



Memorandum

Date: July 14, 2008

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

Subject: FCN 820. Daikin America, Inc. for the use of 2-propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester, polymer with alpha-(1-oxo-2-propen-1-yl)-omega-hydroxypoly(oxy-1,2-ethanediyl) as a grease-proofing agent in food contact paper and paperboard.

To: Regulatory Group 1, DFCN
ATTN: Mark Hepp, Ph.D.

FOOD CONTACT NOTIFICATION (FCN) 000820

Daikin America, Inc.
P.O. Box 2252
Decatur, AL 35609
Submitted via
Keller and Heckman, LLP
1001 G Street, N.W.
Suite 500 West
Washington, DC 20001

RELATED DOCUMENTS

- FCN 542 Hercules Inc. for the use of 2-propen-1-ol, reaction products with 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine (b) (4) CASRN¹: 464178-94-7) as an oil/grease resistant sizing agent in the manufacture of paper and paperboard for addition prior to the sheet-forming stage. *Effective 11/25/05.*
- FCN 599 AGC Chemicals Inc. for copolymer of polyfluorooctyl methacrylate, 2-N,N-diethylaminoethylmethacrylate, 2-hydroxyethylmethacrylate, and 2,2'-ethylenedioxydiethyldimethacrylate (b) (4); CASRN: 863408-19-9) as an oil, grease, and water resistant treatment for paper and paperboard for addition at either the size press or the sheet-forming stage. *Effective 6/29/2005.*
- FCN 604 AGC Chemicals Inc. copolymer of polyfluorooctyl methacrylate, 2-N,N-diethylaminoethylmethacrylate, 2-hydroxyethylmethacrylate, and 2,2'-ethylenedioxydiethyldimethacrylate (b) (4) CASRN: 863408-19-9) as an oil, grease, and water resistant treatment for paper and paperboard microwave susceptors. *Effective 8/5/06.*
- FCN 746 Hercules Inc. for the use of 2-propen-1-ol, reaction products with 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane, dehydroiodinated,

¹ Chemical Abstracts Service Registry Number

reaction products with epichlorohydrin and triethylenetetramine (b) (4)
CASRN: 464178-94-7) as an oil/grease resistant sizing agent in the
manufacture of paper and paperboard for addition at either the size press or the
sheet-forming stage. *Effective 9/17/07.*

FCN 783 Hercules Inc. for the use of 2-propen-1-ol, reaction products with
1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane, dehydroiodinated,
reaction products with epichlorohydrin and triethylenetetramine (b) (4)
CASRN: 464178-94-7) as an oil/grease resistant sizing agent in the
manufacture of paper and paperboard microwave susceptors. *Effective 3/6/08.*

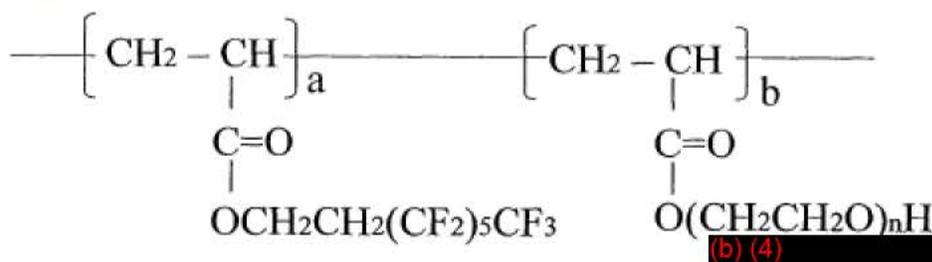
FCN 820: Final Chemistry Memorandum, Arvidson/Hepp, 7/1/08
Final Environmental Memorandum, Lamont/Hepp, 6/24/08

INTRODUCTION

Daikin America, Inc. has notified for the use of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester, polymer with alpha-(1-oxo-2-propen-1-yl)-omega-hydroxypoly(oxy-1,2-ethanediyl) as a grease-proofing additive in the manufacture of food contact paper and paperboard. The food contact substance (FCS) will be used at no more than 0.2 wt-% of the finished paper or paperboard in contact with all food types under conditions of use A-H, as described on CFSAN's website at <http://www.cfsan.fda.gov/~rdb/opa-fcn3.html>.

FOOD CONTACT SUBSTANCE (FCS)

- Name: 2-propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester, polymer with alpha-(1-oxo-2-propen-1-yl)-omega-hydroxypoly(oxy-1,2-ethanediyl)
- CASRN: None
- Trade name: (b) (4)
- Other names: Perfluorohexylethyl acrylate-polyethylene glycol monoacrylate copolymer
- Formula: Not provided
- Structure:



Relative monomer weight percentages: a (b) (4) b = (b) (4)

- Molecular Wt (M_w): (b) (4)
- Molecular No (M_N): (b) (4)

EXPOSURES

Chemistry calculated dietary concentration (DC) and estimated daily intake (EDI) values

(Table 1) for exposure to the FCS and its impurities based on 100% migration of residual levels of impurities in the FC (b) (4)

Table 1

Compound	CAS Reg No.	DC (ppb)	EDI (µg/p/d)
LMWO ² of the FCS (MW<1600 Da)	N/A	0.5	1.5
Perfluoroethylhexyl acrylate (13FA)	17527-29-6	0.002	0.006
Polyethylene glycol monoacrylate (PEGMA)	26403-58-7	0.004	0.01
(b) (4)		0.007	0.02
		0.2	0.6
		0.03	0.09
		0.002	0.006
		0.0006	0.002
		3×10^{-7}	9×10^{-7}
		2×10^{-7}	6×10^{-7}
		Not calculated	Not calculated
		Not calculated	Not calculated

Chemistry did not calculate exposures (b) (4), as these compounds are regulated for the proposed use herein under 21 CFR 176.170 (Paper and paperboard for aqueous and fatty foods).

To confirm that the notifier's estimate of 1600 Da for the molecular weight cutoff for the LMWO was appropriate for characterizing the bioavailable fraction of the oligomers of the FCS, Chemistry compared the solvent-excluded volumes and molecular weights of a representative repeat unit of the FCS versus an analogous hydrocarbon version of that same unit. The results of this analysis, as described in Chemistry's memorandum, confirm that 1600 Da is the appropriate molecular weight cutoff for the LMWO of the FCS herein.

Cumulative EDIs (CEDIs)

(b) (4)

² Low molecular weight oligomers

Assuming additive exposure from the LMWO of the FCS herein to exposure to LMWO of the FCSs notified for in FCNs 542, 599, and 604, the new values for the cumulative DC (CDC) and CEDI for C6-perfluorinated LMWO are 0.5-1 ppb and 1.5-3 µg/p/day, respectively. Chemistry also stated the following regarding the CEDIs for the impurities: “Given the vanishingly small EDIs for the impurities, they would not contribute to their respective CEDIs. Therefore, there will be no change in their cumulative EDIs.”

TOXICOLOGY

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

LMWO of the FCS (maximum CDC of 1 ppb for C6 perfluorinated LMWO):

This compound has not been previously evaluated by the Division of Food Contact Notifications (DFCN). However, Toxicology recently evaluated the LMWO of a similar C6 perfluorinated FCS during review of FCN 783 (Sotomayor/Komolprasert, 2/12/08), concluding that the LMWO of the FCS were of no safety concern based on a calculated DC of 0.45 ppb for the oligomeric migrants and prior reviews by Toxicology of the LMWO of similar FCSs indicating no concern for genotoxicity or carcinogenicity.

For the LMWO of the FCS herein, the notifier has calculated exposure to the ‘absorbable’ fraction of the LMWO, which is based on an estimation of molecular size rather than molecular mass. In the CTP located in Attachment 13 to the FCN, the notifier states that, as oligomeric perfluorinated compounds are smaller on a per gram basis than oligomers composed solely of carbon, hydrogen, and oxygen, the molecular weight cutoff for absorption of perfluorinated oligomers is concomitantly higher than would be expected for non-perfluorinated LMWO. The notifier estimates that the absorption cutoff limit for perfluorinated oligomers is 2.5-fold the limit for non-perfluorinated oligomers and has calculated exposure and evaluated safety of the absorbed fraction accordingly. As discussed in Chemistry’s memorandum, Toxicology and Chemistry consulted with regard to the assumptions presented by the notifier concluding that 1600 Da was the most applicable size cut-off for LMWO.

No data were submitted to support the calculated exposure to the LMWO. Instead, the notifier relied on the data submitted for the constituent monomers to justify the safety of the LMWO, concluding that:

- The weight of the evidence presented indicates that the perfluorinated monomer is not genotoxic.
- Although the data for the PEG-monoacrylate monomer indicates that this compound may be mutagenic (positive in an Ames assay), the monomeric components of the LMWO, including the PEG-monoacrylate component, will not have the mutagenic functional groups that are present on the monomers, due to saturation during the manufacturing process. Thus, the PEG-monoacrylate LMWO will be reduced to PEG-propionate³.

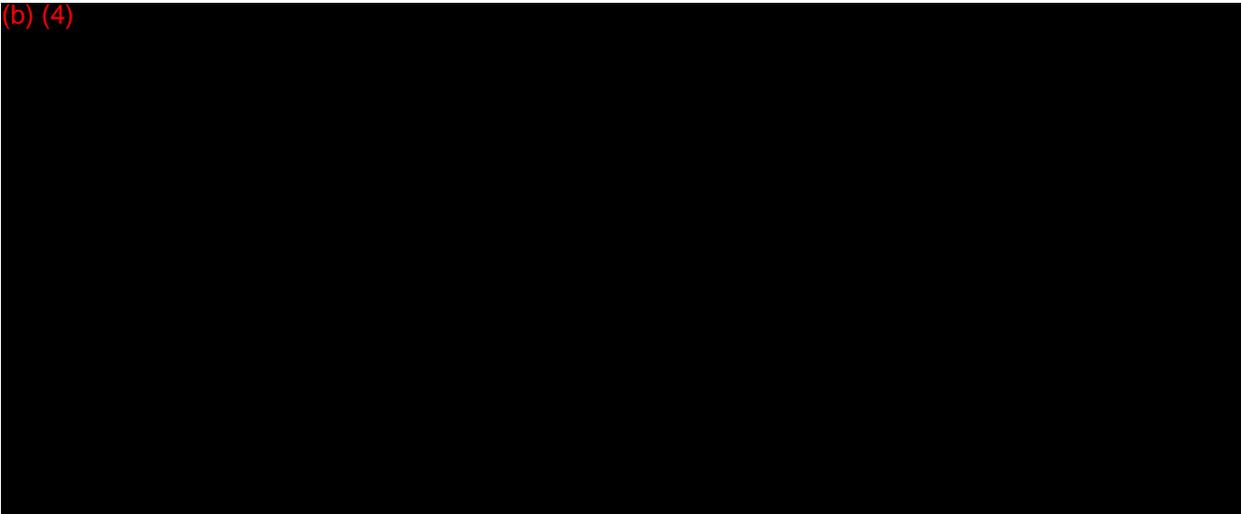
³ The notifier cited PEG-monoacrylate as generally recognized as safe. A search of the CFR and a discussion at the phase 1 meeting did not indicate a clear citation confirming this statement.

Based on Toxicology's review of the data submitted for the monomers (see below), Toxicology agrees that the notifier's approach is suitable for a safety assessment at the calculated exposure and concurs with the conclusion of no concern for the genotoxicity of the LMWO based on the available data on the monomers and perfluoro compounds.

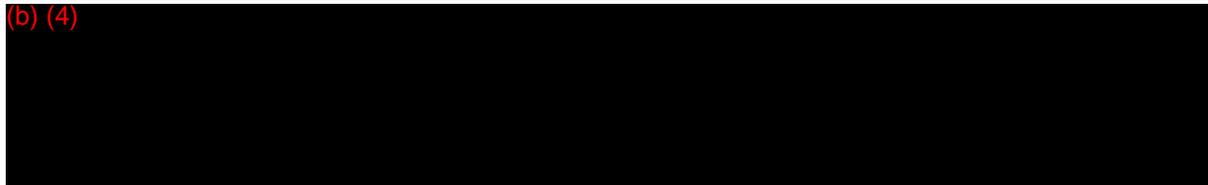
(b) (4)

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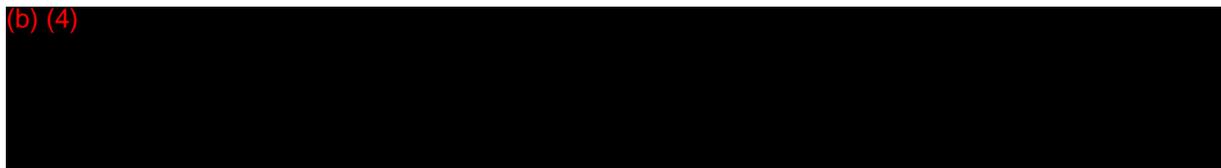
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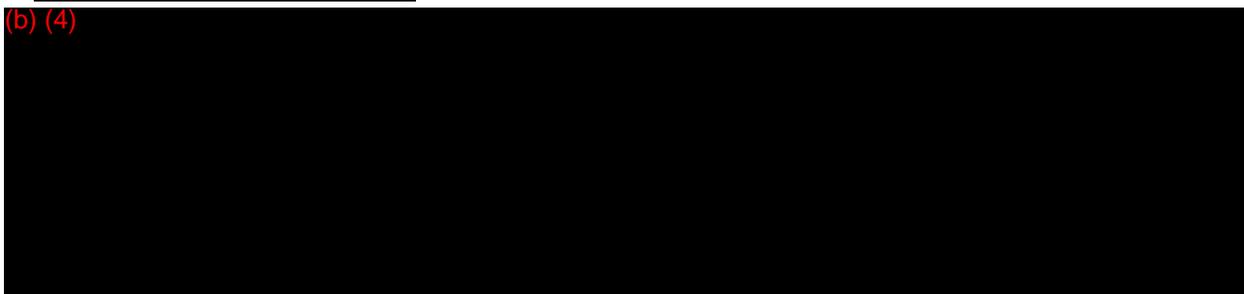
(b) (4)

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Chemistry calculated a new CEDI for C6 perfluorinated LMWO of 1 ppb. Given the available data for the genotoxicity of the monomers as reviewed below indicating a lack of concern for genotoxicity of the LMWO (b) (4) Toxicology has no concern for the safety of the LMWO.

13FA (DC of 2 pptr)

This compound has not been previously regulated for use under 21 CFR, nor is it the subject of an effective FCN. There are no records of previous reviews of this compound by Toxicology. However, Toxicology recently reviewed the toxicity of a C6-perfluoroacrylate monomer (C6-perfluorinated methacrylate⁸; C6FMA; CASRN: 2144-53-8) during evaluation of FCN 599 (McDougal/Honigfort, 6/13/06). Genotoxicity data were submitted, but not reviewed, for the C6FMA monomer in FCN 599. Data were reportedly mixed (negative in Ames and chromosomal aberration; equivocal mouse lymphoma assay). However, Toxicology concluded that exposure to C6FMA was of no concern based on the extremely conservative nature of the estimated DC for that compound (< 78 pptr) and a worst-case lifetime cancer risk (LCR) for exposure to C6FMA derived from structure activity relationship (SAR) analyses of <10⁻⁸, which has historically been considered to be negligible for incremental exposures.

For the FCN herein, the notifier has submitted full study reports of studies conducted with 13FA. Reviews⁹ of these studies are included as attachments to this memorandum:

- Attachment 1: "Mutagenicity test of 13F-SFA using microorganisms (Study Code (b) (4))." Hita Laboratory, Chemicals Evaluation and Research Institute, Japan, February, 2007. Located in Attachment 13A to the FCS, pp. 186-210 in FARM. The test substance was assessed for mutagenic activity in two independent repeats of the pre-incubation version of an Ames assay in 4 strains of *Salmonella typhimurium* (TA 1535, TA 1537, TA 98, TA 100) and *Escherichia coli* strain WP2 *uvrA* with and without metabolic activation by rat liver S9 fraction. Doses of the test article in dehydrated DMSO were 4.88-5000 µg/plate ± S9 in the first assay and 313-5000 µg/plate ± S9 in the confirmatory assay. Toxicology concurred with the study author, that, based on the data presented and under the conditions of the test, the test substance was negative for mutagenic activity.
- Attachment 2: "Chromosome aberration test of 13-SFA using cultured mammalian cells. (Study Code: (b) (4)). Hita Laboratory, Chemicals Evaluation and Research Institute, Japan, study report date March, 2007, located in Attachment 13B on pp. 211-252 in FARM. The test substance was assessed for clastogenic activity in three independent repeats of an *in vitro* cytogenetics assay conducted in Chinese hamster lung fibroblasts (CHL/IU cells). The test substance was dissolved in dehydrated acetone prior to dilution in medium. Cells were exposed to the test substance in medium at 16.3-4180 µg/ml ± S9 fraction for 6 hours, followed by 18

polyolefins. *Effective 10/3/02*). Unit risk calculated to be 0.02 (mg/kg bw/d)⁻¹.

⁸ Compound name: 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl methacrylate

⁹ These data were primary-reviewed at Oak Ridge National Laboratory (ORNL, FDA Interagency Agreement #224-00-2615, Task #2008-15) by B.L. Whitfield, Ph.D. (Attachment 1) and Silvia Milanez, Ph.D., D.A.B.T. (Attachments 2 and 3) and secondary-reviewed by this reviewer.

hours without treatment or for 24 continuous hours in the absence of S9 (Experiment 1); to 26.6-280 µg/ml of the test substance ± S9 for 6 hours followed by 18-hour recovery or to 19-200 µg/ml of the test substance without S9 for 24 hours (Experiment 2); or to 41.9-150 µg/ml of the test substance without S9 for 6 hours followed by 18-hour recovery (Experiment 3). The three highest test substance concentrations up to the limit of cytotoxicity were evaluated for structural aberrations for Experiments 2 and 3; all concentrations in Experiment 1 were evaluated (only 50 metaphases/dose evaluated in Experiment 1). Positive controls were run concurrently for Experiments 2 and 3 only; negative controls were run concurrently for all experiments. Precipitation of the test substance and severe cytotoxicity as measured by reductions in cell growth of > 50%. This reduction was noted under all test conditions at ≥ 131 µg/ml of the test substance in the range-finding experiment. The test substance induced dose-related decreases in cell growth during Experiments 2 and 3, with test article precipitation occurring at approximately the same doses as the doses that induced > 50% cytotoxicity (generally the top 3-4 doses of the test article). No treatment-related increases in the percentages of cells with numerical aberrations were noted under any test condition. No increases in structural aberrations were noted in the +S9 condition. In contrast, a dose-related increase in the percentages of cells with chromosome aberrations were noted in the absence of S9 activation after 24 hours of treatment at the two highest doses of the test article evaluated in Experiment 2 (7.5% and 15.5% at 72.9 µg/ml and 102 µg/ml of the test article vs. 1.5% for solvent control) and the two highest doses of the test article in Experiment 1 (8% and 10% for 2090 µg/ml and 4180 µg/ml of the test article vs. 0% control). At these doses, the cell growth rates were 41.8% and 41.5% (Experiment 2) and 16.4% and 14.9% (Experiment 1) of concurrent negative control values. In addition, increases in percentages of cells with structural aberrations occurred after 6 hours of treatment without S9 in Experiment 1 at doses of 131 µg/ml and 261 µg/ml of the test article (6% and 10% vs. 0% control) at cell growth rates of 23.2% and 28.2% of concurrent negative control values, respectively; this result was not confirmed under the same test conditions in Experiment 3 and was thus judged by the study authors to be not repeatable. Toxicology concurred with the study author, that, based on the data presented and under the conditions of the test, the test substance was positive for clastogenic activity.

- Attachment 3: "*In vivo* mouse bone marrow micronucleus assay." Study No. (b) (4) [REDACTED] Covance Laboratories, Inc., Virginia, US, March, 14, 2008, located in Attachment 13C on pp. 253-309 in FARM. The test article was assessed for clastogenic activity in an *in vivo* bone marrow micronucleus assay in male CD-1 (ICR) BR mice. Mice (n=5/timepoint/group) were administered 0, 100, 200, or 400 mg/kg bw of the test article in olive oil with 0.5% Tween 80 vehicle once by gavage. The highest dose of the test article was based on the results of a pre-experiment to determine the toxicity of the test article. Percentages of micronucleated polychromatic erythrocytes (MNPCEs) were assessed 24 and 48 hours after test article administration. Positive (24 hour timepoint only) and negative controls were assessed in parallel. At 400 mg/kg bw, the test substance induced signs of clinical toxicity, including: hypoactivity, squinted eyes, rough coat, hunched posture, wet perineum, and tremors. The highest dose of the test article was reported to produce significantly decreased percentages of MNPCEs (0.01% vs. 0.08%) and increased PCE:NCE ratios (0.54 vs. 0.25) at the 24-hour timepoint compared to concurrent control. The study authors concluded that this finding was of no biological relevance. The test article did not produce any increases in the frequency of MNPCEs over concurrent controls.

Toxicology concurred with the study author, that, based on the data presented and under the conditions of the test, the test substance was negative for clastogenic activity.

For the first two assays, a statement of “hydrolysis of the test substance to acrylic acid and perfluoroalkylethanol” was noted prior to use in these assays. Analytical evaluations of the test substance and test formulations were not performed before or after conduct of any of these studies. In discussing this conclusion with Chemistry, it was indicated that the results of thermogravimetric analyses on the FCS indicated that the polymer was stable under the proposed use conditions, which include being in contact with aqueous foods. No detailed information was provided on the stability of the isolated monomer in aqueous environments.

Based on the weight-of-the-evidence assessment of no concern for genotoxicity for 13FA from the results of the submitted genotoxicity assays and a DC < 50 pptr, Toxicology has no concern for exposure to 13FA.

PEGMA (DC of 4 pptr)

This compound has not been previously regulated for use under 21 CFR, nor is it the subject of an effective FCN. There are no records of previous reviews of this compound by Toxicology in FARM. Toxicology most recently reviewed the available genotoxicity information for multifunctional acrylates for FCN 772¹⁰ (Sotomayor/McAdams, 2/24/08); based on the results of the submitted genotoxicity studies, Toxicology concluded that there was no concern for genotoxicity for those compounds.

For the FCN herein, the notifier has submitted a full study report of an Ames study conducted with PEGMA. The review¹¹ of this study is included as an attachment to this memorandum:

- Attachment 4: “Mutagenicity test of (b) (4) by using microorganisms (Study Code (b) (4)).” UBE Scientific Analysis Laboratory, Inc., Japan, December 7, 2007. Located in Attachment 13D to the FCS, pp. 311-338 in FARM. The test substance in water vehicle was assessed for mutagenic activity in three independent repeats of the pre-incubation version of an Ames assay in 4 strains of *S. typhimurium* (TA 1535, TA 1537, TA 98, TA 100) and *E. coli* strain WP2 *uvrA* with and without metabolic activation by rat liver S9 fraction at doses of 4.88-5000 µg/plate ± S9 (range-finding assay); 39.1-5000 µg/plate (Mutagenicity tests I and II, -S9); or 156-5000 µg/plate (Mutagenicity tests I and II, +S9). Positive and negative controls were run in parallel. Analytical evaluations of the test substance and test formulations were not performed before or after conduct of the study. Bacteriotoxicity, defined as

¹⁰ FCN 772: Food Packaging Alliance of RadTech International North America for the use of a polymer composed of tripropylene glycol diacrylate (TPGDA); trimethylolpropane ethoxylate triacrylate (TMPEOTA); bisphenol A diglycidyl ether diacrylate (BADGEDA); and alpha-hydroxy ketone, difunctional (ESACURE ONE) (CASRN: TPGDA: 42978-66-5; TMPTA: 15625-89-5; TMPEOTA: 28961-43-5; BADGEDA: 4687-94-9, 53814-24-7, 55127-80-5, 55818-57-0, or 37625-93-7) as coatings (including inks) or components of coatings (including inks) on polymeric substrates, paper and paperboard, metal substrates, or as a component in adhesives, in contact with all food types under Conditions of Use A through H, as described in Tables 1 and 2 of 21 CFR §176.170(c). *Effective 2/27/08.*

¹¹ These data were primary-reviewed at Oak Ridge National Laboratory (ORNL, FDA Interagency Agreement #224-00-2615, Task #2008-15) by B.L. Whitfield, Ph.D. (Attachment 1) and secondary-reviewed by this reviewer.

reduction of background lawn growth, was noted in strains TA100, TA1535, and TA98 at ≥ 1250 $\mu\text{g}/\text{plate}$ and in strain TA1537 at ≥ 2500 $\mu\text{g}/\text{plate}$ in the absence of S9 during the two mutagenicity assays. Increased revertant counts¹² over concurrent control values were noted in strain WP2uvrA at the highest test substance dose in all three assays with and without S9 activation. No precipitation of the test substance was reported. Toxicology concurred with the study author, that, based on the data presented and under the conditions of the test, the test substance was positive for mutagenic activity.

A qualitative SAR analysis performed for the Phase I meeting for FCN 820 reported that the PEGMA monomer contained biophores that were highly concerning for carcinogenicity and genotoxicity; one of these biophores was the acrylate functionality, and the other was the ether linkage contained in the polyethylene glycol (PEG)-function. While the acrylate functionality would not be present in the polymer FCS, the ether moiety would be present. The ether moiety in the PEGMA monomer is derived from the PEG portion of the compound, for which OFAS has reviewed an extensive array of toxicological data.

PEG is regulated for use in adhesives under 21 CFR 175.105 (Adhesives). According to Toxicology's most recent review of the available information on PEG compounds (Rice/Gilliam, 5/10/07, RE: FCN 715¹³), the available genetic toxicology data did not indicate a concern for mutagenicity or genotoxicity of the test substance. Furthermore, Toxicology (Bleiberg/Zajac, 10/23/00, RE FCN 97¹⁴) had previously set¹⁵ acceptable daily intake (ADI) values for PEG 400¹⁶ and higher molecular weight PEG compounds¹⁷ at 600 mg/p/d and 1,200 mg/kg/d, respectively. Therefore, the SAR analysis' identification of the ether linkage in the PEGMA compound as a potentially-concerning biophore is not biologically-relevant for the assessment of the safety of the PEGMA compound herein.

Based on the weight-of-the-evidence assessment of the results of the submitted positive Ames assay, the results of the preliminary positive SAR assessment, and the available ADI data for PEG, and the calculated DC for PEGMA of < 50 pptr, Toxicology has no concern for exposure to PEGMA at the calculated exposure herein.

(b) (4) (DC of 3×10^{-7} ppb)

Toxicology most recently evaluated **(b) (4)**, where the conclusion of no safety concern at a DC of 3 pptr was based on the following factors:

¹² Dose-finding assay: 102 vs. 34 (-S9), 109 vs. 46 (+S9); Mutagenicity test I: 75 vs. 19 (-S9), 56 vs. 26 (+S9); Mutagenicity Test II: 78 vs. 32 (-S9), 101 vs. 46 (+S9)

¹³ FCN 715: 3M, Industrial Adhesives and Tapes Division for the use of ethoxylated tallow alkyl amines (Ethomeen T/25; CASRN: 61791-26-2) as a component of repulpable tape adhesives for use in the manufacture of food contact paper and paperboard. *Effective 6/20/07.*

¹⁴ FCN 97: Betz Dearborn for the use of polyethylene glycol monooleate (CASRN: 9004-96-0) as an anti-corrosive agent in boiler steam lines. *Effective 11/23/00.*

¹⁵ Toxicology reviewed results of published chronic, oral (dietary) toxicity studies in rats and dogs performed with a series of PEG compounds ranging in mean molecular weight from 200-6000 Da (Smyth, Jr. *et al.*, 1955). The results of this study were used to derive the ADI values for PEG compounds.

¹⁶ The ADI value is based on a NOEL in rats of 2% in the diet and a 100-fold safety factor. Higher levels in the diet (4%) were associated with minor effects on growth and cloudy swelling of hepatocytes in rats.

¹⁷ The ADI value was based on a NOEL in rats and dogs of 4% in the diet and a safety factor of 100.

- Reported negative results in an Ames test in two strains of *S. typhimurium* and *E. Coli* pkM101;
- A NOEL of 50 mg/kg bw/day for systemic toxicity derived from a 90-day oral toxicity study in rats reviewed by Toxicology (b) (4)
- Exposure well below the threshold of regulation (TOR).

Toxicology has no questions as to exposure to (b) (4) herein based on no change in the CEDI for this compound from the proposed uses of the FCS herein and published data indicating no concerns for genotoxicity.

(b) (4) (DC of 2 pptr)

Toxicology most recently evaluated (b) (4); Toxicology concluded that (b) (4) presented no safety concern at a DC of 0.22 ppb, based on the weight-of-evidence conclusion of no concern for genotoxic activity from Ames and mouse lymphoma assays conducted with (b) (4)

In this FCN, the notifier has submitted a full study report of an *in vivo* mouse bone marrow micronucleus assay conducted with (b) (4). The review¹⁸ of this study is included as an attachment to this memorandum:

- Attachment 5: “*In vivo* mouse bone marrow micronucleus assay” (b) (4)
 (b) (4). The test substance was evaluated for clastogenicity *in vivo* in a murine bone marrow micronucleus assay conducted in male CD-1 (ICR) BR mice (5/timepoint/dose). Mice were gavaged once with 0, 100, 200, or 400 mg/kg of the test substance in olive oil vehicle; percentages of micronucleated polychromatic erythrocytes (MNPCEs) were evaluated 24 (all doses) and 48 hours (control and high dose only) after dosing. Positive (80 mg/kg cyclophosphamide) and negative controls were run concurrently, although the positive control was run for only the 24-hour time point. Doses for the micronucleus assay were derived from the results of two range-finding toxicity assays in male and female mice¹⁹. During the micronucleus assay, animals in the high dose group exhibited the following clinical signs of toxicity following dosing: squinted eyes, hypoactivity, and mortality (3/13 males²⁰). The test article did not induce significant increases in percentages of MNPCEs at any dose or time point, nor did the test article induce bone marrow toxicity (as measured by PCE:NCE ratios). Toxicology concurred with the study author, that, based on the data presented and under the conditions of the test, the test substance was negative for clastogenic activity.

(b) (4)

During the first range-finding assay, male and female mice (n=3/sex/dose) were administered the test article in olive oil + Tween 80 by gavage at doses of 500, 1000, or 2000 mg/kg bw and observed for up to 2 days for toxicity. In the follow-up range-finder, male and female mice (n=3/sex) were administered 250 mg/kg bw of the test article by gavage in olive oil vehicle only and observed for the same time period. In the first experiment, mortality was observed at all doses in both sexes as follows: 3/3 males and females (2000 mg/kg); 3/3 males, 2/3 females (1000 mg/kg); and 2/3 males, 1/3 females (500 mg/kg). No mortality was observed in the second range-finding study.

²⁰ Extra animals in this dose group were dosed concurrently in the event of mortality.

Toxicology has no questions as to exposure to (b) (4) herein based on no change in the CEDI for this compound from the proposed uses of the FCS herein and data previously reviewed by Toxicology and data reviewed herein indicating no concern for genotoxicity.

Potential Carcinogenic Constituents

Toxicology has no concerns as to exposure to (b) (4) due to Chemistry's conclusion that the exposure herein would not contribute to the CEDIs.

(b) (4) (DC of 0.6 pptr)

Toxicology most recently evaluated (b) (4), where the conclusion of no safety concern was based on the substitutional nature of exposure to (b) (4) the proposed uses therein. (b) (4) has been found to be non-genotoxic in bacterial and mammalian systems *in vitro* and *in vivo*^{25,26}, Toxicology

(b) (4)

No change in the CEDI for this compound is expected from the proposed uses of the FCS herein, accordingly the existing risk assessment for this compound remains unchanged.

Solvents

(b) (4)

For the solvents below, Toxicology has no concerns regarding their exposures based on lack of change in the CEDI for these compounds from the proposed uses of the FCS herein and the lack of new information that alters our previous safety assessments.

(b) (4) (DC of 0.2 ppb)

(b) (4) Toxicology most recently reviewed this compound (b) (4), where the basis of no safety concern was stated to be the highly conservative nature of Chemistry's exposure calculation for the impurity and no change in the CEDI for the compound from the proposed uses of the FCS therein.

Information concerning the toxicity of (b) (4) is located in an internal record of a JECFA evaluation of (b) (4) (b) (4). JECFA concluded that exposures to (b) (4) and other compounds of that class were safe at the current levels based on: the designation of compounds in that class as either structural Class I or Class II substances; the expectation of rapid metabolism endogenous compounds and/or excretion *in vivo*; negative results in tests for mutagenic/genotoxic activity in the majority of a variety of bacterial and mammalian systems *in vitro* and *in vivo*³¹; and no concern for low-dose toxicity or formation of neurotoxic gamma-diketones at current intake levels.

(b) (4) (DC of 0.007 ppb)

(b) (4) is regulated for several uses under 21 CFR³². Toxicology most recently evaluated (b) (4) where the basis of safety was stated to be 'virtually nil' dietary exposure from the proposed uses. For (b) (4) containing data from several published studies, including acute toxicity studies and genotoxicity studies. In the summary review of the submitted safety narrative and studies, Toxicology (b) (4)³⁴ was reportedly negative in genotoxicity studies (Ames, mouse lymphoma, and *in vitro* sister chromatid exchange studies in Chinese hamster ovary (CHO) cells) and reportedly did not increase the frequency of neoplastic lesions in mice when administered at a level of 0.25% in the diet for 2.5 years³⁵. However, Toxicology has not derived an ADI value for (b) (4).

(b) (4)

(b) (4)

The notifier herein submitted a copy of IUCLID (b) (4) [REDACTED], containing detailed summaries of the available toxicity information on this compound. The information contained in this document may be summarized as follows:

- Genotoxicity:
 - Reported negative in: Ames assays, mouse lymphoma, sister chromatid exchange (SCE) assay in CHO cells and rat lymphocytes, induction of polyploidy in *S. cerevisiae*, *in vivo* micronucleus assay in bone marrow of Swiss mice.
 - Mixed results in *in vitro* cytogenetics assays in a variety of cell types. Assays reportedly performed conforming to OECD and/or Redbook specifications reported negative results with (b) (4) [REDACTED] in human lymphocytes and CHO cells. Reports of induction of polyploidy in mammalian and plant cells.
- No observed adverse effect level (NOAEL) for systemic toxicity of 15 mg/kg bw/day from a combined 49-day systemic/one generation reproductive toxicity screening assay in Sprague-Dawley rats. Effects seen at the Lowest Observed Effect Level (LOEL) (50 mg/kg bw/day):
 - Males: ptyalism; decreased bodyweights; decreased cholesterol and triglycerides; increased severity of hepatocellular vacuolation; paleness and accentuated hepatic lobular pattern
 - Females: ptyalism; increased liver weight; liver paleness; minimal to slight hepatocellular hypertrophy; increased incidence and severity of vacuolated hepatocytes; and degenerative cardiomyopathy.
- Reproductive NOEL of 15 mg/kg bw/day from the same study, for the following effects at the LOEL: maternal toxicity (mortality, ptyalism, increased bodyweight gain and feed consumption during exposure and lactation); increased pup weight during lactation; increased numbers of pups dead Postnatal Day (PND) 1-4; decreased viability indices.

CONCLUSIONS

Daikin America, Inc. has notified for the use of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester, polymer with alpha-(1-oxo-2-propen-1-yl)-omega-hydroxypoly(oxy-1,2-ethanediyl) as a grease-proofing additive in the manufacture of food contact paper and paperboard. The FCS will be used at no more than 0.2 wt-% of finished paper or paperboard in contact with all food types under conditions of use A-H, as described in Chemistry's final memorandum. Toxicology has no questions regarding the safety of proposed use of the FCS, based on the exposure estimates and the toxicological evaluation of the available data as indicated above.

Penelope Rice, Ph.D.

Attachment 1: Ames study with 13-FA

(b) (4)

The notifier herein submitted a copy of IUCLID (b) (4), containing detailed summaries of the available toxicity information on this compound. The information contained in this document may be summarized as follows:

- Genotoxicity:
 - Reported negative in: Ames assays, mouse lymphoma, sister chromatid exchange (SCE) assay in CHO cells and rat lymphocytes, induction of polyploidy in *S. cerevisiae*, *in vivo* micronucleus assay in bone marrow of Swiss mice.
 - Mixed results in *in vitro* cytogenetics assays in a variety of cell types. Assays reportedly performed conforming to OECD and/or Redbook specifications reported negative results with (b) (4) human lymphocytes and CHO cells. Reports of induction of polyploidy in mammalian and plant cells.
- No observed adverse effect level (NOAEL) for systemic toxicity of 15 mg/kg bw/day from a combined 49-day systemic/one generation reproductive toxicity screening assay in Sprague-Dawley rats. Effects seen at the Lowest Observed Effect Level (LOEL) (50 mg/kg bw/day):
 - Males: ptyalism; decreased bodyweights; decreased cholesterol and triglycerides; increased severity of hepatocellular vacuolation; paleness and accentuated hepatic lobular pattern
 - Females: ptyalism; increased liver weight; liver paleness; minimal to slight hepatocellular hypertrophy; increased incidence and severity of vacuolated hepatocytes; and degenerative cardiomyopathy.
- Reproductive NOEL of 15 mg/kg bw/day from the same study, for the following effects at the LOEL: maternal toxicity (mortality, ptyalism, increased bodyweight gain and feed consumption during exposure and lactation); increased pup weight during lactation; increased numbers of pups dead Postnatal Day (PND) 1-4; decreased viability indices.

CONCLUSIONS

Daikin America, Inc. has notified for the use of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester, polymer with alpha-(1-oxo-2-propen-1-yl)-omega-hydroxypoly(oxy-1,2-ethanediyl) as a grease-proofing additive in the manufacture of food contact paper and paperboard. The FCS will be used at no more than 0.2 wt-% of finished paper or paperboard in contact with all food types under conditions of use A-H, as described in Chemistry's final memorandum. Toxicology has no questions regarding the safety of proposed use of the FCS, based on the exposure estimates and the toxicological evaluation of the available data as indicated above.

(b) (6)

Penelope Ricé, Ph.D.

Attachment 1: Ames study with 13-FA

(b) (4)

Attachment 2: Chromosome aberration assay with 13-FA
Attachment 3: Micronucleus assay with 13-FA
Attachment 4: Ames assay with PEGMA
Attachment 5: Micronucleus assay with (b) (4)

INIT: MLTwaroski, Ph.D.: 07/14/2008