Memorandum

Date: December 17, 2014

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

Subject: FCN 1493: Archroma Management GmbH for the use of 2-propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester, polymer with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, N-oxides, acetates (CASRN: 1440528-04-0) as a coating for food contact paper and paperboard. *Submission dated 9/2/14. Updates received 10/22/14.*

To: Regulatory Group 2, DFCN
ATTN: Paul Honigfort, Ph.D. (HFS-275)

Food Contact Notification (FCN) 001493

Archroma Management GmbH
Neuhofstrasse 11
Reinach 4153 Switzerland
VIA
Keller and Heckman, LLP
1001 G Street, NW, Suite 500W
Washington, DC 20001

RELATED FILES[1]

FCN 1493: Final Chemistry memorandum, Cureton/Honigfort, 12/17/14
Final Environmental memorandum, Lindheimer/Honigfort, 11/19/14

INTRODUCTION

Archroma Management GmbH, through Keller and Heckman, LLP, has notified for use of 2-propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester, polymer with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, N-oxides, acetates (CASRN: 1440528-04-0). The FCS is intended to be used as a coating on food contact paper and paperboard, applied at either the wet-end or the size press, at a maximum use level of 2.2 g FCS/m^2 of paper and paperboard (0.26 mg polymer solids/sq-in). The FCS will contact all food types under Use Conditions B-H, as described on CFSAN's website[2]. The FCS will not contact infant formula or breast milk.

FOOD CONTACT SUBSTANCE (FCS)

[1] FAP: Food Additive Petition; CASRN: Chemical Abstract Service Registry Number; SAR: Structure Activity Relationship; CFR: Code of Federal Regulations; GRAS: Generally Recognized As Safe.
[2] http://www fda.gov/food/ingredientspackaginglabeling/packagingfcs/foodtypesconditionsofuse/ucm109358.htm

- **Names**: 2-propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester, polymer with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, N-oxides, acetates
- **CASRNs**: 1440528-04-0
- **Trade names**: (b) (4)
- **Other names:** N,N-dimethylaminoethyl methacrylate copolymer with tridecafluorohexylethyl methacrylate, N-oxide, acetate; 2-Dimethylaminoethyl methacrylate copolymer with 1H,1H,2H,2H-perfluorooctyl methacrylate, N-oxide, acetate; Copolymer of 2-(dimethylamino) ethyl methacrylate with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro methacrylate, N-oxide, acetate.
- **Molecular Wt:**

Table 2. MWD for Three Batches of FCS

Batch	M_w	M_n	PDI	Fraction percentage (%), MW <2,000 Da
Poly(methyl methacrylate) Standard Calibration				
(b) (4)				<0.1
				<0.1
				<0.1
				<0.1
				<0.1
				<0.1

EXPOSURES

Chemistry calculated dietary concentration (DC) and estimated daily intake (EDI) values for the LMWO of the FCS and (b) (4) based on the results of migration studies conducted on paper coated with the FCS spiked with an oligomer surrogate, (b) (4) (b) (4) (Attachments 10, 12, 13), applying a LMW cutoff value of 2000 Da in order to account for the relatively high mass:size ratio of the perfluorinated polymer. The migration conditions used for the LMWO exposure calculation resulted in virtually complete extraction of the LMWO from the paper and, as such, represent 100% migration of the LMWO residual content in the FCS. Exposure to (b) (4) was determined based on extraction studies conducted on treated paper (Attachment 11). Exposures to the other impurities were estimated based on the assumption of 100% migration (Attachments 4, 14).

Table 1

Compound	CAS Reg No.	DC (ppb)	EDI (µg/p/d)
FCS LMWO	N/A	< 1.3	< 4
(b) (4)		< 1.6	< 4.8
1H,1H,2H,2H-perfluorooctyl methacrylate (C6MA)	2144-53-8	2.2	7
2-Dimethylaminoethyl methacrylate (DMAMET)	2867-47-2	0.4	1
(b) (4)		2.2	7
		2.9	9
		0.07	0.22

Regarding the compounds listed p.4 of the Form 3480, (b) (4) are GRAS under 21 CFR sections (b) (4) Chemistry has indicated that no exposure would be expected to (b) (4) or (b) (4) although Chemistry's memorandum calculated 'worst-case' exposure values to (b) (4), based on half of the LOD.

Cumulative DCs (CDCs) and EDIs (CEDIs)

Chemistry states that, as this FCS has not previously been authorized for use, the EDI herein is the CEDI for the LMWOs. Exposures to the other impurities would be substitutional for exposures derived from already-authorized uses of C6-perfluorinated FCSs.

TOXICOLOGY

For the compounds listed below, this reviewer searched various databases ((b) (4) 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. The notifier provided a Safety Narrative (SN) on p. 18 of their Form 3480 and a Comprehensive Toxicological Profile (CTP) in Attachment 15, with genotoxicity studies contained in Attachments 16-22. Relevant data are discussed below.

LMWO of the FCS (DC of < 1.3 ppb)

This FCS has not been previously regulated or notified for. Toxicology most recently evaluated the safety of LMWO (< 1880 Da) comprised of the C6-methacrylate monomer herein at a DC of 3 pptr for FCN 1186[3] (Jacobs/McAdams, 8/17/12), where the conclusion of no concern was based on the data available for the constituent monomers indicating no concern for genotoxicity. The cumulative DC (CDC) for C6-oligomers is currently 1 ppb (email communication, Elyashiv-Barad/Honigfort, 6/11/09, RE: FCN 888[4]). Similarly, the notifier's safety assessment for the LMWO bases the conclusion of no concern on the available data for the constituent monomers that indicate lack of genotoxicity in standard battery of assays (see below). Historically, for LMWO DCs of < 50 ppb, OFAS has considered data from genotoxicity studies conducted with the constituent monomers to be applicable to the safety assessment of exposure to the LMWO, provided no new structural alerts are generated in the LMWO during the polymerization process. Therefore, based on a DC of < 50 ppb, the extremely conservative nature of the calculated exposure, and data on the monomers indicating no concern for genotoxicity, Toxicology has no concerns for LMWO exposure.

Monomers

[3] FCN 1186: AGC Chemical America, Inc. for the use of butanedioic acid, 2-methylene-, polymer with 2-hydroxyethyl, 2-methyl-2-propenoate, 2-methyl-2-propenoic acid, and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, sodium salt (CASRN: 1345817-52-8) as a coating for paper and paperboard. *Effective 9/21/12.*

[4] FCN 888: Daikin America, Inc. for the use of 2-propenoic acid, 2-hydroxethyl ester, polymer with alpha-(1-oxo-2-propen-1-yl)omega-hydroxypoly(oxy-1,2-ethanediyl), alpha-(1-oxo2-propen-1-yl)-omega-[(1-oxo-2-propen-1-yl)oxy]poly(oxy-1,2-ethanediyl) and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-propenoate (CASRN: 1012783-70-8) as a greaseproofer for paper and paperboard applied at the size press in microwave susceptors. *Effective 6/18/09.*

C6MA (DC of 2.2 ppb)

Toxicology most recently reviewed this compound for FCN 1186 at a DC of 2.3 ppb, where the basis for no concern was a low calculated DC of 0.17 ppb and lack of concern for genotoxicity based on studies previously reviewed for this compound (see below). For FCN 885[5] (Roth/Honigfort, 6/6/09), Toxicology cursorily-reviewed an Ames assay[6], an *in vitro* chromosome aberration study[7], a mouse lymphoma assay[8], and an *in vivo* micronucleus assay[9] conducted with C6MA; based on the reported results, Toxicology agreed with the study authors' conclusions of lack of genotoxic activity under the test conditions. The mammalian cell and *in vivo* studies have been re-submitted in this FCN. An additional Ames study conducted with C6MA was also submitted in Attachment 16, in which C6MA was reportedly negative for mutagenic activity[10]. In addition, Toxicology fully-reviewed a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells ((b) (4) and a mouse lymphoma assay (b) (4) for FCN 604[11] (McDougal/Honigfort, 8/2/06), concluding that the test substance was negative for clastogenic activity under the test conditions in the chromosome aberration assay and that the results of the mouse lymphoma assay 'were not consistent with a positive result', and were thus not concerning. An additional Ames assay (b) (4) submitted and cursory-reviewed for FCN 599[12] (McDougal/Honigfort, 6/13/06) was also reportedly negative under the test conditions. Based on the previously weight-of-evidence conclusion of no concern for genotoxicity of C6MA and the reportedly negative results of the new Ames assay submitted in Attachment 16, Toxicology did not fully-review any of the submitted studies. The notifier's safety assessment of C6MA discusses the genotoxicity data submitted herein, concluding that the weight of the evidence supports the conclusion of no concern for genotoxicity. Based on Toxicology's previous conclusion of no concern for genotoxicity for this compound and a DC of < 50 ppb, Toxicology has no concerns.

DMAMET (DC of 0.4 ppb)

This compound is not regulated for any uses under 21 CFR. Toxicology most recently reviewed

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[5] FCN 885: DuPont Chemical Solutions Enterprise for the use of 2-propenoic acid, 2-methyl, polymer with 2-(diethylamino)ethyl 2-methyl-2-propenoate, 2-propenoic acid, and 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2 methyl-2-propenoate acetate salt (CASRN: 1071022-26-8) as a greaseproofing aid in food contact paper and paperboard at 0.42 wt-% of the paper under Use Conditions B-H. *Effective 6/9/09.*

[6] (b) (4) Bacterial Reverse Mutation Test. . July 25, 2008.

[7] (b) (4) *In Vitro* Mammalian Chromosome Aberration Test in Human Peripheral Blood Lymphocytes. Dupont (b) (4) July 11, 2008. Located in Attachment 18 herein. Toxicology's memorandum for FCN 885 noted that the test compound was reportedly positive for induction of chromosome aberrations in the absence of metabolic activation under the test conditions; however, the reported negative activity in the other assays cursory-reviewed for this FCN led Toxicology to conclude that the weight of the evidence indicated that C6FMA was non-genotoxic.

[8] (b) (4) *In Vitro* Mammalian Cell Gene Mutation Test (L5178Y/TK +/- Mouse Lymphoma Assay). (b) (4) DuPont (b) (4) June 19, 2008. Located in Attachment 17 herein.

[9] In Vivo Micronucleus and Chromosome Aberration Assay in Mouse Bone Marrow Cells. (b) (4) DuPont (b) (4) September 29, 2008. Located in Attachment 19 herein.

[10] "*Salmonella typhimurium* and *Escherichia col*i reverse mutation assay with Fluowet MA 600", study #(b) (4) conducted at Harlan Cytotest Cell Research GmbH in Rossdorf, Germany, study report date: 6/7/10.

[11] FCN 604: AGC Chemicals Americas, Inc. for the use of a copolymer of polyfluorooctyl metyhacrylate, 2-N,N-diethylaminoethyl methacrylate, 2-hydroxyethyl methacrylate, and 2,2'-ethylenedioxydiethyldimethacrylate (CASRN: 863408-19-9) as a coating for paper and paperboard. *Effective 8/5/06.*

[12] FCN 599: AGC Chemicals Inc. for the use of a copolymer of polyfluorooctyl methacrylate, 2-N,N-diethylaminoethylmethacrylate, 2-hydroxyethylmethacrylate, and 2,2'-ethylenedioxydiethyldimethacrylate as an oil, grease, and water resistant treatment for paper and paperboard employed either prior to the sheet forming operation or at the size press. *Effective 6/29/2005*.

DMAMET for FCN 628[13] (Gu/Komolprasert, 10/6/06) at a DC of 7.3 pptr. Toxicology fully-reviewed an Ames study conducted with DMAMET ([redacted]), concluding that the test substance was negative under the test conditions. Toxicology also cited another reportedly-negative published Ames study (Japan Chemical Industry Ecology-Toxicology and Information Center, 2000).

Additional genotoxicity data are summarized in a US EPA High Production Volume Information System (HPVIS) summary[14] for DMAMET; DMAMET was reportedly positive for genotoxic activity in an Ames test and in chromosome aberration assays in human leukocytes and CHL/IU cells. DMAMET was reportedly negative in a hypoxanthine-phosphoribosyl transferase (HPRT) test in V79 cells, another Ames test, and bone marrow micronucleus assays. The positive result in the Ames test was observed in TA 1537 without S9 at non-toxic concentrations; the effect was reproducible. Likewise, the positive results in the chromosome aberration assays were observed ± S9 in the first assay and without S9 only in the second assay at both cytotoxic and non-cytotoxic concentrations. The notifier's safety assessment discusses these data, pointing out that DMAMET was negative for clastogenic activity in *in vivo* assays and that acrylates are known to produce non-biologically relevant positive results in *in vitro* chromosome aberration assays. Regarding the positive Ames result, the notifier points out that DMAMET was negative in other Ames assays and attributes the positive result to cytotoxicity. The notifier also cites parental and offspring no observed effect level (NOEL) values of 40 (parental males) and 200 mg/kg/d (parental females, offspring) from an OECD 422 screening assay, where adverse effects in the parents were noted in the CNS, stomach, and bone marrow and decreased offspring viability indices were noted at higher doses.

Toxicology reviewed a series of multifunctional acrylate compounds for FCN 772[15] (Sotomayor/McAdams, 2/24/08); Toxicology noted that some of the reviewed compounds were positive for genotoxic activity in mouse lymphoma assays but negative in Ames tests. Reviews of additional data on these compounds in the form of *in vivo* micronucleus assays and, in the case of one compound, an oral carcinogenicity study, in which these compounds were negative for clastogenic and/or carcinogenic activity under the test conditions, led Toxicology to conclude that these compounds were not concerning for carcinogenic activity. In addition to these data, Toxicology referenced a published review[16] of the toxicity of multifunctional acrylates and methacrylates that had been submitted for FCN 772. The authors of the publication state, "*MFAs* [multifunctional acrylates] *are mutagenic in the mouse lymphoma assay, but not the Ames test, and the nature of these results makes their extrapolation to other genotoxicity test systems or to human hazard controversial.*" The authors then note that the majority of the tested MFA were negative for carcinogenic activity in dermal carcinogenicity assays conducted in mice, with the exception of pentaerythritol triacrylate (PETA; CASRN: 3524-68-3) and triethylene glycol diacrylate (TEGDA; CASRN: 1680-21-3), which reportedly induced lymphomas in mice upon dermal administration. It should be noted that the site of action and tumor type induced by

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[13] FCN 628: Clariant Corp. for the use of [redacted] (CASRN: 479029-28-2) as a grease proofing agent in the manufacture of paper and paperboard. *Effective 10/10/06.*

[14] Accessed at http://ofmpub.epa.gov/oppthpv/quicksearch.display?pChem=101982

[15] 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**s**: 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.*

[16] Andrews, L.S. and Clary, J.J. (1986) Review of the toxicity of multifunctional acrylates. *J. Toxicol. Env. Health*, **19**: 149-164. Located in FMF [redacted]

dermal administration of TEGDA differ from those induced by oral administration of ethyl acrylate, which produced forestomach squamous cell papillomas and carcinomas. The differences in carcinogenic activity between these two compounds may be due to use of different routes of administration (dermal versus oral), as well as the different functional groups present on each compound.

Given the totality of the genotoxicity data available for DMAMET, Toxicology concurs with the notifier that this compound does not appear to be concerning for carcinogenicity, based on the lack of clastogenicity *in vivo*, the lack of mutagenicity in mammalian cells in the HPRT assay, and the fact that DMAMET was negative in the majority of the Ames assays performed with this compound. Therefore, based on this conclusion and a DC of < 50 ppb, Toxicology has no concerns.

(b) (4) (DC of < 1.6 ppb)

Toxicology most recently evaluated (b) (4) during evaluation of FCN 1186 at a DC of 2.1 ppb, where the basis of no concern was stated to be previously-reviewed genotoxicity studies in which (b) (4) was negative under the tested conditions (see below). Chemistry has calculated a CEDI of 0.00154 mg/p/day (Elyashiv-Barad/Komolprasert, 2/8/08, RE: FCN 783[17]) for (b) (4) Toxicology has previously evaluated the following studies conducted with (b) (4)

- Genotoxicity: negative in Ames, mouse lymphoma, *in vitro* cytogenetics assays, and an *in vivo* micronucleus assay (Rice/McDougal, 2/24/06 (mouse lymphoma), 5/1/06 (Ames), RE: FCN 599; Roth/Honigfort, 6/6/09, RE: FCN 885 (Ames, mouse lymphoma, chromosomal aberration assay in human peripheral blood lymphocytes); Rice/Hepp, 7/14/08, RE: FCN 820[18] (micronucleus assay));
- Reproductive/developmental toxicity (Rice/File, RE: FCN 599, 6/26/08):
  - No observed adverse effect levels (NOAELs) of 225 and 75 mg/kg bw/day for reproductive and developmental toxicity, respectively, from a combined repeat-dose/one-generation reproductive toxicity screening study (OECD 422; Crl:CD®(SD) rats) for decreases in mean numbers of pups born, postnatal survival, and offspring bodyweight at the lowest observed adverse effect level (LOAEL) (225 mg/kg bw/day);
  - One-generation gavage reproductive toxicity study in rats (DuPont (b) (4) Rice/Honigfort, 3/31/10, RE: FCN 940[19]): NOAEL for parental toxicity of 25 mg/kg/day, based on mortality and decreased weight gain in males, abnormalities in the teeth and other clinical signs in both sexes, decreased weight gain in females during lactation, and increased uterine weight at the LOAEL of 125 mg/kg/day. The NOAEL for offspring toxicity was 25 mg/kg/d, based on increased pup mortality, decreased pup body weight and weight gain, and gross findings (no milk in the stomach of several pups) at the LOAEL of 125 mg/kg bw/day;
- Teratogenicity study in rats (DuPont-(b) (4) Rice/Honigfort, 3/31/10, RE: FCN 940): Maternal

[17] 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.*

[18] 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) ((b) (4) CASRN: N/A) as polymer additive in food contact paper and paperboard. *Effective 7/31/08.*

[19] FCN 940: DuPont Chemical Solutions Enterprise for the use of hexane, 1,6-diisocyanato-, homopolymers, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octanol blocked ((b) (4) CASRN: 357624-15-8) as a grease-proofing agent in food contact paper and paperboard. *Effective 4/3/10.*

and fetal NOELs of 25 mg/kg bw/day for decreased bodyweight gain and feed consumption in the dams and ossification delays in the skull and rib alteration in offspring at 125 mg/kg bw/day;

- Systemic toxicity:
  - NOAEL of 25 mg/kg/day (Rice/File, RE: FCN 599, 6/26/08), based on decreased body weight and body weight gain in parental males at the LOAEL (75 mg/kg bw/day) from a repeated-dose/one-generation reproductive toxicity study (OECD 422; Crl:CD®(SD) rats, total systemic exposure varied from 28 – 52 days, depending on group);
  - 90-Day gavage study in rats (DuPont (b) (4) Rice/Honigfort, 3/31/10, RE: FCN 940): No NOEL for systemic toxicity in females, based on increased thyroid weight parameters down to the lowest dose tested of 5 mg/kg/d; and
- Biopersistence: 75-95% of dose eliminated within 24 hours; (b) (4) cleared faster than (b) (4) in monkey[20]

As noted in the previously reviewed OECD 422 study, "*non-statistically-significant changes in thyroid weights were also noted in mid- and high-dose males, with decreases in absolute (-10%, - 12%), bodyweight-relative (- 17%, both groups), and brainweight-relative (-10,-11 %) thyroid weight parameters noted at terminal necropsy. The effects of treatment on thyroid weights were not present in recovery animals*[21]." The combined results of the systemic data appear to contradict in sex and direction. Both studies were conducted in the same strain and source of rats (Crl:CD(SD), Charles River, Inc., Raleigh, NC), by the same route (oral, gavage), and used the same diet (Purina 5002). However, there are differences in the test material source (different notifiers), purity (98.52% in the combined and 99.7% in the subchronic), and vehicle (corn oil was used as vehicle in the combined and methylcellulose in the subchronic). In addition, the doses were in the same range but slightly different (0, 25, 75, or 225 mg/kg/day for the combined and 0, 5, 25, 125, or 250 mg/kg/day for the subchronic), as were the testing laboratories (WIL Research Laboratories and Charles River, respectively). Furthermore, the durations of the exposure and recovery periods were different, as were the total numbers of doses of the test compound each sex of received in each study. Given the more adequate duration of the subchronic study, it is considered to be more heavily weighted in the analysis, and contributions regarding other differences in testing parameters are considered to be insufficient to mitigate a concern for the observations in the thyroid in recovery animals. Therefore, collectively, it does appear that (b) (4) may have effects on the thyroid. As such, the LOEL of 5 mg/kg bw/day should be used as a conservative point of departure (POD). Given the fact that the (b) (4) exposure herein is substitutional for other (b) (4) exposures from similar uses and that the only (b) (4) exposures from food contact uses are those derived from uses in paper and paperboard, it would be conservative compare the EDI herein of < 4.8 µg/p/d to the POD for risk assessment purposes. The margin of exposure (MOE) between the EDI for (b) (4) of 8 x 10^{-5} mg/kg/d and the LOEL of 5 mg/kg bw/day is 62, 500, which is greater than the 20,000 minimum MOE needed[22] to assure safety.

The notifier has submitted three genotoxicity studies conducted with (b) (4) in full in Attachments 20-22 and also discusses the results of the one-generation, teratogenicity, and 90-day studies conducted by DuPont that had been previously-reviewed for FCN 940. The genotoxicity studies (Ames[23], mouse

[20] IV Absorption, Distribution, Metabolism, Excretion (ADME) studies: Roth/McDougal, 5/24/06, RE: FCN 599.
[21] 14 day recovery period (control and high dose), males and females (n=5/sex/group) received a total of 35 and 40 doses, respectively.
[22] For similar situations, Toxicology has historically used uncertainty factors (UF) of 10 for intra-species variability, 10 for inter-species variability, 10 for less than chronic duration, 2 for lack of non-rodent data and 10 for the use of a LOEL, resulting in a total UF of 20,000.
[23] "(b) (4) Bacterial reverse mutation test", study # DuPont-(b) (4) performed at Haskell Laboratory for Health and

lymphoma assay[24], cytogenetic assay in human lymphocytes[25]) had been previously cursorily-reviewed by Toxicology for FCN 885 (Roth/Honigfort, 6/6/09); based on this cursory review, Toxicology agreed with the reported conclusions of negative genotoxicity for all three studies. Based on these reported results and conclusions from previously fully-reviewed genotoxicity studies of no concern for genotoxicity, Toxicology did not fully-review these three genotoxicity studies. Therefore, based on a DC of < 50 ppb, and adequate MOE between the current CEDI for (b) (4) and the most sensitive oral toxicity study, and lack of concern for genotoxicity, Toxicology has no concerns.

[redacted] (DC of 70 pptr)

Toxicology most recently reviewed (b) (4) or FCN 1186 at a DC of 2.1 pptr, where the basis of no concern was stated to be the extremely low, conservative calculated exposure therein and Toxicology's previous conclusions regarding (b) (4) Toxicology has reviewed or cursory-reviewed, as applicable, the following data on the toxicity of (b) (4)

- Genotoxicity (not reviewed by Toxicology, reported results only): Negative in Ames[26] and an *in vitro* cytogenetics assay in human peripheral blood lymphocytes[27];
- Biopersistence: $T_{1/2}$ ~2-4 hours in rats[28]. 75-95% of dose is eliminated within 24 hours in rats[29], with no biopersistence in tissues[30]; and
- Systemic toxicity: A published 90-day study conducted with (b) (4) [1] reviewed for FCN 940; a combined repeated-dose/one-generation reproductive toxicity study conducted with (b) (4) (Rice/File, RE: FCN 599, 6/26/08); and 90-day studies conducted with (b) (4) (b) (4) (Rice/File, 1/14/09, RE: FMF 799[32]) and (b) (4) (Gu/Komolprasert, 10/17/07, RE: FCN 746[33]) have been reviewed. The lowest reported NOEL from these studies is 10 mg/kg bw/day in males from the published 90-day study on (b) (4) for decreased cholesterol, serum calcium, and bodyweight at 50 mg/kg bw/day.

The notifier's CTP for (b) (4) discusses the above-cited data, which have become publicly-available since the time they were reviewed, as well as the results of a chronic, oral bioassay conducted with

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Environmental Sciences in Newark, DE; study report date of: 8/2/07. Located in Attachment 20.

[24] (b) (4) -*In vitro* mammalian cell gene mutation test (L5178Y/TK+/- mouse lymphoma assay)", study # (b) (4), performed at BioReliance in Rockville, MD, study report date: 5/30/08. Located in Attachment 21.

[25] (b) (4) -*In vitro* mammalian chromosome aberration test in human peripheral blood lymphocytes", study # DuPont-(b), performed at DuPont Haskell Global Centers for Health and Environmental Sciences in Newark, DE, study report date: 8/28/08. Located in Attachment 22.

[26] Myhre, A.: (b) (4) : Bacterial reverse mutation test.", DuPont-(b), Haskell Laboratory for Health and Environmental Sciences, Newark, DE, study report date of 10/30/06. Located in Update Attachment 19 to FMF (b) Test substance: (b) (4) (b) (4).

[27] Glatt, C.M.: (b) (4) : *In vitro* mammalian chromosome aberration test in human peripheral blood lymphocytes." DuPont-(b), Haskell Laboratory for Health and Environmental Sciences, Newark, DE, study report date of 11/7/06. Located in Update Attachment 20 to FMF (b) Test substance: (b) (4).

[28] Analysis of plasma F data from subchronic rat study performed on (b) (4) and submitted with FCN 746, Roth/Gu, 9/11/07.

[29] IV ADME studies (Kirkpatrick, 2005, WIL Study #'s (b) (4) and (b) (4)): Roth/McDougal, 5/24/06, RE: FCN (b)

[30] Carpenter, 2008 (DuPont-(b), 10-day biopersistence study), Roth/Rice, 12/12/08, RE: FMF (b)

[31] Chengelis, C.P., Kirkpatrick, J.B., Radovsky, A., Shinohara, M. (2009) A 90-day repeated dose (oral) gavage toxicity study of (b) (4)) in rats (with functional observational battery and motor activity determinations). *Reprod. Toxicol.*, **27**(3-4): 342-51. In this study, CD rats (n = 10/sex/time point/group) were gavaged with (b) (4) in water at doses of 0, 10, 50, or 200 mg/kg bw/day for 90 days, followed by a 28-day recovery period (control and high-dose groups only).

[32] FMF (b) Information regarding < C8 perfluorocarbons. Submitted by DuPont on 5/20/08.

[33] 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, 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.*

(b) (4) in rats, in which (b) (4) administration did not induce neoplastic effects under the test conditions[34]. Based on the available data indicating lack of concern for carcinogenicity and biopersistence and a DC of < 0.5 ppb, Toxicology has no concerns.

(b) (4) (DC of 2.2 ppb)

Toxicology recently cited the available data for this compound in the memorandum for FCN 1095[35] (Jacobs/McAdams, 7/26/11) and reviewed this compound at a DC of 1.9 ppb for FCN 628. For FCN 628, Toxicology fully-reviewed genotoxicity studies (Ames, mouse lymphoma, *in vitro* cytogenetic assay), concluding that the test substance was negative in all three assays under the test conditions. A reported NOEL of 40 mg/kg/d in rats from a 28-day gavage study was also cited in Toxicology's memorandum for FCN 628, but this study was not fully-reviewed due to the low DC. Target organs were reportedly the liver, kidney, thymus, spleen, and bone marrow. The notifier's safety assessment for this compound discusses these data, citing the negative genotoxicity results in support of the conclusion of no concern. Based on Toxicology's previous conclusion of no concern for genotoxicity and a DC of < 50 ppb, Toxicology has no concerns.

(b) (4) (DC of 2.9 ppb)

Toxicology most recently reviewed this compound during evaluation of FCN 1186 at a DC of 0.44 ppb, where the conclusion of no concern was based on genotoxicity data previously reviewed for FCNs 599 and 604. For these FCNs, Toxicology cursory-reviewed an Ames assay ((b) (4)) and a mouse lymphoma assay (b) (4)[36], both reportedly negative. Toxicology fully-reviewed the Ames assay during evaluation of FCN 604, concluding that (b) (4) was negative under the test conditions. The notifier's safety assessment for (b) (4) cites the lack of concerning findings from a search of public databases for (b) (4), and lack of structural alerts for this compound. Based on the lack of concerning findings in the reviewed genotoxicity studies and a DC of < 50 ppb, Toxicology has no concerns.

CONCLUSIONS

Archroma Management GmbH, through Keller and Heckman, LLP, has notified for use of 2-propenoic acid, 2-methyl-, 2-(dimethylamino)ethyl ester, polymer with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl 2-methyl-2-propenoate, N-oxides, acetates (CASRN: 1440528-04-0). The FCS is intended to be used as a coating on food contact paper and paperboard, applied at either the wet-end or the size press, at a maximum use level of 2.2 g FCS/m^2 of paper and paperboard (0.26 mg polymer solids/sq-in). The FCS will contact all food types under Use Conditions B-H, as described on CFSAN's website. The FCS will not contact infant formula or breast milk. 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 detailed in this memorandum.

Penelope Rice, Ph.D.

INIT: JAungst, Ph.D.: 12/17/14

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[34] (b) (4)

[35] FCN 1095: Dow Chemical Company for the use of maleic anhydride-grafted polypropylene (CASRN: 25722-45-6) as a component of can coatings. *Effective 8/19/11*.

[36] OFAS does not have a final study report for this study; as such, it was only cursory-reviewed.