In Attachment 5, the notifier provided a SEC analysis on six samples. The wt.-% <2500 Daltons ranged from (b) (4). It is unclear why more LMWO was detected from the extraction assays. As the worst-case scenario, the value from the extraction studies of (b) (4) t.-% will be used to calculate exposure to LMWO, which is the same value the notifier used in their exposure calculations.

Exposure

To calculate exposure to the FCS, the notifier used a CF of 0.017 based on information they had provided in FCN 1121 on percent of fluorinated polymers used in all polymers (excluding metal and paper coatings) globally in 2010. Instead of 0.017, the number was rounded up and a revised CF of 0.02 was used to calculate in FCN 1121.¹¹ To be consistent with FCN 1121, a CF of 0.02 will also be used in this this since notification is for the same use. Exposure to LMWO was calculated using the following assumptions:

- 100% migration of LMWO
- Polymer thickness is 0.01 in
- Density of polymer is 1 g/cm³
- 10 g of food contacts 1 in² of film
- Consumption Factor (CF) is 0.02
- Amount of FCS added to polymer is 0.2 wt.-% or 2000 ppm
- Average person consumes 3000 g of food per day

$$\langle M \rangle = \frac{(b) (4) \text{ g LMWO}}{100 \text{ g FCS}} \times \frac{0.2 \text{ g FCS}}{100 \text{ g polymer}} \times \frac{1 \text{ g polymer}}{\text{cm}^3} \times \frac{16.4 \text{ cm}^3}{\text{in}^3} \times 0.01 \text{ in} \times \frac{1 \text{ in}^2 \text{ polymer}}{10 \text{ g food}}$$
$$= \frac{(b) (4)}{(4)} \text{ ppb}$$

$$\text{DC} = \text{CF} \times \langle M \rangle = 0.02 \times \frac{(b) (4)}{(4)} \text{ ppb} = \frac{(b) (4)}{(4)} \text{ ppb}$$

$$\text{EDI} = \frac{(b) (4)}{(4)} \text{ ppb} \times 3 \text{ kg/p/d} = \frac{(b) (4)}{(4)} \text{ } \mu\text{g/p/d}$$

The LMWO exposure was calculated using only the TNE in 95% EtOH. This value is conservative considering: 1) fluorinated compounds were not detected above the calibration limits in the 10% ethanol TNE experiment; 2) the extractions were conducted on the FCS and not a polymer containing the FCS; and 3) less LMWO were detected in the SEC of the FCS as described in Attachment 5. Thus, the DC of $\frac{(b) (4)}{(4)}$ pb and EDI of $\frac{(b) (4)}{(4)}$ $\mu\text{g/p/d}$ for the LMWO are conservative.

(b) (4)

Cumulative Exposure

The current cumulative DC (CDC) for HFP/VDF copolymers (CAS Reg. No. 9011-17-0) is 5.7 ppb, corresponding to a cumulative EDI (CEDI) of 0.017 mg/p/d.^{12,13} The LMWO of the subject

¹¹ Chemistry Memorandum concerning FCN 1121, dated 12/1/12, R. Costantino to A. Chang. In FCN 1121 FDA used the CF for all polymers of 0.4, which does not include the use of the additive in polymer coatings for metal substrates or paper. FDA then utilized market information that demonstrates that only 4.2 % of polymers utilized perfluorinated processing aids ($0.4 \times 4.2\% = \sim 0.02$).

¹² Memorandum concerning cumulative exposure estimates for vinylidene fluoride-hexafluoropropene copolymers, vinylidene fluoride, and hexafluoropropene, dated 2/29/00, R. A. Bailey to M. Cheeseman.

FCS are structurally similar to the LMWO from other HFP/VDF copolymers. There is no increase in the cumulative exposure to HFP/VDF copolymers as a result of this notification. The exposure to VDF and HFP monomers are expected to be “essentially zero.”

Notification Language

The language contained in the acknowledgement letter dated February 19, 2013 is adequate.

Summary

We have no comments.

Jeannie Jeong-Im, Ph.D.

HFS-275 (R/F)

HFS-275:JJeong-Im:240-402-1228:FCN1255_c_memo.pdf:JJJ:3/12/13

Init:KHatwell:3/15/13

Final:JJJ:3/18/13

¹³ There was no increase in the cumulative to HFP/VDF copolymers as a result of FCN 736.



Memorandum

Date: March 21, 2013

From: Toxicology Group 2, Division of Food Contact Notifications (DFCN)
Dan D Levy, Ph.D. (HFS-275)

Subject: Toxicology Review of **FCN 001255**: Copolymer of vinylidene fluoride (VDF)¹ and hexafluoropropene (HFP) for use in all polymers in contact with all food types and temperature conditions of use A through H. Submission dated December 10, 2012 as amended on by the notifier on 1/31/13.

To: Regulatory Group 2, DFCN
Attn: Kenneth McAdams

FOOD CONTACT NOTIFICATION (FCN) 001255

Intertek
1060 Holland Drive Suite G
Boca Raton, Florida 33487
On behalf of:

Dyneon, A 3M Co.l,
3M Center, Building 236-1B-10
St. Paul, Minnesota 55144.
T: 651-737 8557
F: 651-737-9909.

I. RELATED DOCUMENTS

FCN 000736: Dyneon LLC through Ciba Expert Services for the use of 1-Propene 1,1,2,3,3,3-hexafluoro-polymer with 1,1-difluoroethene (CAS# 901 1-17-0) as a polymer processing aid at levels not to exceed 0.1% all polymers in contact with all food types and under Temperature Conditions of Use A through H, as described in 21 CFR 176.170. *Effective October 26, 2007.*

FCN 000260: Dyneon LLC through Keller and Heckmann for the use of tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymers as a processing additive at levels up to 2000 parts per million (ppm) for polyolefins for use in contact with food under Conditions of Use B through H and . in accordance with food additive regulations and effective notifications which incorporate by reference materials cleared in 21 CFR 177.1520 *Effective October 3, 2002.*

FAP 6B3902 3M Company petitioned to allow elastomeric VDF-HFP copolymer as a processing aid for olefin polymers. 21 CFR 177.1520 published in FR 12/1/1986

FAP 9B4169: Pennwalt Corporation petitioned to allow Poly(VDF-HFP) copolymer (CAS No. 901 1-1 7-0) resins as adjuvants in olefin polymers. Modified 21 CFR 177.1520 increase the

¹ Abbreviations used in this document: HFP, hexafluoropropene; VDF, vinylidene fluoride; LMWO low molecular weight oligomers

weight percent of the copolymer used in olefin polymers and to provide for VDF monopolymer.
Published in FR 5/9/1990

FAP 9B4129 3M Company petitioned for revisions of 177.1520 be amended with revised specifications for fluorine content and mooney viscosity and to modify use conditions to increase the level permitted from 0.1 to 0.2 % and to allow use in a wider variety of methods of producing olefin articles. New exposure calculations but no new toxicology data or information submitted.
Published in FR 5/3/1990

FAP 9B4154 3M company petitioned for ethylene-vinyl acetate copolymers modified to allow VDP and HFP co-polymers containing 85-71 percent fluorine and having a Mooney viscosity of at least 28 for use as a processing aid at a level not to exceed 0.2 percent by weight of elthylene-vinylacetete copoloymers. CFR 177.1350 published 5/3/90

FAP 5B1794: E I Dupont De Nemours & Co. Rubber articles intended for repeated use. 21 CFR 177.2600. FR January 9, 1968 Safety based on presumed lack of migration and no specific safety data.

FCN 001255: Chemistry Review Memorandum, Jeong-Im/McAdams 3/18/13
Environmental Review Memorandum, Lindheimer/McAdams 2/20/13.

II. INTRODUCTION

Dyneon, a 3M Company, through Intertek, has submitted this notification (FCN) for a copolymer of vinylidene fluoride (VDF; a.k.a. 1,1- difluoroethene, 60 wt.-% or 80 mole-%) and hexafluoropropene (HFP, 40 wt.-% or 20 mole-%) (CAS Reg. No. 9011-17-0) as a process aid at levels up to 2000 ppm in all polymers (excluding metal and paper coatings) in contact with all food types. Polymers containing the FCS are expected to be used in contact with all food types and under temperature conditions of use A through H, as described in CFSAN's website at [http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm109358.h](http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm109358.htm)
[tm](http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm109358.htm). This notification seeks to expand the use conditions of this polymer by removing the limitations on the types of polymers in which the FCS will be used and by adding use condition A (High temperature heat-sterilized (e.g., over 212 deg. F))

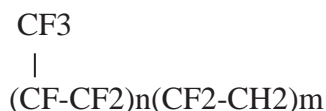
III. IDENTITY OF FOOD CONTACT SUBSTANCE (FCS)

CAS Name: 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene

CAS Registry Number: 9011-17-0

Trade or Common Names: None listed in this notification

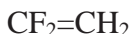
Other Names: 1,1,2,3,3,3-hexafloropropylene, polymer with vinylidene fluoride; HFP/VDF/
Structure:



where m = 60 weight-% (78 mole-%) and n = 40 weight.-% (22 mole-%)

The FCS is a random copolymer with the above stated ratios of the two monomers:

Vinylidene fluoride (VDF) CAS Registry Number 75-38-7



Hexachloropropene (HFP) CAS Registry Number 116-15-4



V. EXPOSURE ESTIMATES

The notifier conducted migration studies using 95% and 10% ethanol for extraction. No fluoropolymer was detected using 10% ethanol. Chemistry calculated exposure of Low Molecular Weight Oligomers (LMWO <2500 Daltons) conservatively to result in a dietary concentration of (b) ppb resulting in an estimated daily intake of (b) µg/p/d. HFP/VDF are already regulated and Chemistry states that the current cumulative dietary concentration of 5.7 ppb, corresponding to a cumulative estimated daily intake of 17 µg/p/d will not increase as a result of this notification. Chemistry states that exposure to VDF and HFP monomers to be “essentially zero”.

VI. TOXICOLOGY

The notifier addressed the safety of the monomers and other impurities of the FCS in a safety narrative (SN) in the notification (Attachment 14).

A. The FCS: copolymer of VDF and HFP (high molecular weight)

The copolymer has several regulatory uses². Searches through OFAS databases by this reviewer found the polymers with the same monomers and similar but not identical specifications, manufacturing and use conditions described in petitions FAP 6B3902, FAP 9B4169, FAP 5B1794, FAP 9B415421 which resulted in the regulations cited above. The same search identified less similar copolymers in FCN 260 and FCN 736 (the FCS used in FCN 260 contained tetrafluoroethylene as a third monomer whereas the FCS for FCN 736 contained the same monomers but a brominated branching aid and both FCNs described different specifications and processing aids not described in the current notification. Data, information and FDA Toxicology memoranda for these notifications and petitions and relevant published literature were reviewed. The data, information and toxicology comments relevant to the FCS, including contaminants and processing aids, are summarized here and in the following sections.

FAP 6B3902 contains a report of a GLP single dose acute toxicity (“LD-50”) study of the entire polymer which had been ground up and suspended in cottonseed oil. Review of the report and related material by the Additives Evaluation Branch resulted in a recommendation that the proposal was suitable for regulation (K.P. Misra to V Anand 7/17/1986)

This reviewer surveyed published literature by reviewing Pubmed, DART, TOXLINE, IRIS and GENETOX with particular focus on the period after the 2007 submission of FCN 000736 and found no published information relevant to the safety of the polymer other than the studies of the monomers as described below.

² 21 CFR 177.1350, 177.1520 & 177.2600

B. LMWO (MW<2,500 Daltons) of the FCS

The notifier states that toxicity testing is not available for oligomers. The notifier states that the safety of the oligomers is a function of the low DC and the lack of toxicity of the monomers, together with an evaluation conducted using the open source TOXTREE³ model. The evaluation was not provided but was said to indicate lack of structural alerts for mutagenicity or carcinogenicity.

FCN 260 contained data from a bacterial mutagenicity test of two ethanol extracts of that FCS. This extract would have LMWOs that are different from those extractable from the current FCS due to the use of a third monomer not used in the current FCS. However, because some of the oligomers are likely to have some polymer termini similar to those in the current FCS and those termini are the most likely source of toxicity, a negative finding in that study is relevant to the safety of the current FCS. The toxicology memorandum (Twaroski/Gilliam, 10/01/2002) indicated that extracts of the polymer tested were reported negative in the bacterial mutagenicity assay, that review of the report by K. Sullivan and K. Altshuler at ICF under contract to FDA resulted in concurrence by the reviewers with the conclusions of the report authors, and that since the oligomers of that FCS did not induce genetic damage under the conditions tested and since no information was found indicating toxic or carcinogenic activity for this compound and that Toxicology had no concerns regarding that FCS of its intended use under its associated exposure as described in FCN 260.

There might be some concern about potential carcinogenicity of the LMWO oligomers due to the genotoxicity of the monomer HFP and the carcinogenicity of tetrafluoroethene, a structural analog of HFP (see HFP section below). However, there is data on analogs of both of these compounds that lack the double bond (i.e. various isomers of hexafluoropropane and of tetrafluoroethane, the “saturated analogs”). Genetox studies on the saturated analogs are uniformly negative. Thus while HFP is geneotoxic, incorporation of HFP into a monomer converts it to a form which is closer to the non-genotoxic hexafluoropropane and tetrafluoroethane than to the original monomer. Thus it is unlikely that the genotoxic properties of HFP monomer are relevant to a safety assessment of the oligomers or other polymers made from the monomer. As a result, Toxicology has no questions about the safety of the LMWO under the exposures conditions for this FCS.

C. VDF monomer

Data and Information in the Notification:

The notifier cites and relies heavily on a toxicological assessment of VDF in a Screening Information Dataset (SIDS) Initial Assessment Report published in 2001. The report was prepared by the US EPA and the American Chemistry Council and was produced under the auspices of the OECD SIDS program for assessment of high production volume industrial chemicals. The report is included as attachment 14-1 to the notification.

The notifier describes the Genetic Toxicology information contained in the SIDS report. It describes

³ R. Benigni, R., C. Bossa, N. Jeliaskova, T. Netzeva and A. Worth. The Benigni / Bossa rulebase for mutagenicity and carcinogenicity – a module of Toxtree. 2008. 68 pp. EUR – Scientific and Technical Research series – ISSN 1018-5593.

an “Ames” (bacterial mutagenicity test) (Russel, 1979)⁴ in which gas phase exposure to 4 *S. typhimurium* strains were exposed to gas phase VDF. A 2.6 fold increase in stain TA 1535 in the presence of metabolic activation and at concentration greater than 10% VDF was described as the only significant increase. A second Ames study (Bartsch, 1979), also in gas phase and also at high concentrations reported non significant increases in the presence of metabolic activation.

An HGPRT test in Chinese hamster ovary cells (CHO) exposed in gas phase reported in 1986 was described. The test report was said to conclude that no mutant increase was observed at any concentration (Rickard, 1986)

A separate report of a chromosome aberrations study in CHO cells (Rickard 1986) following exposure in gas phase was said to report no toxicity or chromosome aberrations at any concentration.

Mutagenic effects were said to be found in other *in vitro*-tests but these results were discounted because the tests were characterized by the notifier and by the SIDS Assessment Report as “older” and “not as adequately detailed” and “not as reliable” as the newer studies.

In vivo micronucleus test in male and female mice was said to show that VDF was not toxic to bone marrow nor to increase the incidence of micronuclei at any of the gas phase concentrations tested (Hodson-Walker, 1988). A Sex Linked Recessive Lethal test in *D. melanogaster* was said not to demonstrate a significant difference in lethality of progeny between exposed and non-exposed males and thus reported not to be mutagenic to the X chromosome in that test (Serneau, 1988).

The SIDS report states that from all the presented tests it can be concluded the VDF does not significantly interfere with the genome of organism. It concludes that the marginal but positive findings in the Ames test may indicate that some metabolite of VDF “may interfere directly or indirectly with the genomic integrity of some selected procaryotic (*sic*) organisms. The notifier concludes that “[o]verall the results suggest that VDF does not present a genotoxic hazard to man.

The SIDS report also describes two carcinogenicity bioassays in rats and mice, respectively. In Sprague Dawley rats inhaling VDF at concentration up to 10,000 ppm for 104 weeks there was decreased food consumption and changes in relative organ weights but no treatment related effects on the incidence of benign or malignant tumors, total number of tumors or total number of tumor bearing animals (Arts 1991). In the mouse study treatment using inhaled concentrations up to 10,000 ppm produced no toxicity or carcinogenicity (Newton 1991). The SIDS report also describes a one year carcinogenicity study in Sprague-Dawley rats gavaged with 0, 4.12 and 8.25 mg/kg BW VDF in corn oil over 52 weeks reported lipoma and liposarcoms (Maltoni 1979). An EPA evaluation was said to note significant deviation from currently prescribed guidelines, noted that the study was not reported in great detail which impedes proper result interpretation and concludes that the study was reported in insufficient detail for proper evaluation.

The notifier also describes the SIDS report evaluation of subchronic inhalation studies in rats and mice. The LOEC of 500 ppm (13,000 mg/m³) was identified in both species based on body, organ weight and clinical chemistry changes in the absence of histopathological changes. A NOEC of 250 ppm was identified in rats. Toxicity occurred in kidney, spleen and testes. The notifier also evaluated summary reports of teratogenic and embryo-fetal toxicity effects in developmental toxicity studies in rats exposed to top to 10,000 ppm during gestation days 6-15 concluding that the NOEL for reproductive effects is >7000 ppm in rats.

⁴ Full citations are contained in the notification. None of these reports have been submitted to FDA for evaluation in this notification or in previous notifications or petitions. With the exception of Bartsch 1979, the reports are all laboratory reports that do not appear to have been published.

The notifier concludes that the chronic toxicity and carcinogenicity studies are the key studies for the evaluation of VDF and quotes the conclusions of the SIDS evaluation: “These two studies were performed according to currently accepted guidelines and GLP standards. Since they are lifetime studies which are reported in great detail, they were considered as the most reliable representation of the toxicological effects of VDF in animals.” In view of the available toxicity data and the very low dietary exposures ((b) (4) ppt) related to the present FCN, the risk of adverse human health effects is considered by the notifier to be negligible.

Previous evaluations by FDA.

Evaluation by this reviewer of the above cited Food Additive Petitions submitted for VDV/HFP polymers determined that toxicity of the monomers was not addressed by petitioners or during FDA review. FCN 260 contained brief descriptions of the genetic toxicology and the carcinogenicity studies described in the SIDS review. Toxicology reviewed that information (M.L. Tworoski to V. Gilliam, October 1, 2002), as well as two IARC reviews that found inadequate evidence for carcinogenicity of VDF based on review of the oral study described above. Toxicology considered that several mutagenicity assays showed predominantly negative findings and the low (<50 ppt) exposure, concluding that there is no positive indication of carcinogenicity by oral exposure for this compound based on the information currently available. FCN 736 incorporated by reference the genetic toxicology information in FCN 260 and cited the conclusions of safety in that FCN. Toxicology considered and concurred with that conclusion (A.O. Adejoke to V. Gilliam October 22, 2007)

Additional available data and information.

This reviewer has searched PUBMED and TOXLINE and found that the SIDS evaluation contained a thorough evaluation of those and other sources of data on the compound up to the time of its publication. This reviewer also found no references relative to the safety of VDP published after the SIDS evaluation was written. Most toxicology information regarding this compound was collected via gas phase/inhalation exposure due to concerns about its toxicity to workers during manufacturing operations. While extrapolation from inhalation to oral exposure introduces some uncertainty, the lack of reproductive toxicity, the relative lack of toxicity including carcinogenicity in two well conducted chronic inhalation studies, and the lack of activity in both *in vitro* and *in vivo* genetic toxicity assays gives a high degree of confidence in the notifier’s conclusion of safety for low level exposure to the monomers or monomer analogues at the ends of LMWO of the FCS.

Conclusion: VDP has been tested and is not genotoxic nor is it a rodent carcinogen under the conditions of the tests. Chemistry states that exposure to this monomer will be ‘essentially zero’. Toxicology has no questions about the safety of the monomer under the exposure conditions for this FCS.

D. HFP monomer

Data and Information in the Notification

The notification contains portions of a Chemical Safety Report (CSR) for HFP. The report is dated August 17, 2010 and was said to have been submitted to the European Chemicals Agency (ECHA) as

part of the ongoing REACH initiative. The submitter is not identified in the portions of the report supplied with the notification and ECHA does not make CSRs public.

The notifier attached test reports for two mammalian cell mutagenicity studies in which Chinese Hamster ovary cells (CHO) were exposed to HFP in the gas phase and evaluated for mutation in the HPRT gene locus. The test report concludes that the test article did not induce an increase mutations at the target locus under the conditions of the test. At least 4 concentrations were tested with and without metabolic activation and at the highest concentrations used the treatment was cytotoxic to the cells. The notifier cites the conclusions of the test report that there were no significant increases in mutant frequency at any of the HFP concentrations tested and no positive linear dose-response relationships. HFP was subsequently re-tested with metabolic activation by the same laboratory. The test report explains that the repeat test was conducted because some of the primary data from the first experiment was not found during the GLP quality control review. The notifier cites the conclusion of the test report that there were no significant increases in mutant frequency at any of the HFP concentrations tested and no positive linear dose-response relationships and concludes that HFP is not mutagenic in the CHO/HPRT Gene Mutation Assay when tested with and without an activation system. An EPA evaluation of the test report included in the notification concludes that the result is equivocal or that the test article is at most a weak clastogen.

The notifier describes a mouse micronucleus assay of HFP in male and female mice. A copy of the test report is not included in the notification. According to the notification, “[t]his study showed weak positive results.” The notifier describes a supplemental test report for this mouse micronucleus assay and included a copy of the supplemental test report in the notification. In the supplemental test, slides from the original test were rescored such that, where possible, a total of 10,000 polychromatic erythrocytes (PCEs) obtained from bone marrow of the male mice were scored per dose group instead of the 1,000 PCEs scored in the initial study. The notifier cites the conclusions of the authors of the test report that there were statistically significant increases in micronucleated PCEs in the high dose males at all three sampling times (24, 48 and 72 hrs post exposure) and their conclusion that HFP induced micronuclei in bone marrow cells of male mice. The notifier attached a memorandum from EPA containing a review of this micronucleus study. The notifier reports the observation of the author of the EPA memorandum that the frequencies of micronucleated PCEs in the HFP-treated males are within the range of spontaneous frequencies in the literature....” and goes on to quote the conclusion drawn by the author of the EPA memorandum that HFP is at most “a weak mutagen in the micronucleus assay ...[and that]... micronucleus data on HFP do not contribute to the weight of evidence that it may be a potential human or animal carcinogen.”

The notification describes an unpublished dominant lethal assay in rats uncovered using a search of the TOXNET database. The notification outlines the conditions of the study, indicating that 20 male Sprague Dawley rats received whole body inhalation exposure prior to mating with female rats. The treatment was described as having no adverse effects on male rat mortality or fertility or mating indices nor on pregnancy rates or pre- or post-implantation in the dams. The notifier concludes that the treatment did not increase the frequency of dominant lethal mutations, indicating that the test compound was not mutagenic to germ cells in the male rat under the conditions of the assay.

The notification also cites from the ECHA CSR a table indicating that the compound was not mutagenic in a bacterial reverse mutation assay conducted in 2010 and an unscheduled DHA synthesis assay in the liver of male rats.

The notification includes a description from the ECHA CSR of 90 day inhalation studies with mice and rats. The notification does not include a copy of the test reports. Four groups of 25 male and 25

female Crl: CD-1(ICR) mice were exposed to 1, 10, 50 or 150 ppm HFP for 6 hours per day, for 5 days per week. The no-observed effect level was 10 ppm both with and without a 28 day recovery period. Toxicity noted at higher concentrations included a variety of kidney lesions such as tubular epithelial necrosis and blue skin color. In rats subjected to the same exposure the males at the 150 ppm dose were described as exhibiting a low mean lymphocyte count which was not observed following 28 days of recovery nor was it associated with additional hematology or pathology findings. The notification, citing the CSR summary, describes as non-adverse or non-biologically significant urinary changes (increased fluoride, increased volume, decreased osmolality) as well as increased water consumption and serum sodium in males exposed to 50 or 150 ppm HFP.

In addition to the studies cited by the notifier, the ECHA CSR report describes several acute toxicity studies conducted in rodents and a study of absorption, metabolism, distribution and elimination in female rats. No studies in humans and chronic or carcinogenicity studies in animals were located or described.

The notifier concludes that “[t]he weight of available evidence supports the conclusion that HFP has a low potential for genotoxic effects. In view of the available toxicity data and the low dietary exposures (b) (4) related to the present FCN, the risk of adverse human health effects is considered negligible.

Previous evaluations by FDA.

Evaluation of the above cited Food Additive Petitions submitted for VDV/HFP polymers by this reviewer determined that toxicity of the monomers was not addressed by petitioners or during FDA review.

FCN 260 contained a literature search of the genetic toxicology studies described in the literature, concluding that HFP was negative in the Ames, CHO/HPRT and dominant lethal inhalation studies described above and that it was weakly positive in the mouse micronucleus assay described above and positive for chromosomal aberrations under conditions of metabolic activations in a study not addressed in FCN 1255. Toxicology reviewed that information (M.L. Tworoski to V Gilliam, October 1, 2002) and had no questions “based on [the] associated exposure of “essentially zero”. FCN 736 incorporated by reference the genetic toxicology information in FCN 260 and cited the conclusions of safety in that FCN. Toxicology considered and concurred with that conclusion (A.O. Adejoke to V. Gilliam 2007 October 22, 2007)

Additional available data and information.

This reviewer has searched PUBMED and TOXLINE and found that the notification and the ECHA report failed to describe three relevant reports of *in vitro* chromosome aberrations studies in CHO cells which found HFP to increase the number of cells with chromosome aberrations under conditions of metabolic activation. These reports are described in TOXLINE and were mentioned in FCN 260 and thus considered previously by FDA in the context of the use of this monomer in similar polymers. This literature search also uncovered an evaluation of HFP by the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC)⁵. The ECETOC report describes the studies discussed above, including the *in vitro* chromosome aberrations study as well as a bacterial mutagenicity study

⁵ Hexafluoropropylene (CAS No. 116-15-4) JACC Report No. 48 (Brussels, 2005)

conducted on cysteine conjugates of HFP. The conjugates were studied based on their role as the principle metabolites of HFP and concern based on their presence in urine and possible role in nephrotoxicity, the most prominent toxicological concern in the subchronic inhalation studies. An examination of the study⁶ by this reviewer indicates that unlike hexachlorobutadiene, trichloroethylene and perchloroethylene, synthesized cysteine conjugates of tetrafluoroethylene and HFP were not mutagenic in the Ames assay with or without metabolic activation by rat kidney S9. There are no reports of chronic toxicity studies, including carcinogenicity studies, for HFP. The ECETOC report notes the similarities in structure, metabolism and nephrotoxicity between HFP and tetrafluoroethylene, that the latter compound exhibited chronic toxicity (including cancer) under relatively high exposure conditions (≥ 156 ppm) and suggests that the relationships between these two compounds might indicate the possibility of carcinogenicity. The carcinogenicity of tetrafluoroethylene has been previously considered by DFCN and unit cancer risks calculated to be 0.0492 mg/kg-bw/day⁷.

Review of an update to the ECETOC report on tetrafluoroethylene⁸ indicates cause for caution in applying these results to an evaluation of dietary exposure HFP. The nephrotoxicity and the carcinogenicity of tetrafluoroethylene were attributed to glutathione and cysteine conjugates formed through metabolism in the kidney and livers of both rats and mice. In addition, the positive genetic toxicity findings for HFP (a clear response of clastogenicity in the presence of metabolic activation in vitro reinforced by a weak clastogenic response in vivo) were not found when tetrafluoroethylene was tested using the in vitro chromosome aberrations assay (by the same laboratory that conducted that test for HFP) or using the mouse micronucleus assay (when tested by the National Toxicology Program), suggesting that the carcinogenicity of tetrafluoroethylene is not related to the genotoxicity of HFP. Thus, significant exposure to the HFP monomer would require a detailed safety analysis. However, Chemistry as reviewed the data and information presented regarding exposure to HFP from use of the FCS and concluded that the exposure would be “essentially zero”. In the absence of significant exposure Toxicology has no questions or concerns regarding HFP monomer in this FCS.

A second potential toxicological concern might arise from polymerized HFP monomer in the FCS, particularly in LMWO that migrate into food. The form of this monomer, once polymerized in the FCS, is chemically modified by, among other things, saturation of the double bond⁹. Thus an appropriate model compound for assessing the genotoxicity of polymerized HFP is hexafluoropropane, a compound lacking the double bond. Genetic toxicology test data for two isomers of this compound are available in the published literature. 1,1,1,3,3,3-hexafluoropropane (CAS# 690-39-1), and 1,1,1,2,3,3-hexachloropropane (CAS 431-63-0) were studied under OECD and EPA GLP and test guidelines by the Dupont Haskell laboratories and the results published¹⁰. While the journal article does not contain the detail that would be present in a full laboratory report, data tables are presented for a bacterial mutagenicity study using *Salmonella typhimurium* strains TA97, 98, 100 and 1535 and *E. coli* WP2uvrA (pKM101), a study of induction of chromosome aberrations in lymphocytes freshly obtained from peripheral blood of human volunteers, and a study of induction of micronuclei in erythrocytes obtained from bone marrow of male and female mice. In each case the

⁶ T. Green and J Odum Structure/activity studies of the nephrotoxic and mutagenic action of cysteine conjugates of chloro- and fluoroalkenes. Chem Biol Interactions 54: 15-31, 1985

⁷ Unit Cancer Risk calculation from Michelle Twoarowski, DFCN to file FCN 260 through David Hattan, April 16, 2003.

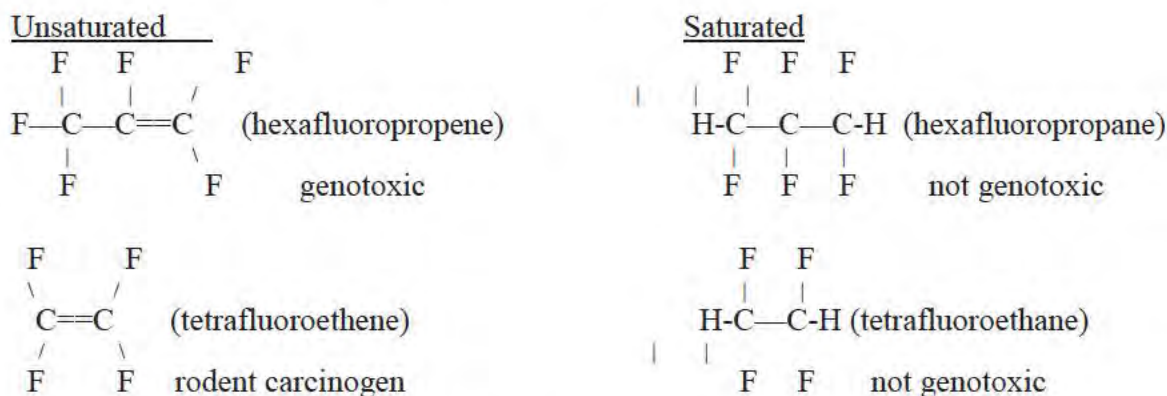
⁸ Corrigendum to JACC no 42 issued 15, December 2004 and Tetrafluoroethylene (CAS No. 116-14-3) JACC Report No. 42 (Brussels, 2003)

⁹ Personal communication Jeannie H. Jeong-Im to Dan D. Levy 13 March 2013.

¹⁰ W.J. Brock, DP Kelly, SM Munley, KS Bentley, KM McGown and R Valentine. Inhalation Toxicity and Genotoxicity of Hydrofluorocarbon (HFC)-236fa and HFC 236ea. International Journal of Toxicology 19: 69-83 (2000).

test articles were administered in gas phase. Summary data presented in tables in the publication support the conclusions of the authors that the test articles did not induce a positive response in any of the three genotox assays. The results of these reports in which the articles were tested under GLP using contemporary test guidelines strongly support the hypothesis that elimination of the double bond, which occurs during polymerization of HFP, reduces the potential for genotoxicity as measured by standard genotoxicity assays. Both isomers of tetrafluoroethane (1,1,2,2-also called FC134 and 1,1,1,2-also called FC134a) have also been tested for genotoxicity. A bacterial mutagenesis assay using *Salmonella typhimurium* TA1535, TA1538, TA98 and TA100 has been published¹¹. The bacteria were exposed to test article in the gas phase both with and without metabolic activation using an S9 mix prepared from livers of Arochlor 1254-induced male Sprague-Dawley rats. Details of the data are absent but the compounds were said to be non-mutagenic. No other relevant literature was found in Pubmed or Toxline and neither compound was found in searches of IRIS, GENETOX, CCRIS or CERES databases.

HFP and analogues which lack the double bond (saturated analogues):



Conclusion: There is evidence that HFP is genotoxic. Tetrafluoroethene, a close analogue, is a rodent carcinogen. Chemistry states that exposure to HFP monomer is “essentially zero”. Toxicology has no questions about the safety of the monomer under the exposure conditions for this FCS.

E. Catalysts and processing aids

- [REDACTED] (b) (4). Chemistry notes that this potential impurity will be removed during the wash step of manufacturing. .
- (b) (4) [REDACTED]
[REDACTED] Chemistry notes that (b) (4) and will be removed in manufacturing during the drying step..
- (b) (4), used as a (b) (4), is regulated under (b) (4) as a

¹¹ E. Longstaff, M Robinson, C. Bradbrook, J.A. Styles and I.F.H. Purchase. Genotoxicity and Carcinogenicity of Fluorocarbons: Assessment by Short-Term in Vitro Tests and Chronic Exposure in Rats Toxicology and Applied Pharmacology 72: 15-3 1 (1984)

¹² (b) (4)

(b) (4)

. Chemistry notes that it would be expected to
which would be removed during the wash step.

(b) (4)

-

(b) (4)

are mentioned in the original FCN. However, the January 31, 2013 response to the deficiency letter sent by DFCN on January 22 clarifies that these are added to polymers along with the FCS and therefore are not part of the FCS which is the subject of this notification. Each of these ingredients can be appropriate for incorporation into an FCS under suitable conditions so their mention in this notification does not raise any safety concerns.

Toxicology has no questions about catalysts and processing aids used to manufacture the FCS.

CONCLUSION(S)

Dyneon, a 3M Company, through Intertek, has notified for a copolymer of vinylidene fluoride and hexafluoropropene (CAS Reg. No. 9011-17-0) as a process aid at levels up to 2000 ppm in all polymers (excluding metal and paper coatings) in contact with all food types conditions of use A through H. Toxicology has no questions regarding the safety of the proposed FCS based on the exposure estimates and the toxicological evaluation of the available data as detailed in this memorandum.

Dan D. Levy, Ph.D.

HFS-275:DDLevy: FCN1255 Tox memo.pdf:DDL: 3/20/13

Init: YGu: 3/21/13

Final: DDL: 3/21/13



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum
Food and Drug Administration
College Park, MD 20740

Date: February 20, 2013

From: Biologist, Regulatory Team 2, Division of Biotechnology and GRAS Notice Review (HFS-255)

Subject: FCN No. 1255 - Copolymer of vinylidene fluoride (VDF) (CAS No. 75-38-7) and hexafluoropropene (HFP) (CAS Reg. No. 116-15-4) as identified by CAS Reg. No. 9011-17-0, intended for use as a processing aid at levels up to 2,000 ppm by weight in all polymers (excluding polymers used in metal and paper coatings). The FCS is intended to contact all food types under Conditions of Use A through H.

Notifier: Intertek c/o 3M

To: Kenneth McAdams, Division of Food Contact Notifications (HFS-275)

Through: Annette M. McCarthy, Ph.D, Senior Science and Policy Staff Am^c

We have reviewed the claim of categorical exclusion for the above referenced notification and have concluded that the categorical exclusion is warranted. The claim of categorical exclusion cites the section, 21 CFR 25.32 (i), under which categorical exclusion is warranted, states compliance with the categorical exclusion criteria, and states that no extraordinary circumstances exist that require the submission of an environmental assessment.

Please let us know if there is any change in the identity or use of the food-contact substance.

A handwritten signature in cursive script, reading "Talia A. Lindheimer".

Talia A. Lindheimer

cc:

HFS-255 Lindheimer
File: FCN No. 1255



Memorandum

Date: December 1, 2011

From: Division of Food Contact Notifications
Chemistry Team II

Subject: FCN 001121 – 3M/Intertek Regulatory Services. Submissions dated 9-14-11 (received 9-19-11) and e-mail dated 10-30-11 (received 11-1-11). Use of tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymers as a processing aid in all polymers.

To: Division of Food Contact Notifications
Regulatory Team I
Attn: A.Chang, Ph.D.

Intertek Regulatory Services, on behalf of 3M, has submitted food contact notification 1121 (FCN 001121) to expand their use of tetrafluoroethylene (TFE)-hexafluoropropylene (HFP)-vinylidene fluoride (VDF) copolymers (FCS) as a processing aid in all polymers (excluding polymers used in metal and paper coatings) in contact with all food types under conditions of use A through H. The FCS may be used at levels up to 2000 ppm in the finished food-contact polymer.

Currently, the FCS is regulated under 21 CFR 177.2600 (Rubber articles intended for repeated use) as a result of an indirect food additive petition, FAP 5B1794. The FCS is also the subject of two FCNs (*i.e.*, FCNs 127 and 260). FCN 127, submitted by Ausimont SPA, provides for the use of the FCS as a base polymer to be used as a component of gaskets and seals in food processing equipment. FCN 260, submitted by Dyneon, LLC (a subsidiary of 3M), provides for the use of the FCS as a processing aid for food-contact polyolefins at levels up to 2000 ppm. Polyolefins containing the FCS may be used in contact with all food types under conditions of use B through H.

The identity information is incorporated by reference from the notifier's previous FCN concerning this FCS and is summarized below.

Identity

CAS Name: 1-propene, 1,1,2,3,3,3-hexafluoro, polymer with 1,1-difluoroethene and 1,1,2,2-tetrafluoroethene

Other Names: ethylene, tetrafluoro-, polymer with 1,1-difluoroethylene and hexafluoro-propene

tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymer

tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride terpolymer

Trade Names: 3M Dynamar (b) (4)

(b) (4)

Structure: (b) (4)

where n = (b) (4)

(b) (4)

An infrared spectrum, which supports the structure of the FCS, is provided in Attachment II of FCN 260.

Manufacture

(b) (4)

Impurities

Residual levels of starting monomers (*i.e.*, tetrafluoroethylene (TFE; bp -76° C), hexafluoropropylene (HFP; bp -30° C), and vinylidene fluoride (VDF; bp -86° C) and chain transfer agent (*i.e.*, (b) (4) (b) (4)) in the FCS are not expected, since all four compounds are gases at room temperature and any remaining TFE, HFP, or VDF would be removed during the extensive degassing and drying of the FCS during its manufacture. In addition, the buffers (b) (4) are highly water soluble and are expected to be removed during the washing of the FCS with water.

The level of residual (b) (4) in the FCS is (b) (4) as determined using high-pressure liquid chromatography (HPLC) analysis with mass spectrometry (MS) detection. The HPLC/MS method and results are described in Attachment 3 of the FCN.

Use/Technical Effect

The FCS is intended to be used as processing aid for all polymers (excluding polymer used in metal and paper coatings) in contact with all food types under conditions of use A through H. The FCS is requested for use at levels up to 2000 ppm in food-contact polymers.

The proposed use of the FCS will improve polymer extrusion. Specifically, the FCS will aid in the elimination of melt fracture and reduce die build-up. The notifier provided sufficient

data to support the improvement of polymer extrusion with levels up to 1000 ppm of the FCS (see Appendix IX of FCN 260). Graphs demonstrating the increased productivity in blow molding of bottles, the reduction and/or elimination of external die build, the reduction in the formation of gels during blown film extrusion, and the improvement in surface and gloss of bottles (*i.e.*, the reduction of melt fracture) were presented and explained adequately.

It is doubtful, from the technical data presented, that there will be any improvement in desirable properties imparted to processed polymers by addition of the FCS beyond 1000 ppm. The use level of 2000 ppm is not adequately justified.

Migration Studies

The migration studies are presented in Section D and in Appendix X of FCN 260 and summarized in our chemistry memorandum dated 9-19-02 and below.

Test Plaques

The FCS (aka (b) (4)) was formulated into plaques with a thickness > 20 mils. The composition of the FCS is as follows: (b) (4) TFE, (b) (4) HFP, and (b) (4) VDF. The test sample met the specifications for the FCS with a melt flow index (MFI) between (b) (4). The specification for MFI of the FCS ranges from (b) (4). Thus, the test plaque represents the “worst-case” plaque.

Protocol

A single plaque (with a double sided surface area of 193 in²) was placed in a two-sided extraction cell capable of withstanding high pressures along with 100 mL of food simulant. This corresponds to a food simulant-to-surface area ratio of 2 mL/in². Migration conditions were as follows:²

10% ethanol: 212° F/240 h

95% ethanol: 212° F/240 h

Six migration samples were prepared for each food simulant. Triplicate samples were analyzed after 2 h and 240 h for total nonvolatile extractives (TNE) and chloroform-soluble extractives (CSE). Blank food simulants were prepared and treated in the same manner.

Analytical Method and Migration Results

The migration samples were evaporated to dryness using a steam bath followed by drying in an oven at 105° C to a constant weight to determine the TNE. A 50-mL portion of chloroform was then added to the TNE. The chloroform solution was warmed and filtered. The chloroform extraction was repeated. The extracts were combined and evaporated to dryness using a steam bath followed by drying in an oven until a constant weight was achieved to

² This migration protocol is more rigorous than we normally recommend for single-service articles for condition of use A.

determine the CSE.

The highest migration results (*i.e.*, after extraction at 212° F for 240 h) for the TNE and CSE of the FCS are presented in Table 2 below. The corrected TNE migration results will be used to determine the LMWO of the FCS.

Table 2. TNE and CSE Migration Results		
Food Simulant	Corrected TNE	Corrected CSE
10% ethanol	(b) (4)	
95% ethanol		

Exposure

Consumption Factor

Previously, the consumption factor (CF) used to estimate exposure to the low molecular weight oligomers (LMWO) of the FCS and its impurities was refined using global polymer market data, as described in FCN 260. Typically, only domestic market data are accepted by the Agency to refine CFs. Since the migration studies in FCN 260 were rigorous and global market data were accepted and used in our review of FCN 260, current global market data may be used to calculate a CF for the notifier proposed use of the FCS. Based on a conservative estimate that (b) of all polymers contain fluorinated processing aids (FPA),³ the revised CF for the FCS is calculated to be (b) (4)

To LMWO of the FCS

Exposure to the LMWO of the FCS from its proposed use in all polymers was calculated using the corrected TNE migration values obtained at 100° C for 240 hours using 10% and 95% ethanol (as described in FCN 260 and presented previously in Table 2) and assuming that 10 g of food contacts each in² of polymer and the use level of the FCS is 2000 ppm (or 0.2%). A sample calculation for the concentration in aqueous and acidic food ($\langle M_{10\% \text{ ethanol}} \rangle$) of the LMWO of the FCS is provided below.

$$\langle M_{10\% \text{ ethanol}} \rangle = (b) (4) = 7.4 \text{ ng LMWO/g food or } 7.4 \text{ ppb}$$

Similarly, the concentration in alcoholic and fatty foods ($\langle M_{95\% \text{ ethanol}} \rangle$) of the FCS was calculated and is tabulated below.

Table 3. $\langle M \rangle$ of the LMWO of the FCS		
Food Simulant	Migration	$\langle M \rangle$

(b) (4)

10% ethanol	(b) (4)
95% ethanol	

Using the <M>s (listed above), the refined CF of (b) (4), and the food-type distribution factors of 0.65 for aqueous and acidic foods (f_{aq+ac}) and of 0.35 for alcoholic and fatty foods (f_{al+fat}) from the general polymer category, the dietary concentration (DC) of the LMWO of the FCS would be:

$$DC = \frac{(b) (4)}{(b) (4)} = 0.37 \text{ ppb}$$

Based on a daily diet of 3000 g food/person/day, the estimated daily intake (EDI) of the LMWO of the FCS from its proposed use in all polymers is 1.1 µg/p/d.

To Impurities

Exposure to the starting monomers (*i.e.*, tetrafluoroethylene (TFE; bp -76° C), hexafluoropropylene (HFP; bp -30° C), and vinylidene fluoride (VDF; bp -86° C) and chain transfer agent (*i.e.*, (b) (4)) is not expected, since all four compounds are gases at room temperature and any remaining TFE, HFP, or VDF would be removed during the extensive degassing and drying of the FCS during its manufacture.

(b) (4)

Cumulative Exposure (CEDI)

The exposure to LMWO of the FCS from its effective use in polyolefins is subsumed by the exposure to LMWO of the FCS from its proposed used in all polymers. Exposure to LMWO

of the FCS from its currently regulated use in repeat-use rubber articles under §177.2600 cannot be determined since no data are provided in the original FAP 5B1794. However, an exposure estimate to LMWO of the FCS from its effective use in repeat-use seals and gaskets has been calculated to be 0.25 ppb in the diet (see our chemistry memorandum dated 6-4-01 concerning FCN 127). Since the exposure to LMWO of the FCS from its effective use in repeat-use seals/gaskets utilizes a CF of (b), we will assume that the exposure to the LMWO of the FCS from its regulated use in repeat-use rubber articles under §177.2600 is covered under the exposure to LMWO of the FCS from its effective repeat use in seals and gaskets. Therefore, the CEDI of the LMWO of the FCS would be 0.62 ppb in the diet or 1.9 µg/p/d.

Notification Language

The acknowledgment letter, as signed by chemistry on 10-12-11, is appropriate as written.

Summary

As mentioned above, the requested use level of 2000 ppm is not supported. Despite the fact that the calculated exposures are for a use level of 2000 ppm, the use level should be limited to 1000 ppm under conditions of use A, to be consistent with our policy of not allowing exposure to additives beyond a demonstrated technical effect level.

Roseann
M.
Costantino

Digitally signed by Roseann
M. Costantino
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
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Roseann M. Costantino, Ph.D.

HFS-275, R/F

HFS-275:RMCostantino:FCN 001121.docx:11-28-11, 12-5-11

R/DInit:MAAdams:12-5-11

Final:rmc:12-5-11



Memorandum

Date January 10th, 2012

From Division of Food Contact Notifications (DFCN)

Subject Toxicology Review of -"Tetrafluoroethylene (TFE)-Hexafluoropropylene (HFP)-Vinylidene Fluoride (VDF) Copolymers as a processing additive for all polymers"

To Anita Chang, Ph.D., CSO, Regulatory Group 2, DFCN

FCN 1121

**Dyneon / 3M Co.
3M Center, Building 236
Saint Paul, MN 55144**

I. INTRODUCTION

Dyneon / 3M Corporation submitted the current Notification to allow modification of the synthesis of the perfluoropolymer used in FCN 260 with a new fluorochemical (b) (4)

The manufacture of (b) (4) has been modified such that the (b) (4) (b) (4)
(b) (4)

Currently, the FCS is regulated under 21 CFR 177.2600 (Rubber articles intended for repeated use, FAP 5B1794). Related FCNs are listed below.

II. NOTIFICATION STATUS

SUBMITTED: September 19th, 2011

ACKNOWLEDGED: November 30th, 2011

III. INTENDED USE

Conditions of use A-H has been proposed to replace the original B-H designation.

The FCS may be used at levels up 2000 ppm in food-contact polymers.

IV. IDENTITY OF THE FOOD CONTACT SUBSTANCE

Chemical Abstracts Name: Ethylene, tetrafluoro-, polymer with 1, 1-difluoroethylene and hexafluoropropene

C.A.S. Registry # : 25190-89-0

Other Names: (See Attachment for structures)

Trade Name: Dynamar™ (b) (4)

V. RELATED NOTIFICATIONS / PETITIONS

FCN 127 (Ausimont), FCN 260, FCN 1065 (Crowell & Moring)

(b) (4)



VI. EXPOSURE ESTIMATES

Oligomers (FCS): The Notifier has computed the exposure estimates from FCN 260 obtaining an almost unchanged value, DC 0.50 ppb, versus 0.45 ppb in the FCN 260. FDA's chemist computed a lower number, **0.37 ppb** using standard use and consumption parameters.

Constituents and Impurities:

(b) (4)



VII.(a) TOXICOLOGY SUMMARY FOR THE FOOD CONTACT SUBSTANCE

1. - PNC (b) (4), cited in this FCN, included a new safety narrative, which refers to genotoxicity studies conducted on the polymer and submitted with FCN 260. The polymer is similar to other regulated (§ 177.2400) poly(tetrafluoroethylene) elastomers and presents no new toxicity concerns.

VII.(b) TOXICOLOGY SUMMARY FOR Constituents and Impurities

(b) (4)



(b) (4)



Date:

William L. Roth

2012.01.11

10:11:43 -05'00'

William L. Roth, Ph.D.

Init: Chingju W. Sheu, Ph.D. : 1/10/2012
attachments (references, study reviews)

References

(b) (4)



(b) (4)



(b) (4)



FDA FCN 1121 - Individual Toxicity Study Reviews

The unpublished studies listed under “References” have all undergone at least cursory reviews. The attachments which follow contain the individual study reviews completed by FDA or TDERs completed by Oak Ridge with secondary review by FDA.



DEPARTMENT OF HEALTH & HUMAN SERVICES

AD



Public Health Service
Food and Drug Administration

Memorandum

Date: June 20, 2012

From: Biologist, Regulatory Team 2, Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety (HFS-255)

Subject: FCN No. 1121 – Tetrafluoroethylene-hexafluoropropylene-
vinylidene fluoride copolymers as a processing additive for all
polymers (excluding polymers used in metal and paper coatings).

3M
3M Center, 236-1B-10
St. Paul, MN 55125

To: Division of Food Contact Notifications (HFS-275)

Attention: Anita Chang, Ph.D.

Through: Annette M. McCarthy, Ph.D., Lead Environmental Review Scientist, AM^c

This memo supercedes the memo dated November 15, 2011 which incorrectly referenced FCN 1126.

We have reviewed the claim of categorical exclusion for the above referenced notification and have concluded that the categorical exclusion is warranted. The claim of categorical exclusion cites the section, 21 *CFR* 25.32 (i), under which categorical exclusion is warranted, states compliance with the categorical exclusion criteria, and states that no extraordinary circumstances exist that require the submission of an environmental assessment.

Please let us know if there is any change in the identity or use of the food-contact substance.

Hoshing W. Chang, Ph.D.

cc:

HFS-255 Chang
File: FCN No.1121



Memorandum

Date: October 15, 2007

From: Division of Food Contact Notifications, HFS-275
Chemistry Team 1
Sharon Elyashiv-Barad, Ph.D.

Subject: **FCN 736:** Ciba Expert Services (Ciba), on behalf of Dyneon (a 3M Company). Copolymer of hexafluoropropylene (HFP), vinylidene fluoride (VDF), and bromodifluoroethylene (BD FE) as a polymer processing aid. Submissions dated April 27, 2007 (initial submission), June 7, 2007 (question regarding low molecular weight oligomers), June 13, 2007 (response to deficiencies), and June 28, 2007 (teleconference and second response to deficiencies).

To: Division of Food Contact Notifications, HFS-275
Regulatory Team 2
Attention: V. Gilliam

FCN 736 was submitted by Ciba Expert Services (Ciba), on behalf of Dyneon (a 3M Company), for a copolymer of hexafluoropropylene (HFP), vinylidene fluoride (VDF, a.k.a. 1,1-difluoroethene), and bromodifluoroethylene (BD FE) intended to function as a processing aid in all polymers, at levels not to exceed 1000 ppm in the finished polymer. The FCS is a major component of a polymer processing additive (PPA) marketed as (b) (4). Polymers containing the FCS will be used in contact with all foods under Conditions of Use A through H as described on our website.

Background

The FCS is not currently regulated in 21 CFR 170-199, nor is it the subject of any effective FCNs. The FCS was the subject (b) (4).

HFP-VDF copolymers are currently regulated as processing aids, at levels not to exceed 0.2 wt.-%, under §177.1350 (Ethylene-vinyl acetate copolymers) and §177.1520 (Olefin polymers), and as the base elastomer under §177.2600 (Rubber articles intended for repeated use).

Dyneon's FCN 260¹ (effective October 3, 2002) was for the terpolymer of tetrafluoroethylene (TFE), HFP, and VDF intended for use as a processing additive at levels up to 2000 ppm in food-contact polyolefins. Polyolefins containing that FCS may be used in contact with all food types under Conditions of Use B through H.

Other fluorinated polymers, structurally related to the FCS, are listed under §177.2400 (Perfluorocarbon cured elastomers) and §177.2600, or are the subject of several effective FCNs (FCN 17, Greene, Tweed and Company, Inc.; FCN 101, DuPont Dow Elastomers; FCNs 126-129, Ausimont).

¹ Chemistry memorandum for FCN 260 dated September 19, 2002 (S. Elyashiv-Barad to V. Gilliam).

Chemistry information is contained in FDA Form 3480 and Attachments 1-9 as follows: 1 (structure and MSDS), 2 (IR, DSC, TGA), 3 (manufacture), 4 (monomer content), 5 (intrinsic viscosity), 6 (molecular weight distribution data), 7 (technical data sheet), 8 (migration study) and 9 (maximum extractability report). Additional data is contained in the June 13 and June 28, 2007 submissions addressing deficiencies outlined in your June 4 and June 22, 2007 letters, respectively.

Identity of the FCS

Information on the identity of the FCS is contained in FDA Form 3480, Section II.A, Section II.C, Attachments 1, 2, 5, and 6, the June 13, 2007 submission (Item 2), and the June 28, 2007 submission (Item 1).

The FCS is a random copolymer of HFP and VDF (b) (4) BDFE. As per our recommendations in the June 4, 2007 deficiency letter, the notifier modified the description of the FCS to: 1-propene, 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene (CAS Reg. No. 9011-17-0) modified with a halogenated ethylene as described in the food contact notification (see Item 1 in the June 28, 2007 submission). This language was used in the notification letters.

Name: 1,1,2,3,3,3-hexafluoropropene, polymer with 1,1-difluoroethene (CAS Reg. No. 9011-17-0) modified with 2-bromo-1,1-difluoroethylene

Other names: (b) (4) (b)(4) ied

Structure: Attachment 1 contains structures of the two primary monomers HFP and VDF.

(b) (4)

- - - - -

- - - - -

- - - - - (b)(4) - - - - -

(b) (4)

----- (b)(4) -----

FCS Properties

Properties (color, density, viscosity, and form) are provided in Form 3480, Section II.C, and the

² The FCS is also referred to as (b) (4) (b)(4)

technical data sheet in Attachment 7. The viscosity test method is provided in-----
material safety data sheet (MSDS), provided in Attachment 1, indicates that the ----- (b)(4)-----
formulation actually consists (b) (4)

Molecular Weight Distribution (MWD)



The weight-average MW (MW_w) was reported (b) (4) the number-average MW (MW_n) was reported (b) (4), and the low molecular weight oligomer (LMWO) fractions were reported as (b) (4)

The Gel Permeation Chromatography (GPC) method and data are contained in Attachment 6 (initial submission) with additional information contained in the June 13 and June 28, 2007 submissions. A more detailed discussion on the LMWO fractions (b) (4) is provided in the **Migrant Levels in Food** Section, below.

Three FCS samples (designated as (b) (4)) were used in the MWD study. Per your June 4, 2007 deficiency letter, Ciba indicated that the sample designation (b) (4) depends on the commercial polymerization kettle and coagulation vessel used in the manufacture of a given batch of the FCS. In some cases, the experimental sample number (b) (4) was used. All samples were obtained from full scale production equipment under the conditions that will be used for commercial production. In all these samples, the FCS is being identified and the fluoropolymers are identical in composition.

Analysis

Infrared (IR) spectra supporting the structure of the FCS were provided in Attachment 2A. A Differential Scanning Calorimetry (DSC) chromatogram and a Thermal Gravimetric Analysis (TGA) chromatogram were provided in Attachments 2B and 2C, respectively. The samples used in these analyses were identical to those used in the molecular weight study (see above).

We have no questions on the identity of the FCS.

Manufacture

Information on the manufacture of the FCS is contained in FDA Form 3480, Section II.B, Attachment 3, and the June 13, 2007 submission (Item 3).

The manufacturing process is provided in Attachment 3. Raw materials used to manufacture the FCS are listed in Section II.B.1, and summarized below. (b) (4)

Table 1: Raw materials used to manufacture the FCS and FCS formulation

(b) (4)

-	-	-	-
-			
-----	-----	-----	
-----	-----	-----	

-	(b)(4)		

-			

(b) (4)

(b)(4)

Impurities

The notifier identified HFP, VDF, and BDFE monomers as potential impurities in the FCS (see Section II.B.3).

In Attachment 4, the notifier provided a report detailing the analysis of residual VDF, HFP and BDFE in the FCS. Three samples of the FCS (identified as (b) (4)) were analyzed in triplicate using Headspace Gas Chromatography (HS-GC) with a mass selective detector. A low concentration of VDF was detected at the level of quantitation (LOQ) of 0.02 ppm, while HFP and BDFE were not detected in any of the samples at the reported LOQ of 0.04 ppm.

The notifier indicated that these LOQs were chosen to be equal to concentrations of the lowest level calibration standards that were analyzed in preparation of the calibration curve. The limit of detection (LOD) for the method was not reported. The analytical method was validated by fortifying each of the samples with two different amounts of the monomers followed by analysis. The notifier provided raw data and representative chromatograms and calibration curves supporting

the reported results.

Under the polymerization reaction conditions described above, the low boiling points of HFP (bp of -84°C), VDF (bp of -29°C), and BDFE (bp of 6°C) would ensure that they would be completely volatilized and removed from the FCS. Therefore, we would expect that exposure to HFP, VDF and BDFE would be “essentially zero.”

We have no questions on the manufacture of and impurities in the FCS.

Intended Use and Technical Effect

Information on the proposed use and technical effect are contained in FDA Form, 3480, Section II.D, and Attachment 7.

The FCS is intended for use as a processing additive, at levels up to 1000 ppm, in food-contact polymers. Polymers containing the FCS may be used in contact with all foods under Conditions of Use A through H depending on the permitted food-types and condition of use of the base polymer.

The FCS is a free-flowing fluoropolymer-based processing additive intended to improve the processing of thermoplastics. A technical data sheet is provided in Attachment 7. The FCS would function in a manner similar to other HFP/VDF copolymers listed under §177.1350, §177.1520, and FCN 260.

We have no questions on the intended use and technical effect of the FCS.

Stability

In Form 3480, Section II.E, the notifier indicated that the FCS is not expected to degrade during the intended use. The DSC and TGA scans in Attachments 2B and 2C, respectively, indicated that the FCS is stable at temperature in excess of 200°C. We expect the stability of the FCS to be similar to other related and permitted FCSs.

We have no questions on the stability of the FCS.

Migrant Levels in Food

Migration studies are summarized in Form 3480, Section II.F, with the full reports contained in Attachments 8 and 9. Additional information is contained in the June 13 and June 28, 2007 submissions.

Attachment 8 contains a migration study report conducted by Ciba on behalf of Dyneon. The report contains nine attachments, denoted as Attachments I through IX, containing the following: I (method for determining the FCS in simulants), II and V (calibration curves), III, IV, VI and VII (representative chromatograms) and VIII and IX (validation).

In Item 2 of the June 13, 2007 submission, Ciba indicated that the migration study submitted in the initial submission contained several typographical errors. These were corrected and the full migration study was resubmitted in the June 13, 2007 submission. Ciba noted that the FCS is referred to as (b) (4) and the final formulation³ is referred to as (b) (4). Ciba indicated that (b) (4) was used to create the LDPE plaques used in the study, but that all of the migration methods and validation were developed around the FCS (b) (4). The migration study is described below.

In addition to the migration study, Ciba performed a fluorine analysis and an exhaustive extraction on the FCS (see Attachments 9b and 9a, respectively, in the initial submission). The June 28, 2007 submission contained additional data clarifying the fluorine analysis and exhaustive extraction on the FCS. The three studies are described below.

Migration Study

Migration Protocol and Analysis

Migration studies were performed (in triplicate) on LDPE plaques (Microthene MN722-00 LDPE, 1 x 2 x 0.038 inch, total 2-sided surface area of 4 in²) loaded with 0.2 wt.-% FCS. Studies were carried out using 10% ethanol and 95% ethanol for 2 hours at 100°C followed by 240 hours at 40°C (migration protocol for Condition of Use A).

Advance composite Teflon lined digestion vessels (manufactured by CEM Corporation) were used for the high temperature exposures. One plaque and solvent (50 mL) were added to each vessel, ensuring that each plaque was totally submerged by the solvent. The solvent volume-to-surface area was 12.5 mL/in². The vessels were sealed and placed in an oven for 2 hours at 100°C after which they were removed from the oven, transferred into 2 oz. Armstrong jars and placed into a preheated oven at 40°C for 240 hours. Samples were then removed from the oven and the plaques removed from the simulant. The solutions were transferred into 50 mL centrifuge tubes and dried under nitrogen. The dried residue was redissolved in THF (~10 mL), sonicated, transferred into test tubes, concentrated (2 mL), filtered through a 0.2µm filter and analyzed for the FCS by GPC after 2, 24, 98 and 240 hours. Controls consisted of solvent blanks and were treated in a similar manner to the test samples.

Calibration curves were prepared from the FCS as described in Attachments I and II of the migration study report. Calibration standards were reported as 0.011, 0.023, 0.044, 0.11 and 0.54 mg/mL. With a final volume of 2 mL and a surface area of 4 in², these standards correspond to a calibration curve range of 0.006 mg/in² to 0.27 mg/in² or, assuming 10 g food/in², 0.6 µg/g (ppm) to 27 ppm.

Migration Results and Validation

The FCS was not detected at a reported limit of detection (LOD) of 0.6 ppm in food in either food simulant. The notifier reported the LOQ as the LOD. As noted above, in reference to monomer

³ The final formulation contains 1000 ppm FCS copolymer in low density polyethylene (LDPE), (b) (4)

residue analysis, the actual LOD for the method would be expected to be lower than the LOQ. The GPC method was validated using separate, 10 day extracts (100°C for 2 hr followed by 40°C for 10 days) in which the polymer was removed and the simulants fortified at the LOQ. Acceptable recoveries were reported. Ciba submitted representative chromatograms and calibration curves supporting the reported migration and validation results.

Fluorine Analysis (Attachment 9b)

Attachment 9b contained the results of analysis of 12 extracts for total fluorine (test samples and controls, 3 replicates, 10 days, both simulants). The 10% ethanol samples were reported as 8 ppb to food, while the 95% ethanol samples were reported as 11, 11 and 27 ppb to food.

As per your deficiency letter, Ciba clarified that the fluorine analysis described in Attachment 9b was conducted on the extracts from the migration study rather than those obtained from the exhaustive study (see below). Dried extract from the migration study was sent to Dyneon for total fluorine analysis. Dyneon reconstituted the migration residue in ethanol (1 mL) and measured total fluorine in ppm. Since the value indicated total fluorine, division by 0.66 (amount of fluorine in the FCS is equal to 66%) gave a value in units of $\mu\text{g/mL}$ FCS. Ciba then multiplied by the total volume (1 mL) to arrive at μg FCS in the migration residue, followed by dividing by 4 in^2 (plaques were 1×2 inch and 40 mil thickness, considering doubled sided, therefore 4 in^2) to derive a value in units of $\mu\text{g FCS/in}^2$. Ciba then assumed that 10 g food comes into contact with 1 in^2 , to get a value in food which was then converted to ppb. A sample calculation is shown below.

$$0.7\text{ }\mu\text{g/mL total fluorine} \div 0.66\text{ (amount of fluorine in FCS)} = 1.06\text{ }\mu\text{g FCS/mL}$$

$$1.06\text{ }\mu\text{g/mL (1 mL total volume)} = 1.06\text{ }\mu\text{g FCS} / 4\text{ in}^2 = 0.27\text{ }\mu\text{g FCS/in}^2$$

$$0.27\text{ }\mu\text{g FCS/in}^2 \times 1\text{ in}^2 / 10\text{ g food} \times 1000\text{ g food/kg food} = 27\text{ }\mu\text{g FCS/kg food (or ppb)}$$

Table 2 of Attachment 9b indicated that the 95% ethanol controls contained 4-8 ppb while the test sample contained 11-27 ppb. The controls and test sample for 10% ethanol were about 8 ppb. Ciba did not account for the controls in previous calculations. Therefore, the 27 ppb value (95% ethanol) was corrected for controls by taking the average values for the three replicates (16.3 ppb) and subtracting the average of the controls (6.7 ppb) to give 9.6 ppb in food. The 10% FCS values were equal to the 10% control values; therefore Ciba did not correct for the blanks, and used 8 ppb in food.

Extract Analysis (Attachment 9a)

Attachment 9a (initial submission) contained a study on the exhaustive extraction of the FCS with 10% ethanol and 95% ethanol at 250°F (121°C) for a total of 21 hours (3 times at 7 hours each). The extracts were evaporated to dryness and analyzed gravimetrically. The residues for 10% ethanol were about 1 mg each time, while those for 95% ethanol were about 75 mg, 17 mg and 7 mg for the three extraction sequences. The first 95% ethanol sample (75 mg) was taken up in chloroform and determined to be 65 mg (insoluble portion) and 10 mg (soluble portion). This chloroform-soluble fraction (residue) was analyzed by NMR (proton), X-ray and GPC. Proton

NMR indicated that the residue originated from the FCS, while X-ray indicated that the residue was organic in nature.

As per your June 13 deficiency letter, Ciba clarified that the extract analysis described in Attachment 9a was intended to be “exhaustive” in that it was conducted under extreme conditions to fully characterize the FCS and any extracted components. The GPC analysis was part of that characterization and slice tables were analyzed. The LMWO fraction (b) (4)

In response to Ciba’s June 7, 2007 inquiry requesting clarification regarding the reason for our concern with a LMWO fraction (b) (4)

however, in the case of perfluoro-compounds, although the MW is higher, the size of the molecule is considered equivalent to a non-perfluorinated compound (b) (4)

was considered a conservative but justified approach to the safety evaluation of these perfluoro-compounds.

Looking at the GPC slice tables again, the LMWO fraction (b) (4)

This will establish then that the LMWO fraction (b) (4). Although the overall GPC analysis of the polymer indicated a range of (b) (4) we believe the GPC on the extract would be more accurate. Most importantly, this experiment established that the LMWO fraction (b) (4) of the ethanol extract, therefore the migration values reported above may be adjusted to account for this LMWO fraction.

We have no questions on the migration studies carried out in support of the proposed use.

Consumer Exposure

Information on consumer exposure is contained in Form 3480, Section II.G, and Attachment 9. Updated estimates were provided in Item 2 of the June 28, 2007 submission.

To the FCS (as LMWOs)

Ciba initially estimated exposure to the FCS using the results of MW analysis on the chloroform-soluble extracts by GPC (250°F or 121°C, for several hours) which indicated a LMWO fraction (b) (4). Using the fluorine analysis from the migration study and the (b) (4) from this exaggerated extraction, Ciba calculated a dietary concentration (DC) of 0.09 ppb using the packaging factors for the general polymer packaging category ($CF=0.4$, $f_{\text{aqueous+acidic}}=0.65$, $f_{\text{alcoholic+fatty}}=0.35$), as shown below.

$$DC = 0.4 \times \{[(27 \text{ ppb}) (0.35) + (8 \text{ ppb})(0.65)] \times (1.5\%)\} = 0.09 \text{ ppb}$$

In the June 28, 2007 submission, Ciba presented a DC of 0.4 ppb for LMWOs (b) (4)

the general polymer packaging category factors as follows:

$$DC = 0.4 \times \{[(9.6 \text{ ppb} \times 0.35) + (8 \text{ ppb} \times 0.65)] \times 11.03\%\} = 0.4 \text{ ppb}$$

We note that the LMWOs of the subject FCS are structurally similar to the LMWOs from other HFP/VDF copolymers. However, since the subject FCS (b) (4)

unique to such oligomers and, therefore, that small portion would not be substitutional to the exposure from HFP/VDF LMWOs.

To Residual Monomers

In the initial submission, Ciba provided exposure estimates for HFP, VDF and BDFE. As indicated above, we would not expect exposure to these monomers, (b) (4)

(b) (4)

We have no questions on consumer exposure.

Notification Language

The acknowledgment letter dated July 6, 2007 is appropriate as written.

Conclusion

We have no questions on this FCN.

Sharon Elyashiv-Barad, Ph.D.

(b) (5)

----- (b)(5) -----

of 0.09 ppb using the packaging factors for the general polymer packaging category ($CF=0.4$, $f_{\text{aqueous+acidic}}=0.65$, $f_{\text{alcoholic+fatty}}=0.35$), as shown below.

$$DC = 0.4 \times \{[(27 \text{ ppb}) (0.35) + (8 \text{ ppb})(0.65)] \times (1.5\%)\} = 0.09 \text{ ppb}$$

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We note that the LMWOs of the subject FCS are structurally similar to the LMWOs from other HFP/VDF copolymers. However, since the subject FCS (b) (4) unique to such oligomers and, therefore, that small portion would not be substitutional to the exposure from HFP/VDF LMWOs.

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(b) (4)

We have no questions on consumer exposure.

Notification Language

The acknowledgment letter dated July 6, 2007 is appropriate as written.

Conclusion

We have no questions on this FCN.

Sharon Elyashiv-Barad
Sharon Elyashiv-Barad, Ph.D.

HFS-275 (Reading File); HFS-705 (Diachenko)



Memorandum

Date: October 22, 2007

From: Toxicology Group 1, Division of Food Contact Notifications (DFCN)
Adejoke O. Ogungbesan, Ph.D. (HFS-275)

Subject: **FCN 000736:** Dyneon, A 3M Co.: Copolymer of hexafluoropropylene (HFP), vinylidene fluoride (VDF), and bromodifluoroethylene (BDFE) as a polymer processing aid. Submissions dated April 27, 2007 and updates of 06/07/2007, 06/13/2007 and 06/28/2007.

To: Regulatory Group 2, DFCN
Attn: Vivian Gilliam

FOOD CONTACT NOTIFICATION (FCN) 000736

Dyneon, A 3M Co.l,
3M Center, Building 236-1B-10
St. Paul, MN 55144.
T: 651-737-8557
F: 651-737-9909.

RELATED DOCUMENTS

(b) (4)

FCN 000260: Dyneon LLC through Keller and Heckmann for the use of tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymers as a processing additive for polyolefins for use in contact with food. *Effective October 16, 2007.*

FCN 000127: Ausimont, Inc. Use of terpolymer of vinylidene fluoride, tetrafluoroethylene and hexafluoropropylene as a gasket or seal in food processing equipment. *Effective July 21, 2001.*

FAP 9B4169: Pennwalt Corporation. Poly(vinylidene fluoride-hexafluoropropylene) copolymer (CAS No. 901 1-1 7-0) resins as adjuvants in olefin polymers. 21 CFR I 77.1520

FAP 5B1794: E I Dupont De Nemours & Co. Rubber articles intended for repeated use. 21 CFR 177.2600.

FCN 000736: Chemistry Review Memorandum, Elyashiv-Barad/Gilliam, 10/15/2007.

Environmental Review Memorandum, Lamont/Gilliam, 08/13/2007.

INTRODUCTION

Dyneon, a 3M Company, through Ciba Expert Services submitted this notification (FCN) for a copolymer of hexafluoropropylene (HFP) and vinylidene fluoride (VDF; a.k.a. 1,1-difluoroethene), and bromodifluoroethylene (BDFE), intended to function as a processing aid in

¹ Abbreviations used in this memorandum include Food Additive Petition (FAP), Prenotification consultation (PNC), Developmental and Reproductive Toxicology (DART), Hazardous Substances Data Bank (HSDB), Integrated Risk Information System (IRIS), Chemical Carcinogenesis Research Information System (CCRIS), International Agency for Research on Cancer (IARC), Hypoxanthine-guanine phosphoribosyltransferase (HPRT), Generally recognized as safe (GRAS), National Toxicology Program (NTP)

all polymers, at levels not exceeding 1000 ppm in the finished product a major component of a polymer processing additive (PPA) marketed as (b) (4) (b)(4). Polymers containing the FCS are expected to be used in contact with all food types and under temperature conditions of use A through H, as described in CFSAN's website at <http://www.cfsan.fda.gov/~rdb/opa-fcn3.html>.

As indicated by Chemistry (b) (4), this compound is not currently regulated in 21 CFR, nor is it the subject of any effective FCNs. However, this FCS is related to several other fluorinated polymers which were the subjects of petitions or notifications (see page 1 of Chemistry's memorandum for a detail discussion).

IDENTITY OF FOOD CONTACT SUBSTANCE (FCS)

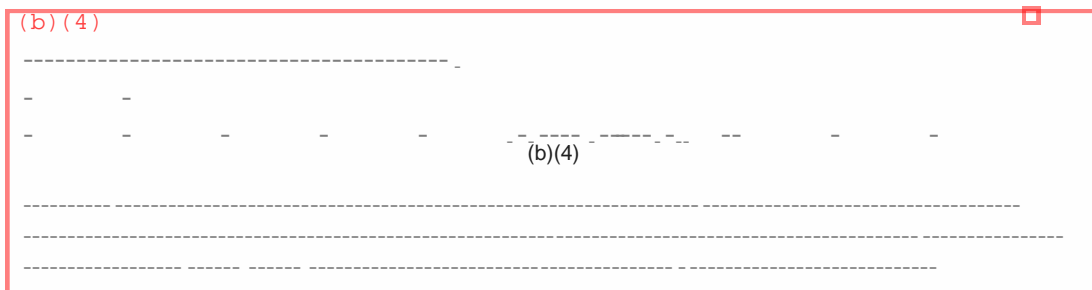
CAS Name: 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene modified with 2-bromo-1,1-difluoroethylene.

CAS Registry Number: 90-----

Trade or Common Names (b) (4)

Other Names: 1,1,2,3,3,3----- modified with 2-bromo-1,1-difluoroethylene; HFP/VDF/BDFE terpolymer; D2598.

Structure:



Formulation: (b) (4)

MW Distribut (b)(4)

EXPOSURE ESTIMATES

Chemistry indicated that dietary exposure to the monomers of the FCS (HFP, VDF, and BDFE) listed below (Table 1) would be "essentially zero". The DC of the low molecular weight oligomers (LMWO) of the FCS (b) (4) was estimated to be 0.09 ppb. According to Chemistry, in previous submissions regarding other types of polymers, the safety evaluation of only the fraction of LMWO (b) (4) was considered. However, in consultation with toxicology it was determined that in the case of perfluoro-compounds, certain properties of the substances (such as spatial size and MW) involved in transport/systemic

² The FCS is also referred to as Dynamar (b) (4).

absorption are considered. Therefore, increasing the MW cut-off (b) (4) was considered a conservative but justified approach to the safety evaluation of perfluoro-compounds. This information was conveyed to the notifier and in the update of June 28, 2007, the notifier calculated the DC of LMWO with (b) (4) to be 0.4 ppb. As stated above, this FCS is related to several authorized or regulated perfluoro-chemicals, (b) (4). Therefore, as noted by Chemistry since the FCS (b) (4) only a small portion of the exposure presented above is unique to such oligomers and therefore, that small portion would not be substitutional to the exposure from the HFP/VDF LMWOs.

Table 1. The constituents/impurities of the FCS

Chemical/Common Name	Function	CAS RN	DC (ppb)
LMWO of the FCS (b) (4)	-	9011-17-0 modified with 359-08-0	0.4 ppb
Hexafluoropropylene (HFP)	Monomer	116-15-4	Essentially zero
Vinylidene fluoride (VDF)	Monomer	75-38-7	

(b) (4)	-----	-----	-----
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-----	(b)(4)	-----	-----
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(b) (4)	-----	-----
-----	(b)(4)	-----
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TOXICOLOGY

The notifier addressed the safety of the monomers and other impurities of the FCS in a safety narrative (SN) in the notification (Attachment 10).

This reviewer searched various databases (SIREN, FARM, TSCAT, ChemIDplus, PAFA, CPDB, IRIS, IARC, NTP, etc.) using CAS No. and names of the impurities. Unless indicated specifically, no relevant information was located on the compound that can be used in the safety assessment.

LMWO (b) (4) of the FCS (DC of 0.4 ppb)

The notifier stated that searches through several databases including TOXLINE, DART, HSDB, IRIS, GENETOX, and CCRIS, did not reveal any data indicating genotoxicity or carcinogenicity. According to the notifier, the VDF/HFP copolymer has little potential to cross cell membranes and is not expected to be of a safety concern since it has an average molecular weight (b) (4)

The copolymer has several regulatory uses³. Searches through OFAS databases and literature searches by this reviewer revealed the last review of a similar copolymer for FCN 260 (difference being the FCS used in FCN 260 contained tetrafluoroethylene whereas this FCS contains DBFE). Toxicology (Twaroski/Gilliam, 10/01/2002) indicated that extracts of the polymer tested were reported negative in the Ames assay. In the review of the subject of FAP 6B3902 Toxicology (Misra/Anand, 07/17/1986) indicated that an acute oral toxicity data with LD₅₀ of > 5g/kg was submitted by the petitioner.

Chemistry indicated that the exposure to the HFP/VDF LMWOs would for the most part be substitutional with only a small portion of the exposure to LMWO (b) (4) would not be substitutional. Accordingly, Toxicology's focus in evaluating the safety of the FCS is on the unique portion of the LMWO, the BFDE. We note that although the BDFE is reportedly related to substances that have mixed results in mutagenicity assays (see below), the structure of the FCS provided does not contain any double bonds, which may be a factor in the weakly mutagenic findings of the compounds structurally related to the monomer.

Data on the Monomers of the FCS (essentially zero)

Although the exposures to the monomers of the FCS are essentially zero, their toxicity may be relevant to examining the toxicity of the LMWO. Accordingly, the available data is summarized as follows:

HFP

In the SN, the notifier cited the mixed results obtained from several genetic toxicity studies on HFP and concluded that HFP "has not been determined to be carcinogenic by IARC, NTP or any other responsible authority".

HFP has several regulatory uses⁴. The data on HFP were summarized in the review of FCN 000260 (Twaroski/Gilliam, 10/01/2002), indicating reported negative results in Ames assay, Chinese Hamster Ovary (CHO)/HPRT assay, and a dominant inhalation study in rats; weakly positive results in mouse micronucleus assay and positive results for chromosomal aberrations in CHO cell (+S9); no data indicating carcinogenicity. Other data were indicated as available including a mutation assay in CHO/HGPRT in (b) (4) and various data at EPA. No tests for carcinogenicity were located.

³ 21 CFR 177.1350, 177.1520 & 177.2600.

⁴ 21 CFR 177.1350, 177.1550 & 177.2600.

VDF

In the SN, the notifier incorporated the safety evaluation of VDF in FCN 000260. VDF has several regulated uses⁵. According to the safety review of FCN 000260 (Twaroski/Gilliam, 10/01/2002), VDF had reportedly negative results in a CHO/HPRT assay, a chromosomal aberration assay using CHO cells, a mouse micronucleus assay, an Ames assay and in *Drosophila melanogaster*; positive results in another Ames assay (increase in histidine revertant colonies observed in TA 1535 in the presence of metabolic activation); a citation from IARC indicating there was inadequate evidence for carcinogenicity in experimental animals. The review of FCN 000260 states:

Literature searches conducted in SIREN/FARM produced a carcinogenicity citation in FAP 9B4169. According to the petitioner (Pennwalt Corporation), rats were dosed with VF2 (VDF) dissolved in olive oil at 4.1 and 8.3 mg/kg for one year followed by an additional year of observation. After which, according to the notifier, the authors incorrectly combined tumor types and tumor sites concluding that there was evidence for carcinogenicity. The citation for the study was Maltoni C and Tovoli D. First experimental evidence of the carcinogenic effects of vinylidene fluoride; long-term bioassays on Sprague-Dawley rats by oral administration. Med Lav 1979 Sept-Oct;70(5):363-8. (This study was apparently republished in 1982 in Ann. N.Y. Acad. Sci. 381 :216-249, and is listed as negative in a ChemIDplus citation.) This study was reviewed by IARC. The endpoint of concern was liposarcomas. Additional searches of ChemIDplus and TSCAT resulted in citations for several mutagenicity and 90-day studies. A bioassay citation was found in TSCAT: Chronic toxicity/carcinogenicity inhalation study of vinylidene fluoride vapour in rats (final report, Doc#: 86-920000883). With regard to the additional carcinogenicity study found concerning VDF, IARC has reviewed the data of vinylidene fluoride, twice, and determined both times that there is inadequate evidence for carcinogenicity. Although IARC did not review the bioassay submitted to EPA, it was determined at the Phase 1 meeting to be unwarranted due to the fact that a) the study is an inhalation study and the previously reviewed oral study was considered to lack evidence by IARC, b) several mutagenicity assays showed predominantly negative findings, and c) the exposure was expected to be low (< 50 ppt). In conclusion, we have found no positive indication of carcinogenicity by oral exposure for this compound based on the information currently available.

BDFE

The notifier indicated that BDFE (b) (4)

of the overall polymer and that literature searches through TOXNET databases (TOXLINE, DART, HSDB, IRIS, GENETOX, and CCRIS) did not reveal any information on genotoxicity or carcinogenicity studies on BDFE. Literature searches on related fluoroalkenes by the notifier revealed that halothane, an inhalation anesthetic, has metabolic products that are similar to BDFE. The notifier cited studies that indicated that negative results were obtained in Ames assays on 2-chloro-1,1,1-trifluoroethane (CF₃CH₂Cl) and 2-bromo-2-chloro-1,1-difluoroethylene (CF₂CB₂Cl). Other Ames studies cited by the notifier

⁵ 21 CFR 177.1350, 177.1380, 177.2510 & 177.2600.

indicated that CF₂CBrCl and 2-chloro-1,1-difluoroethylene (CF₂CHCl) are weakly mutagenic. The notifier indicated that there are no data on CF₂CHCl and CF₂CBrCl indicating carcinogenicity. The available information on mutagenic potential of related fluoroalkenes^{6,7,8} was summarized by the notifier as follows:

Structure of BFDE:

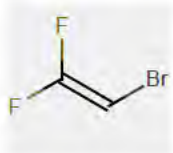


Table 1. Summary of mutagenicity for metabolites of halothane

Name	Structure	Mutagenicity Studies
1,1-Difluoro-2-bromo-2-chloroethylene CAS 758-24-7		<ul style="list-style-type: none"> • Ames Test:¹ (Garro and Phillips 1977) Weakly mutagenic in TA92, TA98, and TA100 strains. • Ames Test:² (Waskell 1979) Non-mutagenic in the standard Ames test in TA98, TA100 strains. • Ames Test:³ (Edmunds 1979) <ul style="list-style-type: none"> - Following the standard Ames protocol, results were negative in TA98, TA100 strains. - When rapidly growing cells were used (TA100 grown in enriched media) the material was weakly mutagenic.
2-Chloro-1,1-difluoroethylene CAS 359-10-4		<ul style="list-style-type: none"> • Ames Test:¹ (Garro and Phillips 1977) Weakly mutagenic in TA92, TA98, and TA100 strains.

Based on these findings on related fluoroalkenes, the notifier suggested that “BDFE can be considered to have weak mutagenic potential.”

In conclusion, based on the available data on related oligomers and the monomers of the FCS and the DC of the LMWO of < 0.5 ppb, which is mostly substitutional to existing authorized fluoropolymers, and the lack of data indicating a concern for carcinogenicity, Toxicology has no questions. Regarding VDF, which does appear to have carcinogenicity data in the literature, the monomer exposure is essentially zero and the exposure in the LMWO fraction is substitutional; accordingly, our previous safety evaluation remains unchanged.

⁶ Garro, AJ and RA Phillips. 1977. Environmental Health Perspectives 21: 65-69.

⁷ Waskell, L. 1979. Anesthesiology 50: 9 – 12.

⁸ Edmunds, HN, JM Baden, and VF Simmon. 1979. Anesthesiology 51: 424-9.

Catalysts and processing aids (no exposure)

Data provided on the catalysts and processing aids, for which no exposure was calculated, are included for completeness of record.

(b) (4)

Since no dietary exposure to the catalysts and processing aids is expected in the use of the FCS, Toxicology has no questions.

CONCLUSION(S)

Toxicology has no questions regarding the proposed use of the FCS, 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene modified with 2-bromo-1,1-difluoroethylene, or its impurities/constituents as described in this notification based on the dietary exposure estimates and the toxicological evaluation of the available data as described above.

Adejoke O. Ogungbesan, Ph.D.

(b) (5)
INIT: M. Twaroski (HFS 275) 10/22/2007

⁹21 CFR 172.210, 172.820, 173.310, 173.340, 175.105, 175.300, 176.180, 178.3750 & 73.1.

¹⁰ 21 CFR 172.892, 175.105, 177.1200, &178.3520

Catalysts and processing aids (no exposure)

Data provided on the catalysts and processing aids, for which no exposure was calculated, are included for completeness of record.

(b) (4)

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CONCLUSION(S)

Toxicology has no questions regarding the proposed use of the FCS, 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene modified with 2-bromo-1,1-difluoroethylene, or its impurities/constituents as described in this notification based on the dietary exposure estimates and the toxicological evaluation of the available data as described above.

(b) (5)
Adejoke O. Ogungbesan
Adejoke O. Ogungbesan, Ph.D.

(b) (5)
INIT: M. Twaroski (HFS 275) 10/22/2007

⁹21 CFR 172.210, 172.820, 173.310, 173.340, 175.105, 175.300, 176.180, 178.3750 & 73.1.

¹⁰ 21 CFR 172.892, 175.105, 177.1200, & 178.3520



Memorandum

Date: August 13, 2007

From: Chemist, Environmental Review Team (ERT)
Office of Food Additive Safety (HFS-246)

Subject: FCN No. 736 – Fluorinated polymer for use as a processing additive for
all polymers for use in contact with food. Dyneon LLC
3M Center, Bldg 236-1B-10
St. Paul, MN 55144

To: Division of Food Contact Notifications (HFS-275)
Attention: Vivian Gilliam
Through: Layla I. Batarseh, Ph.D., Supervisor, ERT _____

The food contact substance for this notification is 1-propene, 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene modified with a halogenated ethylene. We have reviewed the claim of categorical exclusion for the above referenced notification and have concluded that categorical exclusion is warranted. The claim of categorical exclusion cites the section under which categorical exclusion is warranted, 21 *CFR* 25.32 (i), states compliance with the categorical exclusion criteria, and states that no extraordinary circumstances exist that require the submission of an environmental assessment.

Please let us know if there is any change in the identity or use of the food-contact substance.

William H. Lamont

cc:

HFS-246 Lamont
File: FCN No. 736

HFS-246:WHLamont:whl:7/31/07 H:\FCN\FCN736_E_CatEx.doc
FT:WHLamont:whl:8/13/07 P:\EIS Documents\MEMO\FCN736_E_CatEx.doc



Memorandum

Date: August 13, 2007

From: Chemist, Environmental Review Team (ERT)
Office of Food Additive Safety (HFS-246)

Subject: FCN No. 736 – Fluorinated polymer for use as a processing additive for
all polymers for use in contact with food.

To: Division of Food Contact Notifications (HFS-275)
Attention: Vivian Gilliam
Through: Layla I. Batareseh, Ph.D., Supervisor, ERT *L/B*

Dyneon LLC
3M Center, Bldg 236-1B-10
St. Paul, MN 55144

The food contact substance for this notification is 1-propene, 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene modified with a halogenated ethylene. We have reviewed the claim of categorical exclusion for the above referenced notification and have concluded that categorical exclusion is warranted. The claim of categorical exclusion cites the section under which categorical exclusion is warranted, 21 *CFR* 25.32 (i), states compliance with the categorical exclusion criteria, and states that no extraordinary circumstances exist that require the submission of an environmental assessment.

Please let us know if there is any change in the identity or use of the food-contact substance.

William H. Lamont
William H. Lamont

cc:

HFS-246 Lamont
File: FCN No. 736

HFS-246:WHLamont:whl:7/31/07 H:\FCN\FCN736_E_CatEx.doc
FT:WHLamont:whl:8/13/07 P:\EIS Documents\MEMO\FCN736_E_CatEx.doc



Memorandum

Date: September 19, 2002

From: Division of Food Contact Notification, Chemistry Review Group 1

Subject: **FCN 260:** Keller and Heckman LLP, on behalf of Dyneon LLC.
Tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride (TFE-HFP-VDF) terpolymer as processing additives for polyolefins. Submissions dating June 4, 2002 (initial submission) and July 18, 2002.

To: Division of Food Contact Notification, Regulatory Group 2
Attention: Vivian Gilliam

Keller and Heckman LLP (K&H), on behalf of Dyneon LLC, submitted this food contact notification (FCN) for the fluorinated polymer TFE-HFP-VDF produced by the terpolymerization of tetrafluoroethylene (TFE), hexafluoropropylene (HFP) and vinylidene fluoride (VDF). The food contact substance (FCS)¹ is intended for use as a processing additive at levels up to 2000 ppm in food-contact polyolefins. Polyolefins containing the FCS will be used in contact with all food types under conditions of use B-H as described in Tables 1 and 2, respectively, of 21 CFR 176.170(c) (Components of paper and paperboard in contact with aqueous and fatty foods). The fluoro-based terpolymer is not intended to have a technical effect in food.

Background

The FCS is currently regulated under §177.2600 (Rubber articles intended for repeated use) as a result of one food additive petition, FAP 5B1794. The FCS is also the subject of one effective FCN (the FCS is the base polymer in FCN 127², effective date 7/21/01), (b) (4) a request for a cumulative estimated daily intake (CEDI) and an acceptable daily intake (ADI) for oligomers of TFE-HFP-VDF terpolymer, (b) (4) (b) (4) submitted for toxicology concerns.

Other fluorinated polymers related to the FCS are listed under §177.1520 (Olefin polymers), §177.2400 (Perfluorocarbon cured elastomers) and §177.2600, or are the subject of several effective FCNs (FCN 17, Greene, Tweed and Company, Inc.; FCN 101, DuPont Dow Elastomers; FCNs 126-129, Ausimont). These are shown in Attachment 1 to this chemistry memorandum.

Identity

Information on the identity of the FCS is contained in Section C, and several Appendices (I-III, VII and X) in the initial submission.

¹ The terms FCS, terpolymer and (b) (4) are used throughout this chemistry memorandum to describe the food contact substance.

² Chemistry Memorandum on FCN 127 dated June 4, 2001; A. B. Bailey to V. Gilliam.

³ b

001943

CAS name: Ethylene, tetrafluoro-, polymer with 1,1-difluoroethylene and hexafluoropropene

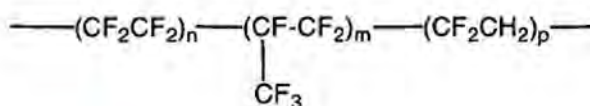
CAS Reg. No.: 25190-89-0

Trade name:

(b) (4)

Other names: Tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymer; Tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride terpolymer; 1-Propene, 1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene and tetrafluoroethene

Structure:



(b) (4)

(b) (4)

Molecular weight:

(b) (4)

The molecular weight of the fluorinated terpolymer was determined by melt rheometry. This procedure is described in Appendix III of the submission dated June 4, 2002 and in Attachment 3 of the submission dated July 18, 2002.

Polymer characterization

The notifier has provided an infrared spectrum (Appendix II) that adequately identifies the FCS.

Polymer specifications

The following specifications were provided by the notifier (Section C and Appendices I, VII-VIII):

Melting point (°C)

(b) (4)

Melt flow index (g/10 min)

(b) (4)

Specific gravity, 25°C/25°C, (g/cc)

(b) (4)

(b) (4) is intended to collectively refer to both (b) (4) in this memorandum.

Three Certificates of Analysis of the FCS are provided in Appendix VIII⁵ of the initial submission.

"End-test" extractions (Appendix X)

The notifier conducted "end-test" extractions (in triplicate) for total nonvolatile extractives (TNE) using water and *n*-hexane at reflux (for 7 hours followed by an additional 2 hours) in accordance with subparagraphs (e) and (f) of §177.2600. For the reflux extractions, glass resin kettles were used for the extraction cells. The FCS meets all extractive limitations as shown below (see Tables 9 and 10 in Appendix X).

Table I: Extraction test results

Solvent	Time (hr)	Mean TNE* (mg/in²)	Limitations (mg/in²)
Water	7	0.0117	20.0
	+2	0.0044	1.0
<i>n</i> -Hexane	7	0.0270	175.0
	+2	0.0083	4.0

* Test samples were corrected for the solvent blank residue weights.

Inspection of Tables 9 and 10 indicate that the reported masses for three out of the four solvent blank weights are reasonable, and therefore, the results reported for mean TNE (above) were corrected for the solvent blank. The solvent blank mass used in the extraction with water (7 hour reflux) was especially high (*i.e.* the solvent blank mass was approximately equal to the mass of the extracted sample). The uncorrected mean TNE for water (7 hours) would be 0.0419 mg/in².

We have no questions on the identity of the FCS.

Manufacture

Information on the manufacture of the FCS is described in the June 4, 2002 submission (Section C and Appendix IV) and the 7/18/02 submission (Attachment 1). Raw material specification sheets are provided in Appendix V of the initial submission.

⁵ The notifier notes that the Certificates of Analysis include a specification for particle size. This is a customer-specific specification that has no bearing on either the chemical or physical properties of the FCS. Furthermore, these specifications may vary as per customer needs. Particle size has therefore, not been included as a general specification for the FCS.

Table II:

(b) (4)

(b) (4)

(b) (4)

Impurities

The terpolymer was analyzed for (b) (4) and the raw materials TFE, HFP and VDF (Appendix VI, June 4, 2002 submission; and Attachment 2, July 18, 2002 submission). Several unidentified substances were also identified as potential impurities (discussed below).

(b) (4),

Five samples of the FCS were submitted for analysis to determine the concentration of (b) (4). (b) (4) was determined as (b) (4) anion, (b) (4) anion, using high-performance liquid chromatography (HPLC) coupled to electrospray mass spectrometry. The samples were cryoground to a fine powder, and 1 gram was mixed with 5 mL of acetonitrile and shaken for ~ 18 hours to extract the impurity. After the sample extracts settled, a portion of each extract was centrifuged and analyzed. The average (b) (4) concentration was (b) (4) and

(b) (4)

maximum was (b) (4) ppm in the FCS.⁷ The maximum (b) (4) level was therefore stated to be (b) (4) in the FCS.

TFE, HFP and VDF

Four samples of the FCS were analyzed twice for the residual fluoromonomers TFE, HFP and VDF using headspace gas chromatography (GC) with FID detection. No monomers were detected at the following reported limits of detection (LOD): 10 µg/kg TFE, 50 µg/kg HFP, and 10 µg/kg VDF.

Unidentified impurities

The GC chromatograms of the four samples analyzed for the residual fluoromonomers showed the presence of additional peaks, which were not identified by the notifier. (We have provided an exposure estimate to the collective "unidentified impurities" described above, in the Exposure section of this memorandum).

(b) (4)

We have no questions on the manufacture of the FCS.

Intended Use and Technical Effect

Dyneon LLC intends to incorporate the terpolymer as a polymer-processing additive (PPA), at levels up to 2000 ppm, in food-contact polyolefins. Polyolefins containing the FCS will be used in contact with all food types (types I-IX) under conditions of use B-H as described in Tables 1 and 2 of §176.170(c), respectively. The FCS may be used in accordance with food additive regulations and effective notifications, which incorporate, by reference olefin polymers permitted in §177.1520. The FCS is not intended to have a technical effect in food.

The subject FCS will be used to improve polymer extrusion. Specifically, the FCS will help eliminate melt fracture and reduce die build-up. Keller and Heckman provided sufficient data to support the improvement of polymer extrusion (Appendix IX, initial submission) with levels up to 1000 ppm of the FCS. Graphs demonstrating the increased productivity in blow molding of bottles (50 mL), the reduction and/or elimination of external die build, the reduction in the formation of gels during blow film extrusion, and the improvement in surface and gloss of bottles, *i.e.* the reduction of melt fracture, were presented and adequately explained.

We have no questions about the intended use and technical effect of the FCS.

⁷ The calibration curve for (b) (4) (b) (4) was prepared by analyzing standard solutions of (b) (4) (b) (4) concentrations were determined as follows:

(b) (4)

Migration Studies

Migration studies are summarized in Section D and in Appendix X of the initial submission.

Migration studies were performed on test samples of (b) (4) plaques (greater than 25 mils thick and approximately 4 inches wide, total 2-sided surface area of 193 in²) using 10% and 95% ethanol at 100°C for 240 hours (the migration protocol used in these studies is more rigorous than what we normally recommend for single-service articles use according to conditions of use A). The tests were conducted in triplicate using two-sided extraction cells, both sides of the cell being exposed to the solvent. Controls consisted of solvent blanks. The samples were analyzed for TNE and chloroform-soluble extractives (CHCl₃-soluble TNE) at 2 hours and 240 hours. The test solutions were evaporated to dryness and the residues were determined gravimetrically. Migration results were taken from Tables 1 and 2 (TNE), and Tables 5 and 6 (CHCl₃-soluble TNE) in Appendix X, and tabulated below (columns 4 in both tables).

Table III: Migration results for TNE

Solvent	Temp (°C)	Time (hr)	Mean TNE: corrected ^a (mg/in ²)	Mean TNE: uncorrected ^b (mg/in ²)
10 % ethanol	100	2	0.0173	0.0276
	100	240	0.0366	0.0550
95 % ethanol	100	2	0.0830	0.0953
	100	240	0.1940	0.2460

^a Test samples were corrected for the solvent blank residue weights.

^b Test samples were not corrected for the solvent blank residue weights.

Table IV: Migration results for CHCl₃-soluble TNE

Solvent	Temp (°C)	Time (hr)	Mean CHCl ₃ -soluble TNE: corrected ^a (mg/in ²)	Mean CHCl ₃ -soluble TNE: uncorrected ^b (mg/in ²)
10 % ethanol	100	2	0.0024	0.0029
	100	240	0.0029	0.0024
95 % ethanol	100	2	0.0223	0.0311
	100	240	0.0992	0.1437

^a Test samples were corrected for the solvent blank residue weights.

^b Test samples were not corrected for the solvent blank residue weights.

Inspection of Tables 1, 2, 5, and 6 show that the blank solvent residues do not appear to be excessively high except with the following samples: Table 1 (TNE: 10% ethanol at 100°C for 2 hours), Table 2 (TNE: 10% ethanol at 100°C for 240 hours) and Table 6 (CHCl₃-soluble TNE: 95% ethanol at 100°C for 240 hours). Therefore, we reported both corrected (column 4) and uncorrected (column 5) migration results in Tables III and IV, above.

We have no questions about the migration studies performed on the FCS.

Exposure

FCS

Notifier' approach:

The notifier determined a dietary concentration (DC) of 0.45 µg/kg (EDI of 1.35 µg/person/day) to low molecular-weight oligomers (LMWO) as follows:

1. Extracted plaque mass (assuming a polymer density of 1.9 g/cm³, a thickness of 25 mil, and a surface area of 193 in², extracted on both sides):

$$\text{Extracted plaque mass} = 25 \text{ mil} \times \frac{1.9 \text{ g polyolefin}}{\text{cm}^3} \times \frac{0.001 \text{ in}}{1 \text{ mil}} \times \left(\frac{2.54 \text{ cm}}{1 \text{ in}} \right)^2 \times \frac{193 \text{ in}^2}{2} = 75.1 \text{ g}$$

2. Mean weight of TNE extracted from the polymer using the mean TNE corrected for 95% ethanol from Table III (0.1940 mg/in²) and a 2-sided surface area (193 in²):

Mean weight TNE from polymer =

$$\frac{\text{mean weight TNE}}{\text{weight of plaque}} = \frac{0.0375 \text{ g}}{75.1 \text{ g}} = 500 \frac{\mu\text{g TNE}}{\text{g}} \text{ or } 0.5 \frac{\mu\text{g}}{\text{mg}}$$

3. Maximum concentration of FCS in food (assuming 100% migration into food, a polymer density of 0.92 g/cm³, a thickness of 10 mil, and an FCS maximum use level of 2000 ppm):

Max conc of FCS in food =

$$10 \text{ mil} \times \frac{0.92 \text{ g polyolefin}}{\text{cm}^3} \times \frac{0.001 \text{ in}}{1 \text{ mil}} \times \left(\frac{2.54 \text{ cm}}{1 \text{ in}} \right)^2 \times \frac{2000 \mu\text{g FCS}}{\text{g polyolefin}} \times \frac{1 \text{ in}^2}{10 \text{ g food}} = 30 \frac{\mu\text{g FCS}}{\text{g food}} = 30 \frac{\text{mg}}{\text{kg}}$$

4. Maximum migration of LMWO into food (<M>):

$$<M_{\text{FCS}}> = \text{mean weight TNE} \times \text{max conc of FCS in food} = \frac{0.5 \mu\text{g TNE}}{\text{mg FCS}} \times \frac{30 \text{ mg FCS}}{\text{kg food}} = 15 \frac{\mu\text{g TNE}}{\text{kg food}}$$

5. DC and EDI:

$$\text{DC} = \text{CF} \times <M_{\text{FCS}}> = 0.03 \times 15 \mu\text{g/kg} = 0.45 \mu\text{g/kg}$$

$$\text{EDI} = \text{DC} \times 3 \text{ kg/person/day} = 1.35 \mu\text{g/p/d}$$

The notifier used a refined consumption factor (CF) of 0.03, determined by multiplying the polyolefin consumption factor (CF_{polyolefin} = 0.35) by the % fluoro-polymer based processing

additives (PPA) used in polyolefin resins globally (6.3%)⁹ (Appendix XI of the initial submission). The value obtained (0.022) was rounded to 0.03.

Our approach:

We determined a DC of 0.07 µg/kg (EDI of 0.2 µg/person/day) to LMWO using the uncorrected CHCl₃-soluble TNE migration values, at 100°C for 240 hours using 10% ethanol (0.0024 mg/in²) and 95% ethanol (0.1437 mg/in²) as provided in Table IV, our default assumption that 10 g food contacts 1 in² surface area, and an average use level of the FCS in polyolefins, 750 ppm.¹⁰

$$M_{10\% \text{ Ethanol}} = \frac{0.0024 \text{ mg}}{\text{in}^2} \times \frac{1 \text{ in}^2}{10 \text{ g food}} \times \frac{1 \text{ g}}{1000 \text{ mg}} \times \frac{750 \text{ } \mu\text{g}}{\text{g}} = 0.18 \times 10^{-3} \frac{\mu\text{g}}{\text{g}} = 0.18 \frac{\mu\text{g}}{\text{kg}}$$

$$M_{95\% \text{ Ethanol}} = \frac{0.1437 \text{ mg}}{\text{in}^2} \times \frac{1 \text{ in}^2}{10 \text{ g food}} \times \frac{1 \text{ g}}{1000 \text{ mg}} \times \frac{750 \text{ } \mu\text{g}}{\text{g}} = 10.8 \times 10^{-3} \frac{\mu\text{g}}{\text{g}} = 10.8 \frac{\mu\text{g}}{\text{kg}}$$

Using these migration values, a refined CF of 0.02 and food-type distribution factors from the polyolefins packaging category (where $f_{\text{aq,acid}} = 0.68$ for aqueous and acidic foods, and $f_{\text{al+fatty}} = 0.32$ for alcoholic and fatty foods), gives a DC of 0.07 µg/kg and an EDI of 0.2 µg/person/day.

$$\begin{aligned} \text{DC} &= \text{CF} \times [(f_{\text{aqueous}} + f_{\text{acidic}})(M_{10\% \text{ ethanol}}) + (f_{\text{alcohol}} + f_{\text{fatty}})(M_{95\% \text{ ethanol}})] \\ &= 0.022 \times [(0.68)(0.18 \text{ } \mu\text{g/kg}) + (0.32)(10.8 \text{ } \mu\text{g/kg})] \\ &= 0.07 \text{ } \mu\text{g/kg} \end{aligned}$$

$$\text{EDI} = \text{DC} \times 3 \text{ kg/person/day} = 0.23 \text{ } \mu\text{g/person/day}$$

A CEDI of 0.75 µg/person/day was established for the terpolymer in our March 19, 2002 chemistry memorandum for (b) (4) (A. Bailey to W. Trotter). Thus, the revised CEDI is 0.95 µg/person/day.

⁹ The % fluoro-polymer based processing additives (PPA) used in polyolefin (PO) resins globally was estimated by Dyneon (information used to support this was provided in Appendix XI): typical use level of a PPA = 750 ppm, global polyolefin market = 120 billion lbs, total global fluoropolymer-based PPA market = 5.7 million lbs.

$$\% \text{ Fluoro-PPA used in PO resins globally} = \frac{5.7 \times 10^6 \text{ lb fluoropolymer-based PPA}}{\frac{750 \times 10^{-6} \text{ lb PPA}}{\text{lb PO}} \times (120 \times 10^9 \text{ lbs PO})} \times 100 = 6.3\%$$

¹⁰ CHCl₃-soluble TNE oligomer migration values in 10% and 95% ethanol were determined for the polyolefin plaque. To obtain migration values more applicable to use in polyolefins, the reported average use level of the FCS in polyolefins was taken into account.

Impurities

(b) (4)

The notifier determined a DC of 90 pg/kg (EDI of 0.27 ng/person/day) to (b) (4) using the maximum concentration of the FCS in food assuming 100% migration (30 mg/kg, from above), the residual level of (b) (4) in the FCS (0.1 mg/kg), and a CF of (b) (4).

We determined a DC of 66 pg/kg (EDI of 0.2 ng/person/day) to (b) (4) using a CF of (b) (4) (rather than (b) (4)).

TFE, HFP and VDF

The notifier calculated upper-bound exposure limits to the fluoromonomers based on the reported LODs (10 µg/kg TFE, 50 µg/kg HFP, and 10 µg/kg VDF), a CF of (b) (4) and the assumption of 100% migration into food.

Above, we concluded that the starting monomers (TFE, HFP and VDF) would not be present in the FCS. Therefore, we conclude that exposure to TFE, HFP and VDF would be "essentially zero".

Unidentified impurities

The GC chromatograms used for the analysis of the fluoromonomers TFE, HFP and VDF showed the presence of 3-4 additional peaks that were not identified by the notifier. An upper-bound limit to the DC for these impurities may be determined by comparing the peak areas of the fluoromonomers to the peak areas of the unknown impurities. Based on this comparison, we conclude that the DC for the unidentified peaks will not exceed 50 ng/kg.

Notification Language

The language in the acknowledgement letter dated August 22, 2002 is appropriate.

Conclusion

We have no questions on this FCN.



Sharon Elyashiv-Barad, Ph.D.

HFS-205 (Kuznesof), 245 (Begley), Chemistry Reading File
HFS-275:SElyashiv-Barad:418-3145:seb:09-19-02 (FCN260_C_memo.doc)
RDInit: ABBailey, 09-19-02
Final: seb, 09-19-02

Attachment 1: Fluorinated polymers in regulations and notifications

§177.1520(b)

1. Poly(vinylidene fluoride) homopolymer (CAS Reg. No. 24937-79-9), having a melt viscosity of 6 to 37 kilopoise at a shear rate of 100¥1 seconds at 232 °C...using a capillary of 15:1 L/D...
2. Vinylidene fluoride-hexafluoropropene copolymer (CAS Reg. No. 9011-17-0) having a fluorine content of 65 to 71 percent and a Mooney viscosity of at least 28...
3. Vinylidene fluoride-hexafluoropropene copolymer (CAS Reg.No. 9011-17-0), having a vinylidene fluoride content of not less than 87 percent but less than 100 percent by weight and a melt viscosity of 12 to 27 kilopoise at a shear rate of 100¥1 seconds at 232 °C...using a capillary of 15:1 L/D...

§177.2400(a)

.... perfluorocarbon-cured elastomers are produced by terpolymerizing tetrafluoroethylene (CAS Reg. No. 116-14-3), perfluoromethyl vinyl ether (CAS Reg. No. 1187-93-5), and perfluoro-2-phenoxypropyl vinyl ether (CAS Reg. No. 24520-19-2) and subsequent curing of the terpolymer (CAS Reg. No. 26658-70-8) using the crosslinking agent, phenol, 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl) ethylidene] bis-, dipotassium salt (CAS Reg. No. 25088-69-1) and accelerator, 1,4,7,10,13,16-hexaoxacyclooctadecane (CAS Reg. No. 17455-13-9).

§177.2600(c)(4)(i)

1. Chlorotrifluoroethylene-vinylidene fluoride copolymer.
2. Vinylidene fluoride-hexafluoropropylene copolymers (minimum number average molecular weight 70,000 as determined by osmotic pressure in methyl ethyl ketone).
3. Vinylidene fluoride-hexafluoropropylene-tetrafluoroethylene copolymers (minimum number average molecular weight 100,000 as determined by osmotic pressure in methyl ethyl ketone).

FCN 17

A perfluorocarbon-cured elastomer (PCE) produced by terpolymerizing tetrafluoroethylene (CAS Registry No. 116-14-3), perfluoro(2,5-dimethyl-3,6-dioxanone vinyl ether) (CAS Registry No. 2599-84-0) and perfluoro(6,6-dihydro-6-iodo-3-oxa-1-hexene) (CAS Registry No. 106108-22-9) and subsequent curing of the terpolymer (CAS Registry No. 106108-23-0) by crosslinking with triallylcyanurate (CAS Registry No. 101-37-1) and vulcanizing with 2,5-dimethyl-2,5-di(t-butylperoxy)hexane (CAS Registry No. 78-63-7), as a 68% dispersion on finely divided silica.

FCN 101

Perfluorocarbon cured elastomers produced by polymerizing perfluoro(methyl vinyl ether) (CAS Reg. No. 1187-93-5) with tetrafluoroethylene (CAS Reg. No. 116-14-3) and perfluoro(8-cyano-5-methyl-3,6-dioxo-1-octene) (CAS Reg. No. 69804-19-9), followed by curing with trimethylallyl isocyanurate (CAS Reg. No. 6291-95-8) and/or triallyl isocyanurate (CAS Reg. No. 1025-15-6), and with 2,5-dimethyl-2,5-di(t-butylperoxy) hexane (CAS Reg. No. 78-63-7) and as further described in this notification.

FCN 126

1,9-Decadiene,3,3,4,4,5,5,6,6,7,7,8,8-dodecafluoro-, polymer with tetrafluoroethene and trifluoro(trifluoromethoxy)ethene (CAS Reg. No. 190062-24-9), manufactured and characterized as further described in the notification.

FCN 127

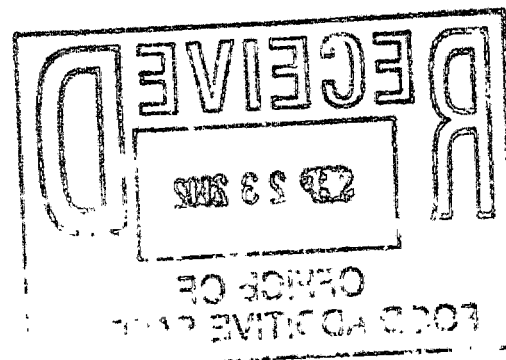
11. 1-Propene,1,1,2,3,3,3-hexafluoro-, polymer with 1,1-difluoroethene and tetrafluoroethene (CAS Reg. No. 25190-89-0) modified with triallyl isocyanurate and 3,3,4,4,5,5,6,6,7,7,8,8-dodecafluoro-1,9-diene, manufactured and characterized as further described in the notification.

FCN 128

A copolymer of tetrafluoroethylene (TFE) and perfluoromethylvinyl ether (PFMVE) (CAS Reg. No. 26425-79-6) modified with 1,3,5-triallyl isocyanurate (TAIC) and 3,3,4,4,5,5,6,6,7,7,8,8-dodecafluoro-1,9-diene, manufactured and characterized as further described in the notification.

FCN 129

Ethene, tetrafluoro-, polymer with 1,1-difluoroethene and trifluoro(trifluoromethoxy)ethene (CAS Reg. No. 56357-87-0) modified with 1,3,5-triallyl isocyanurate (TAIC) and 3,3,4,4,5,5,6,6,7,7,8,8-dodecafluoro-1,9-diene, manufactured and characterized as further described in the notification.





DEPARTMENT OF HEALTH & HUMAN SERVICES

U S Food and Drug Administration, 5100 Paint Branch Parkway, College Park MD 20740

AD



Public Health Service

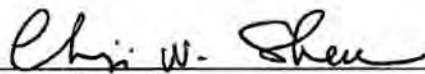
Memorandum

Date September 4, 2002

From Toxicology Group 2, Division of Food Contact Substance Notification Review (DFCSNR)

Subject **FCN 260**, Use of tetrafluorethylene-hexafluoropropylene-vinylidene fluoride copolymers as a processing additive for polyolefins

To FCN 260 File

Through Chingju W. Sheu, Ph.D. 
Supervisor, DFCSNR, Toxicology Group 2

FOOD CONTACT NOTIFICATION No. 260

Dyneon LLC
6744 33rd Street north
Oakdale, Minnesota 55128
651 737 8557 (T) 651.737 9909 (F)

Submitted via: John B. Dubeck
Keller and Heckman LLP
1001 G Street N.W., Suite 500 West
Washington, D.C 20001
(T) 202 434.4125 (F) 202 434.4646

Toxicology studies submitted in support of FCN 260 and reviewed by ICF [Contract No. 223-00-2450, Work Assignment No. 2002-29 (ICF 029)] were:

Task 1

Mutagenicity study on THV Oligomers (b) (4), ethanol extracts of (b) (4) (b) (4)

- *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (b) (4) – ISO
- The study report is contained in FCN 260 on pages numbered 182 – 203
- Toxikon Corporation, Bedford, MA (b) (4) conducted the study in 2001.
- Kate Sullivan and Kara Altshuler, Ph.D reviewed the study at ICF

(b) (4)

001804

(b) (4)

001805

(b) (4)

The TDERs are acceptable as final.


Michelle L. Twaroski, Ph.D.

001806



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

U.S. Food and Drug Administration, 5100 Paint Branch Parkway, College Park MD 20740

Memorandum

AD



Date October 1, 2002

From Division of Food Contact Substance Notification Review (DFCSNR)

Subject **FCN 260**, Use of tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymers as a processing additive for polyolefins

To Regulatory Group 1-DFCSNR
Attn : Vivian Gilliam

Through Chingju W. Sheu, Ph.D. Ching W. Sheu
Supervisor, DFCSNR, Toxicology Group 2

FOOD CONTACT NOTIFICATION No. 260

Dyneon LLC
6744 33rd Street North
Oakdale, Minnesota 55128
651.737.8557 (T) 651.737.9909 (F)

Submitted via John B. Dubeck
Keller and Heckman LLP
1001 G. Street N.W., Suite 500 West
Washington, D.C. 20001
(T) 202.434.4125 (F) 202.434.4646

RELATED PETITIONS/NOTIFICATIONS

	(b) (4)	(b) (4)	FCN 260
FCN 127			Use of terpolymer of vinylidene fluoride, tetrafluoroethylene and hexafluoropropylene as a gasket or seal in food processing equipment. Ausimont, Inc.
FAP 9B4169			Poyl(vinylidene fluoride-hexafluoropropylene) copolymer (CAS No. 9011-17-0) resins as adjuvants in olefin polymers Pennwalt Corporation. 21CFR§177.1520
FAP 5B1794			Rubber articles intended for repeated use. E I Dupont De Nemours & Co. 21CFR§177.2600

PROPOSED USE

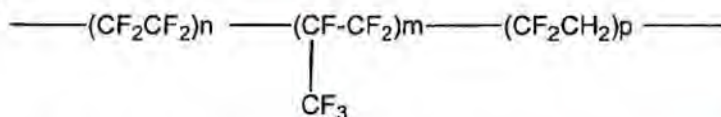
Dyneon LLC proposes to use tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymers (referred to hereafter as the "FCS") as a processing additive for polyolefins used in food contact applications. The FCS will be used at levels up to 2000 ppm in food-contact polyolefins with all food types under conditions of use B - H (boiling water sterilized - frozen or refrigerated storage) of 21CFR§176.170(c) Tables 1 and 2, respectively.

FOOD CONTACT SUBSTANCE

1. Name. Tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymers

001954

2. Trade Name(s): (b) (4)
 3. CAS Name: Ethylene, tetrafluoro-, polymer with 1,1-difluoroethylene and hexafluoropropene
 4. CAS No.: 25190-89-0
 5. Chemical Formula: not stated
 6. MW: (b) (4)
 7. Structure.



Tetrafluoroethylene: (b) (4) hexafluoropropylene: (b) (4) vinylidene fluoride: (b) (4)

Manufacturing process: (b) (4)

8. Impurities: Several impurities were listed in the FCN and Dr. Elyashiv-Barad's memo (Elyashiv-Barad /Gilliam, 09/19/2002, RE FCN 260). The names, CAS No., and maximum residual levels are included in the table below as well as any regulatory information.

CHEMICAL NAME	CAS NO.	MAX. RESIDUAL CONCENTRATION	REGULATORY STATUS
Tetrafluoroethylene (TFE)	116-14-3	<10 µg/kg	21CFR§177.1520 (adjuvants in olefin polymers)
Hexafluoropropylene (HFP)	116-15-4	< 50 µg/kg	21CFR§177.2400 (perfluorocarbon cured elastomers)
Vinylidene fluoride (VDF)	75-38-7	< 10 µg/kg	21CFR§177.2600 (rubber articles intended for repeat use)
(b) (4)			

9. Technical Effect: According to the manufacturer, the FCS is used to improve polymer extrusion. Data provided in Appendix IX of FCN 260 indicate that the FCS helps eliminate melt fracture and reduces die build up.

CURRENT USE AND CUMULATIVE ESTIMAED DAILY INTAKE (EDI)

Dyneon LLC submitted migration studies on the FCS. Studies were reviewed and detailed by Chemistry (Elyashiv-Barad /Gilliam, 09/19/2002, RE FCN 260). Briefly, oligomers of the FCS were extracted using either 10% or 95% ethanol as food simulants with an extraction at 100C for 10 days. Following extraction total nonvolatile extractives (TNE) and CHCl₃-soluble extractives were determined.

FCS: The estimated daily intake (EDI) of the oligomers of the FCS (designated by the notifier as "THV oligomers") is 0.23 µg/p/d (dietary concentration of 0.07 ppb, Elyashiv-Barad /Gilliam, 09/19/2002, RE FCN 260). The current cEDI for THV oligomers is 0.75 µg/p/d. The new cEDI for THV oligomers will be 0.95 µg/p/d (dietary concentration of 0.32 ppb, Elyashiv-Barad /Gilliam, 09/19/2002, RE FCN 260).

¹ According to Chemistry, (b) (4) contain (b) (4) tetrafluoroethylene, (b) (4) (b) (4)

(Elyashiv-Barad /Gilliam, 09/19/2002, RE FCN 260).

001955

Impurities: EDIs for the impurities were estimated based on 100% migration (Elyashiv-Barad /Gilliam, 09/19/2002, RE FCN 260). The following table lists the impurities, their EDIs, and DCs.

IMPURITY	DC	EDI
TFE	"essentially zero"	
HFP		
VDF		
(b) (4)	66 ppq	0.2 ng/p/d
	≤ 50 ppt	≤ 0.15 µg/p/d

CURRENT ACCEPTABLE DAILY INTAKE (ADI) AND BASIS

No ADI is available for the FCS

TOXICOLOGY

Food Contact Substance: For the proposed use of the FCS, Dyneon LLC submitted one mutagenicity study in the original submission: Mutagenicity study on THV Oligomers (b) (4), ethanol extracts of (b) (4) wt -% tetrafluoroethylene, (b) (4) hexafluoropropylene, and (b) (4) vinylidene fluoride]:

- *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay (b) (4) – ISO
 - The study report is contained in FCN 260 on pages numbered 182 – 203.
 - Toxikon Corporation, Bedford, MA (study number (b) (4)) conducted the study in 2001.
 - Kate Sullivan and Kara Altshuler, PhD reviewed the study at ICF [Contract No (b) (4), Work Assignment (b) (4)]
 - Conclusion: "The study author concluded that the test article, (b) (4) was not mutagenic in this microbial mutagenicity assay. Our reviewers agree with the study author's conclusions."

In an update dated 07/18/2002, Dyneon LLC provided the following:

- American National Standard "Biological evaluation of medical devices-Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity". 1993.
- International Standard (ISO 10993-12) "Biological evaluation of medical devices-Part 12: Sample preparation and reference materials".
- Toxikon test protocol FDA GLP guidelines file copy: *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay– ISO

This information was submitted to clarify the actual concentration of test substance used in the Ames assay. In the letter accompanying the protocols the notifier indicates that 4 g of ground polymer were extracted in 20 ml of 95% ethanol or 5% ethanol for 72 hours at 50C. For the tests, 25 µl of this extract was used. No indication of the concentration is given.

Literature searches in SIREN/FARM produced a citation for FCN 127, Use of terpolymer of vinylidene fluoride, tetrafluoroethylene and hexafluoropropylene as a gasket or seal in food processing equipment; however no relevant toxicology information was present in the FCN. A search of Chem/Dplus (contains ToxLine) and TSCAT did not result in additional information.

In summary, the oligomers of the FCS did not induce genetic damage under the conditions tested and no information was found indicating toxic or carcinogenic activity for this compound. Accordingly, Toxicology has no concerns regarding the FCS for the intended use and its associated exposure (<0.5 ppb) as described in FCN 260.

Impurities: Dyneon LLC submitted a safety analysis on the impurities TFE, HFP, VDF, and (b) (4) based on their associated exposures as constituents of the FCS. According to Chemistry, exposures to TFE, HFP and VDF are "essentially zero" (Elyashiv-Barad /Gilliam, 09/19/2002, RE FCN 260). Conversely, (b) (4) has a calculated EDI of 0.2 ng/p/d and the (b) (4) have an EDI of ≤ 0.15 µg/p/d (Elyashiv-Barad /Gilliam, 09/19/2002, RE FCN 260).

- TFE: The carcinogenicity of TFE was addressed by the notifier in their "Comprehensive Toxicology Profile" and supporting documentation consisting of a literature search and risk assessment were submitted in Appendix XIV of FCN 260. The risk assessment was conducted using the National Toxicology Program (NTP), "Toxicology and Carcinogenesis Studies of Tetrafluoroethylene (CAS No. 116-14-3) in F344 Rats and B6C3F1 Mice (Inhalation Studies)"³, reported in (b) (4). The unit cancer risk calculated by the notifier is 0.0536 (mg/kg bw/day)⁻¹ based on statistically significant findings in the female mouse of hepatocellular adenomas or carcinomas, hemangiosarcomas, renal tubule adenomas or carcinomas, mononuclear cell leukemia, and histiocytic sarcomas (all organs). The NTP study cited in the risk assessment was contract reviewed in FCN 101. The contract review of this study was conducted by S. G. Donkin, Ph.D. and J. Liccione, Ph.D. at Sciences International, Inc. (Contract (b) (4) work assignment number (b) (4)) and is located in FCN 000101 on pages 00184 - 00213. The TDER was secondary reviewed and accepted as final by A. Chang, Ph.D. (Chang/Zajac, 12/14/2000, RE FCN101), however, due to the conclusion by Chemistry that TFE was not likely to be present in the FCS, no unit cancer risk was calculated. As in FCN 101, Chemistry has determined that TFE is not likely to be present in the FCS in FCN 260; accordingly, the calculation of the unit cancer risk and worst-case lifetime cancer risk is unwarranted.
- HFP: The mutagenicity and carcinogenicity of HFP was addressed by the notifier in their "Comprehensive Toxicology Profile" and supporting documentation consisting of a literature search was submitted in Appendix XIV of FCN 260. According to the safety narrative, HFP was negative in Ames, CHO/HPRT, and a dominant lethal inhalation study in rats. HFP was weakly positive for clastogenicity in the mouse micronucleus assay and positive for chromosomal aberrations under conditions of metabolic activation in CHO cells. According to the notifier, HFP has not been tested for carcinogenicity.

Literature searches conducted in SIREN/FARM produced a citation for a mutation assay (CHO/HGPRT) in (b) (4). In addition, searches in Chem/Dplus and TSCAT produced numerous citations for LD50, 90 day, and mutagenicity studies. In agreement with the notifier's conclusion, HFP does not appear to have been tested for carcinogenicity.

- VDF: The mutagenicity and carcinogenicity of VDF was addressed by the notifier in their "Comprehensive Toxicology Profile" and supporting documentation of a literature search was submitted in Appendix XIV of the submission. According to the safety narrative, VDF was negative in the CHO/HPRT assay, the *in vitro* chromosome aberration assay using CHO cells, the mouse micronucleus assay, and the sex-linked recessive lethal assay in *Drosophila*. VDF was negative in one Ames assay and positive in another. An IARC summary report (1985, 1998) was included in the submission. According to the report, there is "inadequate evidence" of carcinogenicity for VDF.

Literature searches conducted in SIREN/FARM produced a carcinogenicity citation in FAP 9B4169. According to the petitioner (Pennwalt Corporation), rats were dosed with VF2 (VDF) dissolved in olive oil at 4.1 and 8.3 mg/kg for one year followed by an additional year of observation. After which, according to the notifier, the authors incorrectly combined tumor types and tumor sites concluding that there was evidence for carcinogenicity. The citation for the study was Maltoni C and Tovati D. First experimental evidence of the carcinogenic effects of vinylidene fluoride; long-term bioassays on Sprague-Dawley rats by oral administration. *Med Lav* 1979 Sep-Oct;70(5):363-8⁴. This study was reviewed by IARC. The endpoint of concern was liposarcomas. Additional searches of Chem/Dplus and TSCAT resulted in citations for several mutagenicity and 90-day studies. A bioassay citation was found in TSCAT: Chronic toxicity/carcinogenicity inhalation study of vinylidene fluoride vapour in rats (b) (4). With regard to the additional carcinogenicity study found concerning VDF, IARC has reviewed the data of vinylidene fluoride, twice, and determined both times that there is inadequate evidence for carcinogenicity. Although IARC did not review the bioassay submitted to EPA, it was determined at the Phase 1 meeting to be unwarranted due

³ National Toxicology Program. P.O. Box 12233 Research Triangle Park, NC 27709, April 1997. Toxicology and Carcinogenesis Studies of Tetrafluoroethylene (CAS No. 116-14-3) in F344 Rats and B6C3F1 Mice (Inhalation Studies), (b) (4).

⁴ This study was apparently republished in 1982 in *Ann. N.Y. Acad. Sci.* 381:216-249, and is listed as negative in a Chem/Dplus citation.

to the fact that a) the study is an inhalation study and the previously reviewed oral study was considered to lack evidence by IARC, b) several mutagenicity assays showed predominantly negative findings, and c) the exposure was expected to be low (< 50 ppt). In conclusion, we have found no positive indication of carcinogenicity by oral exposure for this compound based on the information currently available.

- Unidentified impurities: No information was included in the notification on the (b) (4), nor was there any way for Toxicology to ascertain the toxicology of these impurities by searching databases. A quick search of the other starting materials, not listed as impurities, (b) (4) and (b) (4) does not indicate a concern.

Toxicology has no questions regarding the exposure to TFE, HFP and VDF as constituents of the FCS based on their associated exposure of "essentially zero". In addition, Toxicology has no questions regarding the safety of the "unidentified impurities" based on their exposure estimate of ≤ 0.05 ppb and the lack of information indicating that they have been tested for carcinogenesis.

- (b) (4) For the proposed use of the FCS, Dyneon LLC submitted two mutagenicity studies and two bioassays on (b) (4). In addition, Dyneon LLC submitted four mutagenicity studies on (b) (4). Dyneon LLC submitted a risk assessment for (b) (4) determining the unit cancer risk to be $0.0148 \text{ (mg/kg bw/day)}^{-1}$. Literature searches conducted in SIREN/FARM, Chem/Dplus, and TSCAT produced numerous citations for (b) (4) and other less pivotal toxicology studies (epidemiology studies, LD50, and enzyme analysis). The conclusions of the submitted studies are provided below.

Mutagenicity studies concerning (b) (4).

(b) (4)

(b) (4)

(b) (4)




(b) (4)

In summary, (b) (4) is assumed to be a carcinogen with a unit cancer risk of $0.020 \text{ (mg/kg bw/day)}^{-1}$. Based on the EDI of 0.2 ng/p/d , the worst-case lifetime cancer risk from exposure to (b) (4) from its presence as a constituent of the FCS is 6.67×10^{-11} . Toxicology considers this risk to be of low concern based on the historically acceptable levels of cancer risk. Accordingly, Toxicology has no questions regarding the presence of (b) (4) in the FCS being notified for based on its associated exposure and the calculated cancer risk.

CONCLUSION(S)

Dyneon LLC proposes to use tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymers as a processing additive for polyolefins used in food contact applications. The FCS will be used at levels up to 2000 ppm in food-contact polyolefins with all food types under conditions of use B - H (boiling water sterilized - frozen or refrigerated storage) of 21CFR§176.170(c) Tables 1 and 2, respectively. Based on the EDI of $0.23 \text{ } \mu\text{g/person/day}$ (which corresponds to a dietary concentration of 0.07 ppb) for the oligomers of the FCS, the negative results of one genetic toxicology study and the lack of data indicating carcinogenic concerns for the FCS as well as an acceptable level of carcinogenic risk for the constituent (b) (4) Toxicology has no objection to the proposed use of the FCS as described in FCN 260.


Michelle L. Twaroski, Ph.D.
HFS-275

(b) (4)

(b) (4)

(b)

(4)

(b) (4)

(b) (4)



001962

(b) (4)



001963

(B) (4)

001964

(b) (4)



001965

(b) (4)

001966

(b) (4)

001968

(b) (4)



(b) (4)

001970

(b) (4)

001971

(b) (4)



001972

(b) (4)



(b) (4)



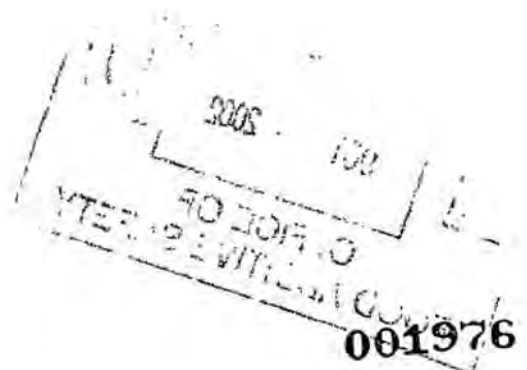
001974

(b) (4)

001975

(b) (4)


Michelle L. Twaroski, Ph.D.





DEPARTMENT OF HEALTH & HUMAN SERVICES

U.S. Food and Drug Administration, 5100 Paint Branch Parkway, College Park MD 20740

Public Health Service

Memorandum

AD

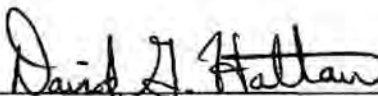


Date October 1, 2002

From Division of Food Contact Substance Notification Review (DFCSNR)

Subject Worst-case estimate of the unit cancer risk for (b) (4)

To Regulatory Group 1-DFCSNR
Attn.: Vivian Gilliam

Through David G. Hattan, Ph.D. 
Toxicology Review and CAC/QRAC Coordinator

FOOD CONTACT NOTIFICATION No. 260

Dyneon LLC
6744 33rd Street North
Oakdale, Minnesota 55128
651.737.8557 (T) 651.737.9909 (F)

Submitted via John B. Dubeck
Keller and Heckman LLP
1001 G. Street N.W., Suite 500 West
Washington, D.C. 20001
(T) 202.434.4125 (F) 202.434.4646

RELATED PETITIONS/NOTIFICATIONS

(b) (4)

INTRODUCTION

(b) (4)

001977

(b) (4)



(b) (4)



001979

(b) (4)


Michelle L. Twaroski, Ph D.
HFS-275

(b) (4)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: August 29, 2002
From: Director, Division of General Scientific Support
Subject: (b) (4) - Comments
To: Michelle Twaroski, Ph.D.
Office of Food Additive Safety, HFS-275

(b) (4)

001981

(b) (4)

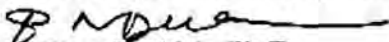


001982

(b) (4)



Let me know if you have any questions.


Prem N. Dua, D.V.M., Ph.D.

001983

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001992



Computer Technology Services, Inc.



DEPARTMENT OF HEALTH & HUMAN SERVICES

U S Food and Drug Administration, 5100 Paint Branch Parkway, College Park MD 20740

Public Health Service

Memorandum

AD

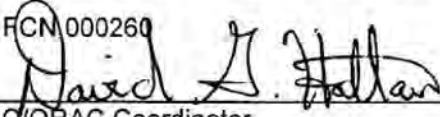


Date April 16, 2003

From Division of Food Contact Notifications (DFCN)

Subject Worst-case estimate of the unit cancer risk for tetrafluoroethylene (TFE)

To Memorandum to the file of FCN 000260

Through David G. Hattan, Ph D. 
Toxicology Review and CAC/QRAC Coordinator

FOOD CONTACT NOTIFICATION No. 260

Dyneon LLC
6744 33rd Street North
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651.737 8557 (T) 651 737 9909 (F)

Submitted via John B Dubeck
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1001 G Street N W , Suite 500 West
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INTRODUCTION

This memorandum calculates the worst-case unit cancer risk for tetrafluoroethylene (TFE, CAS No 116-14-3) using the most potent estimate derived from the review of two bioassays on TFE. The bioassays conducted by the National Toxicology Program (NTP), "Toxicology and Carcinogenesis Studies of Tetrafluoroethylene (CAS No 116-14-3) in F344 Rats and B6C3F1 Mice (Inhalation Studies)"¹, were reported in TR-450. This data was previously submitted in FCN 000101. The contract review of this study was conducted by S G Donkin, Ph D, and J. Liccione, Ph D., at Sciences International, Inc (Contract No (b) (4) work assignment number (b) (4) and is located in FCN 000101 on pages 00184 - 00213. The TDER was secondary reviewed and accepted as final by A Chang, Ph D (Chang/Zajac, 12/14/2000, RE FCN101), however, due to the conclusion by Chemistry that TFE was not likely to be present in the FCS, no unit cancer risk was calculated. Again, in FCN 000260, use of tetrafluoroethylene-hexafluoropropylene-vinylidene fluoride copolymers as a processing additive for polyolefins for use in contact with food, TFE was concluded to be "essentially zero" (Elyashiv-Barad /Gilliam, 09/19/2002, RE FCN 260). For the reason that the data have been reviewed and the unit cancer risk (UCR) calculated, this memorandum is being finalized to the file.

001993

¹ National Toxicology Program P O Box 12233 Research Triangle Park, NC 27709, April 1997 Toxicology and Carcinogenesis Studies of Tetrafluoroethylene (CAS No 116-14-3) in F344 Rats and B6C3F1 Mice (Inhalation Studies), TR-450

MUTAGENICITY

According to the NTP homepage, TFE tested negative in the micronucleus assay (male and female) and is currently the subject of an Ames assay using *Salmonella*².

CARCINOGENICITY

Rat Bioassay

In the NTP rat study, 60 F344N rats/group/sex were administered TFE at 0, 156, 312, and 625 ppm (males) or 0, 312, 625, and 1,250 ppm (females) via inhalation. Animals were exposed for 6 hours per day, 5 days per week, for 104 weeks and were observed for 11 days following the final exposure. According to NTP's classification system, there was "clear evidence" for carcinogenesis in male and female rats exposed to TFE. The authors of the study reported that long-term inhalation of TFE caused significant increases in renal tubule adenomas or carcinomas (combined) and hepatocellular adenomas or carcinomas (combined) in male and female rats. The incidence of mononuclear cell leukemia was increased in both sexes, while the incidence of hemangiosarcomas was increased in females treated with TFE. The neoplastic incidence data and the calculated unit cancer risk derived from this data are detailed below.

Male Rats

LESION	MALES			
	0	156	312	625
Renal tubule, adenoma or carcinoma (single and step sections combined) ^{3,4}	3/50	5/50	9/50	13/50*
Hepatocellular adenoma or carcinoma (overall rate) ⁵	4/50	7/50	15/50*	8/50
Mononuclear cell leukemia (all organs) ⁶	34/50	43/50*	38/50	31/50
Testis, interstitial cell adenoma ⁷	39/50	40/50	48/50*	47/50*

*Statistically significant at $p \leq 0.05$

Female Rats

LESION	FEMALES			
	0	312	625	1250
Renal Tubule, adenoma or carcinoma (single and step combined) ^{4,8}	0/50	3/50	3/50	10/50*
Hepatocellular adenoma or carcinoma (overall rate) ⁵	0/50	7/50*	12/50*	8/50*
Hemangiosarcoma (overall rate) ⁵	0/50	0/50	5/50*	1/50
Mononuclear cell leukemia (all organs) ⁶	16/50	31/50*	23/50*	36/50*

*Statistically significant at $p \leq 0.05$

² http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/Res_Stat/iH_Res_Stat_Frames.html

³ Renal tubule, adenoma or carcinoma (single) was not significantly positive, but the author's conclusion is the compound is a renal carcinogen

⁴ Incidence data for the "Single Sections or Standard Evaluation" for males and females can be found in the TDER on page 16, Table 2, however, the "Single and Step Sections (Combined)" are not summarized in the NDER. These data are summarized for males on page 45, Table 9 and for females on page 46, Table 9 of the NTP report. The NTP report table contains details of the statistical analysis results.

⁵ Incidence data can be found in the TDER on page 18, Table 3 and on page 48, Table 10 (males) and page 49, Table 10 (females) of the NTP report. The NTP report table contains details of the statistical analysis results.

⁶ The incidence of mononuclear cell leukemia is discussed in the TDER on page 19. Tabulated incidence data for males and females are presented in the NTP report on page 51, Table 11. The NTP report table contains details of the statistical analysis results.

⁷ The incidence of interstitial cell adenoma of the testes is discussed in the TDER on page 19 and in the NTP report on page 71. Incidence data are presented on page 11 of the NTP report and discussed on page 71.

⁸ Renal tubule, adenoma or carcinoma (single) was significantly positive for high dose females, but was counted in the single and step combined data.

In the absence of scientific data that suggests a more appropriate approach, the following assumptions have been made in order to calculate a unit cancer risk for TFE based on the NTP study in rats: 1) the UCR is defined as the slope of the dose-response curve drawn from the lowest apparent effect dose of TFE to zero; 2) that tumors arising at multiple sites or from different tissues at the same site are independent of each other and are additive in calculating the UCR; 3) the lowest dose at which the incidence of neoplastic effects was significant is used to calculate the UCR; and 4) the following assumptions are acceptable to use in converting ppm to mg/kg bw/day⁹.

- The molecular weight of TFE is 100.0156
- Doses are converted from ppm (administered) to mg/m³ (absorbed) using the following equation. (molecular weight/24.45) x ppm, assuming standard temperature (25C) and pressure (760 mm Hg)
- Rat alveolar ventilation rate is 52.9 ml/min/100 g equivalent to 8 L/hour/rat for 250 g rat (assumed average)¹⁰⁻¹¹
- The alveolar absorption of TFE is 10%¹²

For example, based on the above-mentioned assumptions, the mg/kg bw/day of a rat on this study treated with 156 ppm of TFE would be:

mg/m³/hour absorbed:

$$(156 \text{ ppm}) \times (100.0156 / 24.45) = 638.1363 \text{ mg/m}^3$$

Adjusted for exposure duration:

$$(638.1363 \text{ mg/m}^3) \times (6 \text{ hours} / 24 \text{ hours}) \times (5 \text{ days} / 7 \text{ days}) = 113.9529 \text{ mg/m}^3/\text{hour}$$

Adjusted for absorption:

$$(113.9529 \text{ mg/m}^3) \times (10\%) = 11.3953 \text{ mg/m}^3/\text{hour}$$

mg/m³/hour converted to mg/day/rat:

$$[(11.3953 \text{ mg/m}^3) / (\text{m}^3 / 1000 \text{ L})] \times (8 \text{ L/hour/rat}) \times (24 \text{ hours/day}) = 2.1879 \text{ mg/rat/day}$$

mg/rat/day converted to mg/kg bw/day:

$$(2.1879 \text{ mg/rat/day}) / (0.250 \text{ kg bw/rat}) = 8.7516 \text{ mg/kg bw/day}$$

Accordingly, the converted doses are as follows.

ppm	156	312	625	1250
mg/kg bw/day	8.75	17.50	35.06	70.12

$$\begin{aligned} \text{Unit cancer risk}_{\text{males}} &= ((13/50 - 3/50) / 35.06) + ((15/50 - 4/50) / 17.50) + ((43/50 - 34/50) / 8.75) + ((48/50 - 39/50) / 17.50) \\ &= 0.0057 + 0.0126 + 0.0206 + 0.0103 \\ &= 0.0492 (\text{mg/kg bw/day})^{-1} \end{aligned}$$

$$\begin{aligned} \text{Unit cancer risk}_{\text{females}} &= ((10/50 - 0/50) / 70.12) + ((7/50 - 0/50) / 17.50) + ((5/50 - 0/50) / 35.06) + ((31/50 - 16/50) / 17.50) \\ &= 0.0028 + 0.0080 + 0.0028 + 0.0171 \\ &= 0.0307 (\text{mg/kg bw/day})^{-1} \end{aligned}$$

⁹ Model used for calculation is that for 1,3-butadiene detailed in Ekelman/Lorentzen, 03/03/2000, RE worst-case estimate of human cancer risk for 1,3-butadiene ..

¹⁰ Brown RP, Delp MD, Lindstedt SL, Rhomberg IR and Belliles RP (1997). Physiological parameter values for physiologically based pharmacokinetic models. *Toxicol Ind Health* 13(4) 407-484.

¹¹ 8L/hour/rat represents the rate for males, however this number can be used for both sexes due to the fact that both body weight and breathing rate are lower in females

¹² 10% is the lower bound of the range for rats and rabbits based on conclusions drawn by William L. Roth, Ph.D., DABT (Attachment - Roth/Twaroski, 04/02/03, RE Absorption, Distribution, Metabolism and Elimination of fluoroethanes) which considered the study cited NTP TR-450 on page 16: Ding, X.Z., Yu, H.T., Hu, M., Liu, C.F., and Ko, F.Z. (1980) Studies on the absorption, distribution, and elimination of four organofluorine compounds in rabbits. *Chung Hua Yu Fang I Hsueh Tsa Chih* 14, 39-42. The NTP cited study indicated 6.76% absorption for TFE in rabbits.

Mouse Bioassay

Briefly, 58 B6C3F1 mice/group/sex were administered TFE at 0, 312, 625, and 1,250 ppm via inhalation. Animals were exposed for 6 hours per day, 5 days per week, for 95 to 96 weeks. Due to decreased survival, the study was terminated during week 96. According to NTP's classification system, there was "clear evidence" for carcinogenesis in male and female mice exposed to TFE. The authors noted that long-term inhalation of TFE caused an increase incidence in histiocytic sarcomas and hepatic (adenomas, carcinomas, hemangiomas, and hemangiosarcomas) lesions in male and female mice. The neoplastic incidence data and the calculated unit cancer risk derived from this data are detailed below.

Male Mice

LESION	PPM			
	0	312	625	1250
Hemangioma or hemangiosarcoma ¹³	0/48	26/48*	30/48*	38/48*
Hepatocellular adenoma or carcinoma ¹³	26/48	34/48*	39/48*	35/48*
Histiocytic sarcoma (overall rate, all organs) ¹⁴	0/48	12/48*	7/48*	7/48*

*Statistically significant at $p \leq 0.05$.

Female Mice

LESION	PPM			
	0	312	625	1250
Hemangioma or hemangiosarcoma ¹³	0/48	31/48*	28/47*	35/47*
Hepatocellular adenoma or carcinoma ¹³	17/48	33/48*	29/47*	28/47*
Histiocytic sarcoma (overall rate, all organs) ¹⁴	1/48	21/48*	19/47*	18/48*

*Statistically significant at $p \leq 0.05$.

In the absence of scientific data that suggests a more appropriate approach, the following assumptions have been made in order to calculate a unit cancer risk for TFE based on the NTP study in mice: 1) the UCR is defined as the slope of the dose-response curve drawn from the lowest apparent effect dose of TFE to zero; 2) that tumors arising at multiple sites or from different tissues at the same site are independent of each other and are additive in calculating the UCR; 3) the lowest dose at which the incidence of neoplastic effects was significant is used to calculate the UCR; and 4) the following assumptions are acceptable to use in converting ppm to mg/kg bw/day¹⁵:

- The molecular weight of TFE is (b) (4)
- Doses are converted from ppm (administered) to mg/m³ (absorbed) using the following equation. (molecular weight/24.45) x ppm, assuming standard temperature (25C) and pressure (760 mm Hg)
- Mouse alveolar ventilation rate is 116.5 ml/min/100 g equivalent to 2.1 L/hour/mouse for 30 g mouse (assumed average)¹⁶⁻¹⁷
- The alveolar absorption of TFE is 10%¹⁸

¹³ Incidence data can be found in the TDER on page 25-26, Table 6 and on page 62, Table 19 (males) and page 63, Table 19 (females) of the NTP report. The NTP report table contains details of the statistical analysis results

¹⁴ Histiocytic sarcoma is discussed on page 26 on the TDER. Table 20 on page 65 of the NTP report contains the tabulated incidence data. The NTP report table contains details of the statistical analysis results

¹⁵ Model used for calculation is that for 1,3-butadiene detailed in Ekelman/Lorentzen, 03/03/2000, RE worst-case estimate of human cancer risk for 1,3-butadiene

¹⁶ Brown RP, Delp MD, Lindstedt SL, Rhomberg IR and Beliles RP (1997) Physiological parameter values for physiologically based pharmacokinetic models. *Toxicol Ind Health* 13(4) 407-484

¹⁷ 2.1 L/hour/mouse represents the rate for males, however this number can be used for both sexes due to the fact that both body weight and breathing rate are lower in females

¹⁸ 10% is the lower bound of the range for rats and rabbits based on conclusions drawn by William L. Roth, Ph.D., DABT (Attachment - Roth/Twaroski, 04/02/03, RE Absorption, Distribution, Metabolism and Elimination of fluorocarbons) which considered the study cited NTP TR-450 on page 16. Ding, X.Z., Yu, H.T., Hu, M., Liu, C.F., and Ko, F.Z. (1980). Studies on the absorption, distribution, and elimination of four

For example, based on the above-mentioned assumptions, the mg/kg bw/day of a mouse on this study treated with 312 ppm of TFE would be

$$\begin{aligned}
 &\text{mg/m}^3/\text{hour absorbed} && (312 \text{ ppm}) \times (100 \text{ 0156/24 45}) = 1276 \text{ 2727 mg/m}^3 \\
 &\text{Adjusted for exposure duration} && (1276 \text{ 2727 mg/m}^3) \times (6 \text{ hours/24 hours}) \times (5 \text{ days/7 days}) = 227 \text{ 9058 mg/m}^3/\text{hour} \\
 &\text{Adjusted for absorption} && (227 \text{ 9058 mg/m}^3) \times (10\%) = 22 \text{ 7906 mg/m}^3/\text{hour} \\
 &\text{mg/m}^3/\text{hour converted to mg/day/mouse} && [(22 \text{ 7906 mg/m}^3) / (\text{m}^3/1000 \text{ L})] \times (2 \text{ 1 L/hour/mouse}) \times (24 \text{ hours/day}) = 1 \text{ 1486 mg/mouse/day} \\
 &\text{mg/mouse/day converted to mg/kg bw/day} && (1 \text{ 1486 mg/mouse/day}) / (0 \text{ 030 kg bw/mouse}) = 38 \text{ 29 mg/kg bw/day}
 \end{aligned}$$

Accordingly, the converted doses are as follows

ppm	312	625	1250
mg/kg bw/day	38 29	76 70	153 40

$$\begin{aligned}
 \text{Unit cancer risk}_{\text{male}} &= ((26/48-0/48)/38 \text{ 29}) + ((34/48-26/48)/38 \text{ 29}) + ((12/48-0/48)/38 \text{ 29}) \\
 &= 0 \text{ 0141} + 0 \text{ 0044} + 0 \text{ 0065} \\
 &= 0 \text{ 0250 (mg/kg bw/day)}^{-1}
 \end{aligned}$$

$$\begin{aligned}
 \text{Unit cancer risk}_{\text{female}} &= ((31/48-0/48)/38 \text{ 29}) + ((33/48-17/48)/38 \text{ 29}) + ((21/48-1/48)/38 \text{ 29}) \\
 &= 0 \text{ 0169} + 0 \text{ 0087} + 0 \text{ 0109} \\
 &= 0 \text{ 0365 (mg/kg bw/day)}^{-1}
 \end{aligned}$$

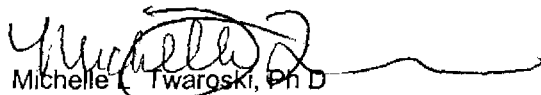
For this unit cancer risk calculation, the test substance (TFE) is assumed to be a carcinogen and the sex, species and study that results in the highest unit cancer risk for the test substance is used in future risk assessments for that chemical. Bioassays in rats and mice have been reviewed and both species show potentially positive tumor responses to TFE and are of suitable quality for use in a quantitative risk assessment. The unit cancer risks derived from the rat data are 0 0492 and 0 0307 (mg/kg bw/day)⁻¹ in males and females, respectively. The unit cancer risks derived from the mice data are 0 0250 and 0 0365 (mg/kg bw/day)⁻¹ in males and females, respectively. Therefore, the worst-case unit cancer risk for TFE is 0 0492 (mg/kg bw/day)⁻¹.

CONCLUSION

This memorandum summarizes the neoplastic findings from NTP bioassays on TFE, an impurity of the FCS being notified for in FCN 260, and the calculated unit cancer risks derived from these studies. The unit cancer risk derived from this analysis is based upon the conservative but unproven assumption that TFE is a carcinogen and that data derived from the rodent studies on TFE summarized herein can be used to estimate human cancer risk from exposure to TFE. This estimation of the unit cancer risk associated with TFE does not constitute a Center or Agency decision that the chemical is a carcinogen and data contained herein should be used for the sole purpose of estimating risk and not as supporting data for the development of policy or modeling of carcinogenic chemicals.

001997

We ask your concurrence with the method used to calculate the unit cancer risk for TFE and the resulting conclusions



Michelle L. Twaroski, Ph.D.

Attachment Roth/Twaroski, 04/02/03, RE Absorption, Distribution, Metabolism and Elimination of fluoroethanes
HFS-275

001998



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date April 2nd, 2003

From Division of Food Contact Notifications (DFCN)

Subject (b) (4)

To Michelle Twaroski, Ph.D., DFCN
Primary Reviewer, FCN 260

Through Chingju Sheu, Ph.D. *Chi W. Sheu*
Group Leader, Toxicology Group 2, DFCN

(b) (4)

001999

(b) (4)



William L. Roth, Ph.D., D.A.B.T.

cc: Yan Gu, Ph.D., DFCN

attachments

002000

(b) (4)



002001

Attachment 1

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002002

(b) (4)



(b) (4)

Attachment 2

