DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: September 21, 2006

From: Division of Food Contact Notifications, HFS-275
Chemistry Review Group 1
Petra Turowski, Ph.D.

Subject: **FCN 628:** Clariant Corporation, via Keller and Heckman LLP. Copolymer of 2-perfluoroalkylethyl acrylate, 2-(dimethylamino)ethyl methacrylate, and oxidized 2-(dimethylamino)ethyl methacrylate as a grease proofing agent in the manufacture of paper and paperboard. Submissions received 4/17/06 (initial), 5/26/06 (1st amendment), 6/12/06 (2nd amendment), 6/22/06 (clarification), and 7/24/06 (revised notification language).

To: Division of Food Contact Notifications, HFS-275
Regulatory Group 2
Attention: Vanee Komolprasert, Ph.D.

Clariant Corporation (CLA), through their agent Keller and Heckman LLP (K&H), submitted this notification for the use of the food contact substance (FCS) identified as a copolymer of 2-perfluoroalkylethyl acrylate (PFAA), 2-(dimethylamino)ethyl methacrylate (DMAEMA), and oxidized 2-(dimethylamino)ethyl methacrylate (DMAOEMA) as a grease proofing agent in the manufacture of paper and paperboard. CLA proposes use of the FCS for 1) wet-end application in the papermaking process, at a level not to exceed (NTE) 0.5 wt-% in the finished paper, under Conditions of Use A-H, or 2) size press application in the papermaking process, at a level NTE 0.7 wt-% in the finished paper, under Conditions of Use C-G.

The initial submission contains FDA Form 3480 and 22 Attachments, which consist of the Comprehensive Toxicological Profile (CTP) and the 21 numbered Attachments listed in Part IV of Form 3480. Chemistry information is contained in Form 3480 and Attachments 1-15 and 21, Items 1-5 and 2 attachments (Attachments A and B) to the 5/26/06 amendment, Items 1-3 and 3 attachments (Attachments C-E) to the 6/12/06 submission, and in the 6/22/06 submission with one attachment (Attachment F).

(b) (4) [redacted]. The FCS is not regulated or effectively notified for use as a component of food-contact articles.

As discussed below, the dietary concentration (DC) of FCS oligomers is 18 μg/kg (EDI of 54 μg/p/d). The DCs for all other migrants range from 0.001 to 0.3 μg/kg as shown in Table 4 of this memorandum.

Unless otherwise specified, percentages are in percent by weight (wt-%).

Identity

Information on the identity of the FCS is contained in Form 3480, Section II.A, and supported in

Attachments 1-2. The FCS is marketed as an aqueous formulation containing dipropylene glycol.

Name: Copolymer of 2-perfluoroalkylethyl acrylate, 2-(dimethylamino)ethyl methacrylate, and oxidized 2-(dimethylamino)ethyl methacrylate

CAS Reg. No.: 479029-28-2

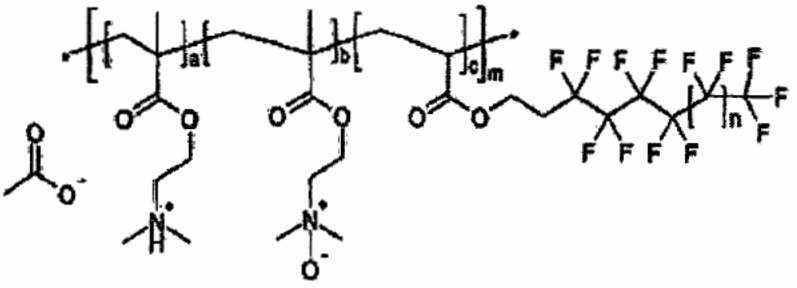
CAS Name: 2-Propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester, polymers with 2-γ-ω-perfluoro-C_{8-14}-alkyl acrylate, acetates, N-oxides

Trade Name: (b) (4) [redacted]

Formulation: (b) (4) [redacted]

Molecular weight: [redacted]

Structure:



The FCS is a polyacrylate material containing perfluoroalkyl ester, (dimethylamino)ethyl ester and oxidized (dimethylamino)ethyl ester side-chains. The units derived from each monomer are as follows: (b) (4) [redacted]% PFAA, (b) (4) [redacted]% DMAOEMA, and (b) (4) [redacted]% DMAEMA. The major monomer, PFAA, reportedly consists of perfluoroalcohol moieties where (b) (4) [redacted], [redacted] expressed in another manner, a range of C_8, C_{10}, C_{12} and C_{14} homologues (including all carbons in the alcohol moiety). The predominant alcohol moiety is $CF_3(CF_2)_7(CH_2)_2O$- (the C_{10} homologue where n=3).

The FCS was characterized by an infrared (IR) spectrum, which is provided in Attachment 2 and is consistent with the structure.

We have no questions on the identity of the FCS.

Manufacture

Manufacturing information is contained in Form 3480 (Part II.B) and in Attachment 3. Information on starting materials and manufacturing impurities are provided in Attachments 4 and 5, respectively.

(b) (4)

[redacted]

Table 1. Impurities in the wet formulation (from Form 3480, Part II.B.3)[1]

Substance	Abbreviation	CAS #	Function	Residual Level
Perfluoroalkylethyl acrylate	PFAA	85631-54-5	Monomer	(b) (4)
Perfluoroalkylethanol	PFOH		Hydrolysis by-product	
(b) (4)				
2-(Dimethylamino)ethyl methacrylate	DMAEMA	2867-47-2	Monomer	
Oxidized DMAEMA	DMAOEMA		"	
(b) (4)				

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

Physical Properties and Specifications

Information on the physical properties and specifications of the FCS formulation is presented in (b) (4) density of 1.13 g/mL. The notifier reported a DMAEMA level of <0.05% as a specification.

We have no questions on the physical properties or specifications of the FCS.

[1] As described in Attachment 5, PFAA, PFOH, PFAE, (b) DMAEMA, and (b) were analyzed by gas chromatography (GC) with mass spectrum (MS) detection. According to Form 3480 Part II.B.3, the DMAOEMA level is estimated by multiplying the DMAEMA residual by a factor of 1.4, whereas the residual initiator decomposition products were calculated from the amount of initiator used in the manufacture (details in Attachment 6).

Intended Use and Technical Effect

Information on the intended use and technical effect of the FCS is contained in Form 3480, Part II.D, and Attachments 5 (technical leaflet) and 8 (technical effect data). The FCS is intended for use as a grease-proofing agent in the manufacture of food-contact paper and paperboard. The FCS may be added by:

1. wet-end application, at a level NTE 0.5 wt-% in the finished paper, under Conditions of Use A-H, or
2. size press application, at a level NTE 0.7 wt-% in the finished paper, under Conditions of Use C-G.

Attachment 8 contains data on the grease resistance and water repellent properties of the FCS added at the wet-end or at the size press. Grease resistance data (Kit test) and water absorption data ($Cobb_{60}$ test) were provided from 0.06-0.36 g FCS/m^2 (0.08-0.47 wt-% using a paper basis weight of 80 g/m^2) at the size press and 5-25 kg formulation/ton (0.11-0.55 wt-% FCS, using 22 wt-% FCS in formulation) at the wet-end. Increasing Kit values and decreasing water absorption were observed.

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

Stability

Information on the stability of the FCS is contained in Form 3480, Section II.E, Attachments 9 (thermal stability studies) and 10 (hydrolytic stability studies). Additional information on the thermal stability is provided in Items 2 of the 5/26/06 submission. Additional information on the hydrolytic stability is provided in Item 3 of the 5/26/06 submission, in Items 1 and 2 of the 6/12/06 submission, and in Attachments A (narrative for Attachment 10), C (GC/MS method used in hydrolytic stability studies), and D (data on PFOH content in FCS formulations).

The FCS is a polyacrylate material containing perfluoroalkyl ester, (dimethylamino)ethyl ester and oxidized (dimethylamino)ethyl ester side-chains. The notifier conducted several thermal and hydrolytic stability studies to demonstrate that the perfluoroalkyl side-chain is reasonably stable during storage of the FCS formulations and under the intended conditions of use. (Thermolysis or hydrolysis of the perfluroalkyl side-chain would produce PFOH.)

The thermal stability of the "wet" and "dry" FCS was studied using thermal gravimetric analysis (TGA) with analysis of the volatile components from "dry" FCS by head-space GC-MS. In the first report (sample identified as CLA 374), Figure 1 ("wet" FCS) of Attachment 9 indicates the loss of water (~80-90°C, 45% mass loss), glycol (~150-180°C, 20% mass loss), and degradation of the polymer backbone (300-350°C, 100% mass loss). Figure 2 ("dry" FCS) of Attachment 9 indicates a mass loss of ~5% up to 150°C with degradation occurring in the range of 250-350°C. At 90°C, water and glycol were detected, while at 120°C, traces of PFOH and acetic acid were detected. At 180°C, increasing amounts of PFOH and (dimethylamino)ethanol were observed.

The hydrolytic stability of the FCS at 50°C was studied using "dry" FCS, diluted FCS formulations (~10 wt.-% FCS in water) at pH 4-9, and paper containing the FCS added at the size

press. (The results of paper extractions will be discussed below in the "Migrant Levels in Food" section.) The greatest extent of hydrolysis was observed in diluted FCS formulations at 50°C after 3 months. After correcting for the dilution, the PFOH content in the FCS formulation was found to increase from 0.8 to 1.4 wt-% (see Attachment 10, p 5 (p. 182), and Attachment A, p.7). CLA also provided PFOH measurements on an undiluted (commercial) FCS formulation stored for up to 1 year at room temperature, in which levels as high as 1 wt-% PFOH were observed (see Attachment A, p. 5 and 6/12/06 submission, Item 2).

We will conservatively assume that the PFOH content of the FCS formulation is 1.4 %, as found in the diluted formulation stored for 3 months at 50°C. As reproduced in Table 1, the typical PFOH content in the formulation (of unspecified age) is 0.95 %, whereas the average PFOH content in fresh formulations is apparently only 0.56 % (see Attachments A (p. 5) and D).

We have no questions regarding the stability of the FCS.

Migrant Levels in Food

Information on migrant levels in food is contained in Form 3480, Part II.F, and in Attachments 11 (migration calculations for wet-end use), 12 (migration study report for size-press use) and 14 (migration calculations for size-press use). The migration studies in 10% and 50% aqueous ethanol (Attachment 12) were conducted by Covance Laboratories. CLA also conducted an aqueous extraction of treated paper (size press) at 50°C and various pH values (Attachments 10 and A). Additional information on these studies is contained in the 5/26/06 submission (Items 3.1 and 5, Attachments A and B), in the 6/12/06 submission (Items 1-3, Attachments C and E), and in the 6/22/06 submission, including Attachment F.

Paper Samples. As described in the 5/26/06 submission (Items 3.1 and 5.1), samples used for testing were coated with the FCS at the size press using a substrate paper with a basis weight of 85 g/m^2 (55 mg/in^2). The paper was treated with an 8% starch size formulation containing 0.7 % of the FCS (3.5% of formulation). The dry pick-up was 0.40-0.42 g/m^2 FCS, which is 0.47-0.50 wt-% FCS in the dry, finished paper (*e.g.*, 0.40-0.42 g FCS/m^2/85 g paper/m^2). In the 6/12/06 submission (Item 2), the notifier stated that the FCS formulation was more than 9 months old. As stated in Attachment 12 (p. 9), control articles consisted of paper without the FCS.

Migration Testing by Covance (Attachment 12). Protocol. As discussed in the 5/26/06 submission (Item 5.1), triplicate migration tests in 10% and 50% ethanol were performed using 1.5 sheets of paper (8.375" x 11.625" per sheet) for each replicate (146.04 in^2). The sheets were reportedly cut into three strips,[2] which were separated by Teflon screens and rolled into bundles tied with steel wire. According to Attachment 12 (p.10), test articles had a single-sided surface area of 146 in^2 and were extracted with 584 mL of extraction solvent (4 mL/in^2; no cloudiness was observed in the extracts) using the migration protocol for Conditions of Use C (2 h at 66°C followed by 238 h at 40°C).

Analysis. The migration extracts were sampled after 2 h, 4 d, and 10 d, and analyzed for MIB, (b) (4), PFOH and PFAA. PFOH and PFAA were analyzed using GC with an electron capture

[2] Although the surface area used in the tests was well defined, the number of strips was not.

detector (ECD) after a hexane extraction procedure, as described in Appendix A of Attachment 12 (pp. 34-35) and in the 6/22/06 submission. Analysis methods for (b) (4) using head-space GC with flame ionization detector (FID) and PFOA using high performance liquid chromatography (HPLC) with MS detection are also described in Appendix A of Attachment 12 (pp. 32-33).

Method calibration. The preparation of calibration standards was described in Appendix B of Attachment A (pp. 32-35), whereas standard concentrations, calibration curves, and standard chromatograms are contained in Appendix B of Attachment A (pp. 37-78). Standard chromatograms containing 0.05 to 1.33 μg/mL (b) (4) were prepared from serial dilution in 10% or 50% ethanol of a stock solution in 95% ethanol (Attachment 12, pp. 32, 37-39, and 44-46). A stock solution of (b) (4) was prepared in methanol and diluted with 10% or 50% ethanol to concentrations of 5-100 ng/mL (Attachment 12, pp. 33, 51-53, and 57-59). For PFOH, stock and standard solutions (0.25-2 μg/mL) were prepared in hexane. A 1.0 mL portion of each standard was extracted with 49 mL of 10% or 50% ethanol in a 50 mL volumetric flask and 2 μL of the hexane layer was analyzed by GC-ECD (Attachment 12, pp. 34, 62-64, and 69-71). Stock and standard solutions (0.5-0.48 μg/mL) of PFAA in hexane were prepared for analysis without prior extraction with aqueous ethanol (pp. 35, 76-78).

Results. Sample and control chromatograms were provided in Appendix B and C of Attachment 12 (pp. 40-86, 89-91). Migration test results were provided in Form 3480 (Part II.F), Attachment 12 and amended in the 6/12/06 submission, including Attachment E. Covance reported no detectable migration of (b) (4) and (b) (4), with limits of detection (LODs) of 10 ng/in^2 and 100 ng/in^2, respectively. According to the original submission, PFOH and PFAA were not detected or barely detected at levels of <10-11.6 ng/in^2 or <10-10.6 ng/in^2, respectively. According to Attachment E (6/12/06 submission), PFOH was not detected (<10 ng/in^2) in 10% ethanol extracts and only detected at a level of 10 ng/in^2 in 50% ethanol extracts after 2 h.

We note that the LODs reported in the Covance study should be multiplied by a factor of two to account for their erroneous use of the double-sided surface area rather than the single-sided surface area in calculations. Thus, the LOD for (b) (4), PFOH, and PFAA is 20 ng/in^2, whereas that for MIB is 200 ng/in^2.

Method validation. The validation of the analytical methods was briefly described in Attachment 12 (p. 13 and Tables 9-16). A detailed description of the validation for PFOH was provided in the 6/22/06 submission, including Attachment E. Validation chromatograms, mostly at the LOD, are contained in Appendix B of Attachment 12 (pp. 43, 50, 56, 61, 68, 75, 82-83, and 87). Validation experiments were conducted on paper controls rather than on the test samples. Nevertheless, taking into account the information contained in the 6/22/06 submission and carefully comparing chromatograms contained in Appendix B of Attachment 12, we believe that the migration study results were adequately validated.

On inspection of the PFOH chromatograms of 10% ethanol extracts, it appeared to us that the PFOH signals with retention times near 3 min and 11 min were not clearly observed at the LOD (p. 255). Since the PFOH chromatograms of 50% ethanol extracts did not include data beyond a retention time of 10 min, all signals attributed to PFOH cannot be compared. Moreover, two peaks appeared to be observed in the standard chromatograms for PFOH in 50% ethanol while one peak was observed in 10% ethanol. We inquired about these observations in the 5/12/06 and

6/5/06 letters to the notifier. The notifier explained that using all four PFOH signals to plot calibration curves led to "poor linearity and calibration curves," so only the 3-minute peak was originally used for the 10% ethanol data, whereas the first two peaks were used for the 50% ethanol data (see 6/12/06 submission, Item 3). The notifier recalculated the 10% ethanol results using the only first two peaks. Since all the peaks are not visible in the chromatograms spiked with PFOH at the lowest level, it appears to us that the real LOD for PFOH corresponds to twice the corrected reported LOD of 20 ng/in^2, or 40 ng/in^2.

To summarize the results of migration testing and incorporating our correction values, PFOH was not detected at 40 ng/in^2, (b) (4) and PFAA were not detected at 20 ng/in^2, and (b) (4) not detected at 200 ng/in^2.

Extraction Testing by CLA (Attachment 10). Paper samples prepared as described above were immersed in aqueous food simulants (water, pH 4 phthalate buffer, ph 7 phosphate buffer and pH 9 borate buffer) for periods of 8 days or 3 months at 50°C at a ratio of 50 g paper/L buffer. As described in Attachment C, extracts were dried, re-dissolved in acetonitrile and filtered, prior to analysis for PFOH by GC/MS using internal and external standards. After 8 days, a level of up to 2.8 mg PFOH was detected in the pH 9 extracts per kg of paper. Using a paper basis weight of 55 mg/in^2, this corresponds to a PFOH migration of up to 150 ng/in^2. The analytical method is described briefly in Attachment 10 and clarified in the 5/26/06 (Attachment A) and 6/12/06 (Item 1 and Attachment C) submissions.

Summary of Migration and Extraction Testing Results. Results of migration and extraction testing are summarized in Table 2, below. The values in µg/kg food were calculated assuming 10 g of food is in contact per in^2 of paper and were further multiplied by a factor of 1.44 to account for the actual level of FCS in the paper (0.47-0.5 %), which was less than the intended level of use at the size press (0.7 %). Given that PFOH levels in food were determined to be <40 ng/in^2 based on validated analytical method, we used the lower reported value and a combined food-type distribution factor (f_T) of 1 to calculate a weighted-average migration of PFOH (<M>) as follows:

$$\langle M\rangle_{PFOH} = [(M_{nonfatty})(f_{nonfatty}) + (M_{fatty})(f_{fatty})]$$

$$= [(5.8\ \mu g/kg)(1)]$$

$$= 6\ \mu g/kg \text{ (rounded)}$$

Table 2. Empirical migration for size press addition

Migrant	PFOH	PFAA	(b) (4)
Migration (ng/in^2) for 0.5 % FCS	<40[a]/150[b]	<20	
Migration (µg/kg) for 0.7% FCS	<5.8[a]/22[b]	<3	
<M> (µg/kg)	<6	<3	

[a] In aqueous ethanol. [b] In aqueous buffer, pH 9.

Migration Calculations. To determine all migrant levels in food for wet-end addition and for other migrants for size press addition (other than PFOH, PFAA, and (b)), residue levels were used to approximate the maximum expected exposure to oligomers and impurities, as addressed in Form 3480 (Part II.F.2) and Attachments 11 and 14.

Wet-end use. As discussed in Form 3480 (Part II.F.2) and Attachment 11, the notifier calculated migration levels based on residual levels (see Table 1, above) and the fraction of low molecular weight oligomers (LMWO) with a MW < 2000, assuming that only LMWOs are substantive to paper and that 98% of the non-substantive substances would remain in the whitewater. Further assumptions included a paper basis weight of 50 mg/in^2, 10 g of food in contact per in^2 of paper, 0.5% FCS in the paper, and 24% "dry" FCS in the formulation. We note that formulations used to determine impurity levels actually contained an average of 22.4 % "dry" FCS. We also note that our typical assumptions for non-substantive, wet-end additives do not take into account the extensive recycling of whitewater that occurs during the papermaking process. In the future, the DFCN may wish to investigate the effect of whitewater recycling on the cumulative concentration of non-substantive additives and other migrants.

Size-press use. As discussed in Attachment 14, the notifier used the same assumptions as for wet-end use, except that there would be no removal of migrants in whitewater. Furthermore, the intended use level is 0.7%.

Migration to food. Calculated migration values for wet-end and size press addition are summarized in Table 3, below. Our calculated values were slightly higher than the notifier's (see Attachment 15), since we used the actual FCS concentration of 22.4 % (rather than 24%). Since (b) (4) [redacted]

Table 3. Summary of Calculated and Experimental Migrant Levels in Food (μg/kg)

Migrant	Wet-end	Size-press
LMWO of the FCS	1270	1780
PFAA	0.075	3 (exp.)
PFOH	21.2	6 (exp.)
(b) (4) [redacted]		
DMAEMA	0.045	3.1
DMAOEMA	0.063	4.4
(b) (4) [redacted]		

We have no questions regarding migrant levels resulting from use of the FCS.

Consumer Exposure

Consumer exposure to the FCS was addressed in Form 3480 (Part II.G) and Attachments 13 (market-based consumption factor [CF] calculations) and 15 (exposure calculations).

To calculate a refined CF, the notifier used market volume limitations (350 metric tons of the formulation/yr used at the wet end; 100 metric tons of the formulation/yr used at the size press) as shown in Attachment 13. They used the same assumptions described in the migration section (above) as well as a typical FCS level in formulations of 24%, a US population of 290 million people, and a daily intake of 3000 g food/person/day. Thus, the refined CFs for this FCS were calculated as 0.011 for wet-end addition (32 g food/person/day packaged in FCS wet-end treated paper) and 0.0022 for size press addition (6.5 g food/p/d packaged in FCS size-press treated paper).

To calculate the DC for the FCS migrants, we multiplied migration values shown in Table 3 (above) by the appropriate refined CF (using 2 significant digits)[3] as follows:

$DC_{migrant} = CF_{wet\ end} \times \langle M \rangle_{wet\ end} + CF_{size\ press} \times \langle M \rangle_{size\ press}$

The estimated daily intake (EDI) was calculated assuming a diet of 3 kg per person per day (3 kg/p/d). The DCs and EDIs are displayed in Table 4, below.

Table 4. Consumer Exposure

Migrant	$DC_{wet\ end}$ (ng/kg)	$DC_{size\ press}$ (ng/kg)	DC (ng/kg)	EDI (ng/p/d)
FCS oligomers	14,000	3,800	18,000	54,000
PFAA	0.8	6.5	7.3	22
PFOH	230	13	250	750
(b) (4) [redacted]				
DMAEMA	0.5	6.8	7.3	22
DMOMA	0.7	9.5	10.2	31
(b) (4) [redacted]				

We note that, based on the hydrolytic stability studies conducted on the FCS, it appears that PFOH is formed to some extent during the manufacture and proposed use of the FCS. We are unable to comment on whether the FCS oligomers or PFAA would form PFOH upon ingestion.

Cumulative Exposure. Since the FCS was not used previously in contact with food, the cumulative EDI (CEDI) is equal to the EDI.

We have no questions regarding consumer exposure to migrants of the FCS.

Notification Language

The language in the 6/28/06 acknowledgment letter, as amended in your 7/25/06 status letter, is acceptable.

[3] The notifier used only one significant digit.

Conclusion

The DCs and EDIs of the FCS oligomers and other migrants are presented in Table 4

We have no questions.

Petra Turowski, Ph.D.

HFS-245 (Begley); Chemistry Reading File
HFS-275:PTurowski:436-1249:FCN0628_c_memo.doc:Pt:9/8/06
Init:ABailey:9/21/06
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