FORM FOR NOTIFICATION
OF FINAL REGULATORY ACTION TO BAN OR SEVERELY RESTRICT A CHEMICAL

Country: Canada

SECTION 1 IDENTITY OF CHEMICAL SUBJECT TO THE FINAL REGULATORY ACTION

1.1	**Common name**	**2-Propen-1-ol, reaction products with pentafluoroiodoethane tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine**
1.2	**Chemical name according to an internationally recognized nomenclature (e.g. IUPAC), where such nomenclature exists**	**2-Propen-1-ol, reaction products with pentafluoroiodoethane tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine**
1.3	**Trade names and names of preparations**	**2-Propen-1-ol, reaction products with pentafluoroiodoethane tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine**

1.4 Code numbers

1.4.1	CAS number	464178-90-3
1.4.2	Harmonized System customs code	N/A
1.4.3	Other numbers (specify the numbering system)	New Substances Notification (NSN): 13211, 13395

1.5 Indication regarding previous notification on this chemical, if any

1.5.1 ☒ This is a first time notification of final regulatory action on this chemical.

1.5.2 ☐ This notification replaces all previously submitted notifications on this chemical.
Date of issue of the previous notification: _____

SECTION 2 FINAL REGULATORY ACTION

2.1 The chemical is: ☒ **banned** **OR** ☐ **severely restricted**

2.2 Information specific to the final regulatory action

2.2.1 Summary of the final regulatory action

The Prohibition of Certain Toxic Substances Regulations, 2012 prohibit the manufacture, use, sale, offer for sale and import of toxic substances listed in Schedules 1 and 2. This notified substance is found in Part 2 of Schedule 1, which lists prohibited toxic substances subject to total prohibition, unless present in manufactured items.

2.2.2 Reference to the regulatory document, e.g. where decision is recorded or published

Regulations Amending the Prohibition of Certain Toxic Substances Regulations, 2005 (Four New Fluorotelomer-based Substances) (SOR/2010-211) under the *Canadian Environmental Protection Act, 1999.*
http://canadagazette.gc.ca/rp-pr/p2/2010/2010-10-13/html/sor-dors211-eng.html

The current version of the regulations can be accessed here: *Prohibition of Certain Toxic Substances Regulations, 2012* (SOR/2012-285) under the *Canadian Environmental Protection Act, 1999.*
http://laws-lois.justice.gc.ca/eng/regulations/SOR-2012-285/FullText.html

2.2.3 Date of entry into force of the final regulatory action

October 13, 2010.

2.3 Category or categories where the final regulatory action has been taken

2.3.1 All use or uses of the chemical in your country prior to the final regulatory action

The substance has never been manufactured in Canada. Any import that may have occurred would not have exceeded 1000 kg/yr.

The fluorotelomer-based polymer is reported to be used as a sizing agent in the treatment of food-contact paper containers and related products. Given its structural and functional similarity to other fluorotelomer-based polymers, it is expected that it could also be used in a number of other consumer and industrial products including paint additives, as surface protectors for textiles, and other materials.

The current uses for polymers which contain perfluorinated alkyl groups are many and varied, including use as a dry soil resistant agent for carpets; as stain and water protection agents for carpeting, leather goods, fabrics, tiles, grout and ceramic surfaces; as leveling agents and flow agents for plastics, paints, automotive finishes and inks; and as dispersant agents for industrial powder coatings.

2.3.2 Final regulatory action has been taken for the category ☒ Industrial

Use or uses prohibited by the final regulatory action

The prohibition prevents industry from importing, manufacturing, using, selling and offering for sale these substances, unless they are present in manufactured items.

Use or uses that remain allowed (only in case of a severe restriction)

N/A

2.3.3 Final regulatory action has been taken for the category ☐ Pesticide

Formulation(s) and use or uses prohibited by the final regulatory action

N/A

Formulation(s) and use or uses that remain allowed
(only in case of a severe restriction)

N/A

2.4 Was the final regulatory action based on a risk or hazard evaluation? ☒ Yes

☐ **No** (If no, you may also complete section 2.5.3.3)

2.4.1 If yes, reference to the relevant documentation, which describes the hazard or risk evaluation

New Substances Evaluation Report (New Substances Notifications 13211 and 13395). *Canadian Environmental Protection Act, 1999*. Government of Canada. Available upon request: http://www.ec.gc.ca/subsnouvelles-newsubs/default.asp?lang=En&n=6F22A1D6-1

2.4.2 Summary description of the risk or hazard evaluation upon which the ban or severe restriction was based.

2.4.2.1 Is the reason for the final regulatory action relevant to human health? ☒ Yes ☐ No

If yes, give summary of the hazard or risk evaluation related to human health, including the health of consumers and workers

Based on the available information on the physical and chemical properties of the fluorotelomer-based polymer, direct and indirect exposure of the general population to the fluorotelomer-based polymer and the hazardous degradation products is expected to be low at the currently intended annual import quantities.

Based on available data, as well as surrogate data, the fluorotelomer-based polymer is expected to show low acute oral toxicity and low skin and eye irritation potential, and low reproductive and developmental toxicity; however it is likely to display moderate subchronic oral toxicity, with possible effects on the thyroid, liver, and kidney.

The toxicological profile of the anticipated ultimate degradation products of the fluorotelomer-based polymer (i.e. perfluorocarboxylic acids (PFCAs)) is not expected to differ significantly from that of perfluorooctanoic acid (PFOA) and its salts. Based on available data, PFOA and its salts are not genotoxic but are tumourigenic and immunotoxic in rodents, and display moderate reproductive and developmental toxicity in rodents and moderate to high subchronic oral toxicity in rodents and monkeys. As a result, there is reason to suspect that the degradation products of the fluorotelomer-based polymer, and in particular the PFCAs, may have the potential to cause adverse health effects in humans.

Direct Exposure to Humans:
The fluorotelomer-based polymer is expected to react almost completely with paper fibres during the paper sizing process and prior to the sheet forming

operation in the manufacture of single-use household paper containers. Supplementary information provided in the Food Contact Notification for the United States Food and Drug Administration (US FDA) gave typical levels of residual fluorinated starting materials and intermediates present in the fluorotelomer-based polymer. Residual fluorinated starting materials and intermediates are on the order of 300 ppm (total) on a dry weight basis of fluorotelomer-based polymer; whereas, fluorinated propenol byproducts are approximately 3000 ppm. It is predicted that these byproducts would be released to the environment during the paper product manufacturing process and they would be converted quickly in the environment to the corresponding PFCAs. At the projected import quantity of 17 000 kg/yr, the amount of fluorinated alcohol byproducts entering the environment would represent approximately 50 kg/yr.

Expected effect of the final regulatory action

The Regulations prevent the introduction of new sources of PFCAs into Canada, thereby protecting the environment and human health. The prohibition prevents industry from importing, manufacturing, using, selling and offering for sale these substances, unless they are present in manufactured items.

2.4.2.2 Is the reason for the final regulatory action relevant to the environment?

☒ Yes

☐ No

If yes, give summary of the hazard or risk evaluation related to the environment

The fluorotelomer-based polymer, in its undegraded form, is expected to have limited exposure to the aquatic environment. Based on the exposure scenarios for paper product manufacture and general blending release, an environmental risk quotient of 6.1×10^{-5} is calculated from the lowest predicted environmental concentration (PEC) (Merickville) and the predicted no effects concentration (PNEC). This risk quotient is much less than one, so there is little immediate concern from aquatic exposure of the fluorotelomer-based polymer to aquatic organisms. It is important to note, that because the substance would tend to partition to the sediment, toxicity to sediment dwelling organisms would be more appropriate; however, based on the toxicity results for aquatic organisms, the PEC/PNECs for sediment dwelling organisms would not be expected to exceed 1. Based on these results, the fluorotelomer-based polymer, in its undegraded form, is not expected to induce adverse effects to the environment and would not be considered "toxic" under the *Canadian Environmental Protection Act, 1999*; however, the fluorotelomer-based polymer is expected to degrade and release substances of higher concern.

The assessment has concluded that PFCA precursors are released from the fluorotelomer-based polymer as unreacted residuals or as degradation products, and are expected to further degrade to the highly persistent PFCAs. All of the

PFCAs formed are expected to remain in the environment as there are no known environmental degradation mechanisms.

Although the experimental evidence is not available demonstrating the occurrence, mechanism or rate of degradation from the fluorotelomer-based polymer, the release of PFCA precursors can be expected based on the chemistry of the notified substance and the available evidence suggesting susceptibility of this chemistry to degradation The rate of release may be faster or slower than rates observed in surrogate chemicals due to such factors as steric hindrance, however the rate is not considered of significant environmental importance given the exceptional stability of the ultimate degradation product, PFCAs.

Atmospheric long range transport of some PFCA precursors can be used to explain the presence of the longer chain PFCAs in biota in remote regions of Canada. The measurements of longer chain PFCAs in remote regions of Canada give support to this transport mechanism and provide a scientifically defensible explanation of their presence. It is important to emphasise that the presence of PFCAs in remote regions should not be solely attributed to the notified substance or any single fluorinated substance, single source or single mechanism of transport, as local sources of contaminants and emissions from other jurisdictions may also contribute.

Although acute toxicity to aquatic organisms following exposure to the degradation products appears to be low, evidence for chronic effects remains unknown. Toxicity studies to laboratory mammals indicate the potential to cause adverse health effects in wildlife.

In summary, the fluorotelomer-based polymer is expected to degrade, release polyfluorinated substances, undergo long range atmospheric transport and/or degrade further to PFCAs. Available evidence indicates that the longer chain PFCAs (≥C9) are susceptible to bioaccumulation and biomagnification, have been found in remote regions, and notably exhibit characteristics of persistent organic pollutants (POPs). These unique characteristics combined with the potential for long term adverse effects, warrant concern for the environment.

Expected effect of the final regulatory action

The Regulations prevent the introduction of new sources of PFCAs into Canada, thereby protecting the environment and human health. The prohibition prevents industry from importing, manufacturing, using, selling and offering for sale these substances, unless they are present in manufactured items.

2.5 Other relevant information regarding the final regulatory action

2.5.1 Estimated quantity of the chemical produced, imported, exported and used

	Quantity per year (MT)	Year
produced	N/A	N/A
imported	N/A	N/A
exported	N/A	N/A
used	N/A	N/A

2.5.2 Indication, to the extent possible, of the likely relevance of the final regulatory action to other states and regions

The substance has never been manufactured in Canada. Any import that may have occurred would not have exceeded 1000 kg/yr. The substance is present and used globally. There is a possibility that the final regulatory action may be slightly relevant and could be used for other states and regions, but because of the available chemical alternatives the impact should be minimal.

2.5.3 Other relevant information that may cover:

2.5.3.1 Assessment of socio-economic effects of the final regulatory action

The notified substance is not produced in Canada; the Regulations prevent the introduction of this fluorotelomer-based polymer into Canada. Canadian Industry will not be able to introduce the regulated substance into Canada. Thus, industry will not have the opportunity to use this substance in a number of applications. The availability of other fluorotelomer-based substances as well as hydrocarbon-based and silicone-based polymer with similar properties indicates that this lost opportunity will likely result in negligible, if any, incremental costs to the Canadian industry.

The number of companies involved with these substances is relatively small. Therefore, Canadian Government costs associated with promoting compliance and enforcing the Regulations are minimal.

2.5.3.2 Information on alternatives and their relative risks, e.g. IPM, chemical and non-chemical alternatives

N/A

2.5.3.3 Basis for the final regulatory action if other than hazard or risk evaluation

N/A

2.5.3.4 Additional information related to the chemical or the final regulatory action, if any

Communication between the manufacturer and another regulatory body indicated that the degradation products and the products from incomplete combustion may be very similar to PFOA and therefore persistence and bioaccumulation of these products would be of similar concern. In addition, significant concerns are raised towards chronic effects in humans and wildlife. All the reactants used to produce the fluorotelomer-based polymer are listed on the domestic substances list (DSL) or the non-domestic substances list (NDSL). The fluorotelomer-based polymer is neither on the NDSL nor *Toxic Substances Control Act* (TSCA) inventories. It has been notified to the US FDA and was approved for use in food-contact paper products, April 23, 2003.

SECTION 3 PROPERTIES

3.1 Information on hazard classification where the chemical is subject to classification requirements

International classification systems **e.g. WHO, IARC, etc.**	**Hazard class**
N/A	N/A

Other classification systems **e.g. EU, USEPA**	**Hazard class**
N/A	N/A

3.2 Further information on the properties of the chemical

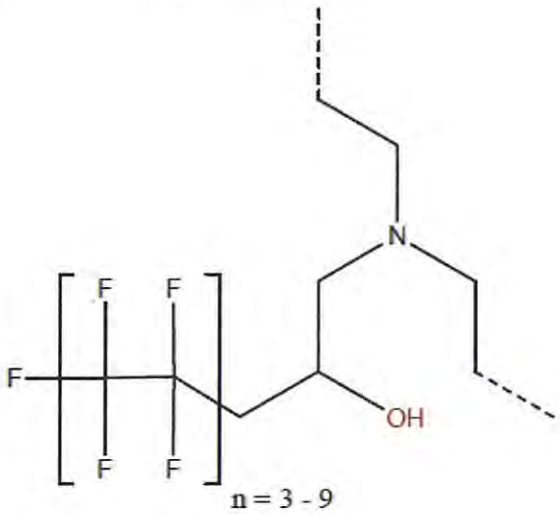
3.2.1 Description of physico-chemical properties of the chemical

Structural Features: The notified substance is a fluoroalkylaminoalcohol polymer. The percent of

polymer below Mn of 500 is 2.96% and that below 1000 is reported to be 3.14%.

Based on the cationic nature of the fluorotelomer-based polymer it is considered "not low concern" (NLC) according to the New Substances Notification regulations. The cationicity is provided by the triethylenetetramine reactant (Mw = 146) incorporated at 10%. As such, the functional group equivalent weight (FGEW) meets the <5000 criteria for NLC.

The fluorotelomer-based polymer is heavily cross linked and formed from a number of reactants including tetrafluoroethylene telomer at 51% which give it the pendant perfluorinated alkyl groups.



Representative structure of the notified polymer.

The product is a tan coloured, syrupy liquid that contains 14.0 - 16.0 weight% solids and has a pH value of 3.5 - 6.5 according to the Material Safety Data Sheet (MSDS). The notified substance has a reported 98% degree of purity of the technical grade product tested.

Physical and chemical properties of Notified Substance:

- Physical state: Liquid
- Boiling point: N/A
- Solubility in water: Not miscible 3 x 10^{-154} (calc. EPI)
- Dispersibility in water: Dispersible
- Vapour pressure: N/A

Reference

New Substances Evaluation Report (New Substances Notifications 13211 and 13395). *Canadian Environmental Protection Act, 1999*. Government of Canada. Available upon request: http://www.ec.gc.ca/subsnouvelles-newsubs/default.asp?lang=En&n=6F22A1D6-1

3.2.2 Description of toxicological properties of the chemical

Fluorotelomer-based polymer:

Toxicity studies were conducted with a formulated product (a 15% dispersion of the fluorotelomer-based polymer in water), and submitted with this notification package. All tests except the skin irritation test, the eye irritation test and the skin sensitization test took into consideration the purity of the test substance when dosing.

Acute toxicity:

The fluorotelomer-based polymer exhibited low acute oral toxicity in rats with an estimated LD50 of greater than 2000 mg fluorotelomer-based polymer/kg bw. Following dosing of 2000 mg fluorotelomer-based polymer/kg bw, all rats (3M/3F, Wistar) survived until terminal necropsy and showed normal body weight gain. Clinical signs observed during the observation period consisted of piloerection and hunched posture on day 1 and 2 only. No abnormal lesions were observed at terminal necropsy on day 14.

The test substance, containing 15% fluorotelomer-based polymer in water, was non-irritating to the skin of rabbits with a Primary Irritation Index (PII) of 0.0/8.0. No erythema or edema was observed in 3 male rabbits (NZW) 1, 24, 48 or 72 hours after exposure (4hrs, semi-occlusive dressing).

The test substance, containing 15% fluorotelomer-based polymer in water, was minimally irritating to the eyes of rabbits, with a Maximum Average Score (MAS) of 11.3/110. No corneal or iridial irritation was observed in 3 female rabbits (NZW); however, conjunctival redness, chemosis and discharge was observed shortly after exposure, but animals recovered within 48 hours.

Sensitization:

The test substance, containing 15% fluorotelomer-based polymer in water, exhibited weak skin sensitization potential in guinea pigs following a Guinea Pig Maximization Test (GPMT). No signs of sensitization were observed in 10 female guinea pigs (Dunkin Hartley) following challenge with 100% test substance. The

intradermal and topical concentrations used were 5 and 100% respectively.

Repeated dose oral toxicity:

The fluorotelomer-based polymer exhibited moderate repeated dose oral toxicity in rats with a NOEL of 50 mg fluorotelomer-based polymer/kg bw/day. Male and female Wistar rats (5/sex/group) were dosed 0, 50, 150 or 1000 mg fluorotelomer-based polymer/kg bw/day, by oral gavage, once daily, for 28 consecutive days. Additional animals were added to the control and high dose groups to allow for recovery group animals; these animals were kept alive an additional 14-days following exposure in order to observe the reversibility of effects.

There were no test article related deaths during the study. Body weight gain and food consumption were comparable to control animals at all dose levels. Test article related clinical signs were mainly manifested in high dose animals, however more prominently in males, and included hunched posture, alopecia, piloerection, ocular secretions and red staining. High dose group and medium dose group males showed decreased motor activity when compared to control (recovered after cessation of treatment). During the opthalmology examination, retinal haemorrhage was observed in two females in the high dose group. The toxicological significance of this finding remains uncertain.

At study termination, very slight decreases (although statistically significant), of haemoglobin (Hb), haematocrit (Hct), mean cell volume (MCV) and mean corpuscular haemoglobin (MCH) were observed in high dose group males and may be indicative of a slight anaemic response. These parameters remained lower in the high dose recovery group males after the recovery period. Other changes noted in treated animals at the end of the dosing period included a slight decrease in activated partial thromboplastin time (APTT), prothrombin time (PT), in MCV and MCH. However due to the slight difference from control animals and the lack of a doseresponse relationship, these findings are considered not toxicologically significant.

Two high dose group males also showed increased alanine amino transferase (ALT) (1 male) and aspartate amino transferase (AST) (2 males), which correlated with the histopathological observations of hepatocellular necrosis. Slightly increased cholesterol and triglycerides were observed in high dose group females, however the toxicological significance remains unclear. Other changes in creatinine, chloride, albumin, alkaline phosphatase (decrease) were considered not toxicologically significant and/or considered secondary to the clinical condition of the animals. At termination of the recovery period, no toxicologically significant differences were observed.

Following terminal necropsy, no animals showed treatment related macroscopic abnormalities. Organ weight changes were, however, observed in the high dose group animals. Specifically, slight but statistically significant increases in relative organ to body weight ratios for liver and kidney were observed. By the end of the recovery period, the liver and kidney weights returned to control values in the females, however the male relative kidney weights were still slightly elevated.

Upon histopathological examination, the most significant findings in the high dose group animals were hepatocellular necrosis (2 males), lymphogranulocytic inflamation of the submucosa in combination with apoptotic bodies of the glandular epithelium in the stomach (all), and vacuolation of the squamous epithelium of the limiting ridge of the stomach (2/10 males and 10/10 females). Similar gastrointestinal tract findings were observed in some medium dose group animals. Low dose group animals showed no toxicologically relevant changes from controls. No significant histopathological abnormalities were observed in the kidney.

Target organs appear to be the gastrointestinal tract, liver and potentially the kidney. Since adverse histopathological effects to the gastrointestinal tract were observed in animals dosed 150 mg fluorotelomer-based polymer/kg bw/day and no significant adverse effects were observed in animals dosed 50 mg fluorotelomer-based polymer/kg bw/day, a NOEL of 50 mg fluorotelomer-based polymer/kg bw/day was determined.

Genotoxicity:

The fluorotelomer-based polymer was non-mutagenic in the Ames reverse mutation assay. No reproducible or biologically significant increase in the number of revertant colonies per plate was observed in any of the tester strains of *S. typhimurium* (TA98, TA100, TA1535, TA1537) or *E. coli* (WP2uvrA) in the presence or absence of metabolic activation, when using the plate incorporation method, at doses up to 5000 µg/plate.

The fluorotelomer-based polymer produced equivocal results in an in vitro chromosomal aberration test in human peripheral blood lymphocytes. Duplicate cell cultures were exposed to the test substance at concentrations ranging from 33 to 333 µg/ml (precipitate was observed at concentrations above 333 µg/ml) in the presence and absence of S9 metabolic activation in two separate experiments. In the first experiment, cells were exposed to the test substance for 3 hours in either the presence or absence of metabolic activation, with harvest times of 24 hours. No significant increase in the number of cells with chromosomal aberrations was observed in the presence or absence of S9 metabolic activation in the first experiment. In a repeat experiment, cells were exposed to the test substance in the absence of metabolic activation for 24 or 48 hours, with harvest times of 48

hours; in the presence of metabolic activation, cells were exposed for 3 hours, with a harvest time of 48 hours. A significant increase in the number of cells with chromosomal aberrations was observed at the highest dose (333 µg/ml) in the absence of metabolic activation when the exposure period was 48 hours and the harvest time was also 48 hours (precipitate was observed). No other increases in the number of cells with chromosomal aberrations were observed under the other test conditions in the second experiment. The authors of the study suggest that the positive result in the second experiment was as a result of cytotoxicity; however, this was not supported by a decrease in the mitotic index. The evidence for clastogenic potential in the absence of metabolic activation is considered equivocal.

The fluorotelomer-based polymer was not clastogenic to mouse bone marrow following an in vivo mouse micronucleus test. Male and female mice (5/sex/group) were administered doses of 25, 50 or 100 mg/kg bw, by intraperitoneal injection, and sacrificed 24 hours after administration. An additional group of animals was added to the high dose group and sacrificed 48 hrs after dose administration. The fluorotelomer-based polymer was well tolerated by most of the treatment animals. Some animals from the high dose and medium dose groups showed hunched posture and/or rough coat after treatment. All medium dose group animals appeared normal 2 hours after dosing and all high dose group animals appeared normal 20 hours after dosing. Following sacrifice, there was no significant decrease in the PCE/NCE ratio of the treatment animals (indicating a lack of toxic effect on erythropoiesis) and there were no significant increases in the number of micronucleated PCE in any of the treatment animals. Since there was no evident effect to the PCE/NCE ratio, it is uncertain whether the test substance reached the target organ (i.e., the bone marrow). Therefore, the equivocal results from the in-vitro chromosomal aberration test are not mitigated.

Overall, the fluorotelomer-based polymer is considered to possess moderate genotoxicity potential.

<u>Toxicity of Degradation Products:</u>

The fluorotelomer-based polymer contains C_6-C_{18} perfluorinated alkyl groups which are of concern to human health due to their extreme persistence in the environment and in organisms, their potential for bioaccumulation due to their very slow elimination rates, and the toxicity observed in a range of toxicological studies.

The perfluorinated alkyl containing chemicals which are intermediates and/or byproducts in the manufacture of the fluorotelomer-based polymer have been tested for their ability to bind serum proteins. No other toxicity testing is available

for these chemicals.

According to a serum steroid displacement assay, none of these perfluorinated alkyl chemicals significantly displaced estrogen or testosterone bound to carp serum proteins, in contrast to the ability for PFOS and PFOA to displace estrogen. According to an equilibrium partitioning method, which measures protein binding by measuring the effect of serum proteins on the partitioning of the target chemicals between an aqueous solution phase and an inert organic phase, long chain perfluorinated alkyl chemicals showed the greatest propensity to remain in aqueous solution when serum proteins were present; short chain perfluorinated alkyl chemicals transferred almost completely to the organic chemical phase, whether or not serum proteins were present; and medium chain perfluorinated alkyl chemicals showed intermediate results between those seen by the long chain perfluorinated alkyl chemicals and those seen by the short chain perfluorinated alkyl chemicals. The relevance to human serum binding potential remains unclear.

Information on the toxicological properties of perfluorooctanoic acid (PFOA) and its ammonium salt (APFO) will be reviewed in order to assess the potential toxicity of the proposed degradation products (PFCAs) of the fluorotelomer-based polymer.

The following information is from test data provided by chemical companies, published literature, or the US EPA Hazard Assessment of PFOA (US EPA, 2002).

Toxicokinetics:

After absorption, PFOA distributes primarily to plasma, the liver and the kidney. The estimated serum half-life values of PFOA range from 1.9 to 24 hrs in female and 4.4 to 9 days in male rats. PFOA is not metabolized and urine is the major route of excretion in the female rat, while the urine and the faeces are both major routes of excretion in male rats (Vanden Heuvel et al, 1991).

There is evidence indicating that urine clearance of perfluorinated carboxylic acids (PFCAs) decreases as carbon chain length increases, especially in the male rat (Kudo, 2003; Kudo, 2001). In humans, PFOA has been detected in the serum of both industrial workers and the general population; in the US, the highest arithmetic mean serum PFOA level reported in occupationally exposed individuals was 6.8 ppm (range 0.0-114.1 ppm). According to a biomonitoring study in the US general population, PFOA has been detected in the serum of children, adults, and the elderly; the geometric mean serum PFOA concentrations were in the range of 4-5 ppb and were quantifiable in over 90% of the serum samples (cited in Butenhoff et al, 2004a). More recent studies have reported the presence of PFOA in blood samples from volunteers in Canada, Colombia, Poland, Belgium, Korea and Japan (Kubwabo et al., 2004; Kannan et al., 2004; Harada et al., 2004). Based

on findings in 9 retired factory workers, the median half-life for elimination of PFOA from humans was estimated to be 4.37 years (range: 1.50-13.49 years, SD=3.53), indicative of very slow serum clearance.

Systemic toxicity:

PFOA was administered to rats in the diet for 90 days at doses of 0, 10, 30, 100, 300, or 1000 ppm (corresponding to ca. 0, 0.65, 2.0, 6.65, 20 or 70 mg/kg bw/day) (Griffith, 1980). The LOAEL was determined to be 30 ppm (corresponding to ca. 2 mg/kg.bw/day), based on hematopoietic effects (decreased erythrocytes and leukocytes), increased liver weight, and hepatocellular hypertrophy.

APFO was administered to rats in the diet for 90 days at doses of 0, 1, 10, 30, or 100 ppm (corresponding to ca. 0, 0.05, 0.47, 1.44 or 4.97 mg/kg bw/day) (Perkins, 1992). The LOAEL was determined to be 10 ppm (corresponding to ca. 0.47 mg/kg bw/day), based on decreased body weight and body weight gain, increased liver weight, and hepatocellular hypertrophy. In addition, increased levels of hepatic β-oxidation - a likely indicator of peroxisome proliferation - were also observed in high dose group animals in this study. Since peroxisome proliferation occurs at a much higher level in rodents than in humans, the toxicity implications and significance in humans of peroxisome proliferation and associated toxicity changes observed in rodents, is not fully understood.

In a 4-week range finding study, groups of 3 male monkeys were administered APFO at 2 or 20 mg/kg bw/day. The control group consisted of two male monkeys. In the treatment groups there were no mortalities, no treatment related clinical signs, no blood chemistry differences from control animals and no gross or histopathological treatment-related findings. One animal in the 20 mg/kg bw/day group exhibited no or low food consumption throughout the study.

Based on the above results, a study was designed in which groups of male monkeys were to be given APFO by oral capsule for six-months at dose levels of 0, 3, 10, or 30 mg/kg bw/day (6, 4, 6 and 6 animals/group, respectively) followed by a 13-week recovery period. The dosing had to be discontinued in the 30 mg/kg bw/day group due to systemic signs of toxicity including decreased body weights resulting from low or no food consumption. Treatment was resumed in these animals on Day 22 at a decreased dose level of 20 mg/kg bw/day. One of these high dose monkeys died on Day 29 and three other monkeys did not complete the scheduled dosing period due to systemic clinical signs which consisted of decreased body weights and no faeces resulting from decreased food consumption. Treatment-related microscopic lesions were observed in the liver, including centrilobular and midzonal hepatocellular degeneration and necrosis, diffuse hepatocellular vacuolation, and hepatocyte basophilia in centrilobular areas

(liver regeneration). One monkey dosed at 3 mg/kg bw/day was sacrificed on Day 137 due to its clinical condition, possibly related to APFO treatment. Clinical signs for this animal included limited use and paralysis of hind limbs, ataxia, hypoactive behaviour, few faeces and no food consumption. No clear histological findings could be attributed to the test article.

In general, in all dose groups, clinical signs relating to decreased body weight gain (more severe in the high dose group) occurred and animals at all dose levels required veterinary care during the study. The absolute liver weights were increased by 35, 38, and 50% in the 3, 10 and 30/20 mg/kg bw/day groups respectively. Alanine aminotransferase and aspartate aminotransferase were significantly increased in high dose animals correlating to increased liver weights, hepatotoxicity noted in the euthanized/deceased animals and microscopic evidence of an increase in mitochondrial proliferation. All changes were comparable to controls after the recovery period, indicating a reversibility of effects.

In an earlier study, groups of 4 monkeys (2/sex) were dosed orally with 0, 3, 10, 30 or 100 mg/kg bw/day for 90 days. All animals of the 100 mg/kg bw/day group died and 3 of 4 animals of the 30 mg/kg bw/day also died. Clinical signs manifested throughout all groups with increasing severity and intensity at the higher dose levels. Although there were changes in hematology, blood biochemistry and organ weights, histological examinations were not conducted during the study and therefore a biological correlate could not be ascertained for these changes (cited in USEPA, 2002 and Butenhoff et al., 2002).

Reproductive and Developmental Toxicity:

Preliminary results indicate that PFOA is likely to have high developmental toxicity in the rat and rabbit (NOAEL of 3 and 5 mg/kg bw/day, respectively). In a two-generation reproductive toxicity study in rats exposed to 0, 1, 3, 10, or 30 mg/kg bw/day APFO, the LOAEL for both F0 parental males and F1 generation males is considered to be 1 mg/kg bw/day, based on decreases in body weights and body weight gains, and significant changes in absolute liver and spleen weights and in the ratios of liver, kidney, and spleen weight-to-brain weights, and liver hepatocellular hypertrophy. The NOAEL and LOAEL for both F0 parental females and F1 generation females are considered to be 10 and 30 mg/kg bw/day, respectively, based on statistically significant increases in postweaning mortality, delays in sexual maturation (time to vaginal patency), decreases in body weight and body weight gains and decreases in absolute food consumption. The NOAEL for the F2 generation offspring was considered to be 30 mg/kg bw/day as no treatment-related effects were observed at any doses tested in the study when pups were sacrificed at weaning (Butenhoff et al., 2004b).

Genotoxicity:

APFO has been shown to be non-mutagenic to *Salmonella typhimurium* and *E. coli* bacteria in the presence or absence of metabolic activation in two separate Ames tests. APFO did not induce chromosomal aberrations in human lymphocytes in two separate in vitro chromosomal aberration studies; however, APFO induced significant increases in chromosomal aberrations and polyploidy in Chinese hamster ovary cells (CHO cells) in the presence of metabolic activation in two separate assays. APFO has been shown to be negative in a cell transformation assay and in two separate mouse micronucleus assays (cited in Kennedy et al., 2004).

Tumourigenicity:

Based on results from a two-year dietary carcinogenicity study in rats, APFO induced significant increases in the incidence of Leydig cell adenomas (males) and mammary fibroadenomas (females). A mechanistic two-year dietary study in male rats reported an increase in pancreatic acinar cell adenomas/carcinomas (9.2%) and hepatocellular adenomas (13%), in addition to Leydig cell adenomas (11%) (O'Connor, 2001 and unpublished results cited in Butenhoff et al, 2004a). In an unpublished study, dietary treatment at the dose level of 300 or 30 mg/kg.bw/day administered for two years slightly increased the hepatocellular tumor incidence in the high-dose male rats only.

The relevance of the tumourigenicity data to humans is uncertain at this time as it was postulated that APFO may affect estradiol levels through binding to and activating the PPAR-α receptor in the liver thus causing Leydig cell hyperplasia and tumour formation by acting as a mitogen and/or by enhancing growth factor secretion (US EPA, 2002).

Immunotoxicity:

Dietary treatment of PFOA at the dose level of 0.02% (corresponding to ca. 40 mg/kg bw/day) for up to 10 days resulted in a significant increase, relative to control, in liver weights but decrease in thymus and spleen weights in male mice. The number of thymocytes expressing both CD4 and CD8 decreased by 95%. For the splenocytes, both T cells (CD3) and B cells (CD19) decreased by 75% and 86%, respectively. The decreased numbers of thymocytes was shown to be caused by inhibition of thymocyte proliferation. The above findings indicated potential immunological toxicity of PFOA in mice.

Epidemiological Studies:

PFOA has been detected in the sera of workers as well as the general population worldwide. Several epidemiological studies on the effects of PFOA in humans have

been conducted on workers at three 3M factories where PFOA is produced and used; the majority of production workers were male. Two mortality studies, a morbidity study, and studies examining effects on the liver, pancreas, endocrine system, and lipid metabolism were conducted. In one study, positive associations were seen with increased PFOA exposure during employment and/or high PFOA serum levels for the following: prostate cancer mortality, estradiol levels, cholesterol and triglyceride levels, and T3 hormone levels in some studies (Gilliand and Mandel, 1993). However, subsequent investigations did not confirm the positive associations (Alexander et al., 2003; Olsen et al., 1998, 2003a,b,c). Negative associations with increased PFOA exposures have been noted for cholecystokinin-33 (CCK) values, and HDL levels (Olsen et al., 2000). Therefore, overall, results of epidemiological studies remain inconclusive.

Health Hazard Summary and Conclusions:

The fluorotelomer-based polymer exhibited low acute oral toxicity in rats, no skin irritation in rabbits, minimal eye irritation in rabbits, weak skin sensitization potency in guinea pigs, moderate repeated dose oral toxicity in rats and low to moderate genotoxicity potential (based on equivocal results in the in vitro chromosomal aberration test and the lack of evidence for delivery of the test substance to the bone marrow at 100 mg/kg bw, the highest dose tested in the in vivo study).

The fluorotelomer-based polymer is expected to eventually degrade and release the corresponding perfluorinated carboxylic acids (PFCAs), of which PFOA and its ammonium salt have been extensively studied. Results of these studies indicate that PFOA and its salts are not genotoxic but are tumourigenic and immunotoxic in rodents, and display moderate reproductive and developmental toxicity in rodents and moderate to high subchronic oral toxicity in rodents and monkeys. The toxicological profile of the similar PFCA degradation products of the fluorotelomer-based polymer is not expected to differ significantly from that of PFOA and its salts. Results of extensive studies indicate that PFOA and its salts are not genotoxic but are tumourigenic and immunotoxic in rodents, and display moderate reproductive and developmental toxicity in rodents and moderate to high subchronic oral toxicity in rodents and monkeys.

Human exposure to PFCAs is expected to increase over time as a result of expanding commercialization and use of their precursors, the perfluorinated polymers and similar substances. As a result, the levels of PFOA and longer chain PFCAs in human blood are expected to increase over time, based on their reported extreme persistence and very slow serum clearance. In fact, it has been reported that serum levels of PFOA in females have increased over the past 25 years (Harada et al., 2004).

Based on information summarized above, there is reason to suspect that the degradation products of the fluorotelomer-based polymer, and in particular the PFCAs, may cause serious health effects in humans.

Reference

New Substances Evaluation Report (New Substances Notifications 13211 and 13395). *Canadian Environmental Protection Act, 1999*. Government of Canada. Available upon request: http://www.ec.gc.ca/subsnouvelles-newsubs/default.asp?lang=En&n=6F22A1D6-1

3.2.3 Description of ecotoxicological properties of the chemical

Fluorotelomer-based polymer:

By definition, the fluorotelomer-based polymer is considered to meet the regulatory criteria for "not low concern" fluorotelomer-based polymers of the *New Substances Notification Regulations* due to the presence of cationic functional groups of concern (FGEW <5,000 Daltons). Available databases do not contain ecotoxicity data on this specific fluorotelomer-based polymer or analogous structures. Cationic polymers are known to have a moderate to high level of toxicity to aquatic biota (algae in particular) depending on the number of cationic groups in the structure.

The notifier provided an acute base set of toxicity data and one chronic test based on testing of the formulated product, which according to the MSDS is a viscous liquid containing the fluorotelomer-based polymer in an aqueous solution at 15% w/w. The tests were conducted according to OECD protocols and were corrected to 100% active ingredient. A mitigation factor of 110 to account for DOC complexation in natural water was applied in accordance with US EPA recommendations for a fluorotelomer-based polymer containing cationic groups at a FGEW of 365 (Boethling and Nabholz 1997). The test data were reviewed and deemed acceptable for use in this assessment.

Based on the data provided by the notifier, the fluorotelomer-based polymer is expected to have a low level of acute and chronic toxicity to pelagic biota. Given the high adsorption potential of the fluorotelomer-based polymer, based on results provided in the biodegradation study, toxic impacts to sediment dwelling organisms may be more pertinent, but are not expected to be significantly higher.

Toxicity of degradation products:

Toxicity data on the intermediate degradation products are lacking. Toxicity data for the PFCA compounds, considered the ultimate degradation products are also lacking with the exception of the C8 carboxylate, PFOA.

The impact from a 35 day exposure of a zooplankton community to PFOA through an indoor microcosm resulted in LOECs between 10 and 70 mg/L for the various species with Daphnia magna reported to be the most sensitive. Over the 35 days, the ecosystem was reported to change from a diverse community dominated by larger species towards a less diverse community dominated by smaller more robust species (Sanderson et al., 2003).

Laboratory animal studies can provide evidence of the effects that may occur in mammalian wildlife following exposure to PFOA. Results of these studies indicate that PFOA and its salts are not genotoxic but are tumourigenic and immunotoxic in rodents, and display moderate reproductive and developmental toxicity in rodents and moderate to high subchronic oral toxicity in rodents and monkeys. The toxicological profile of similar potential degradation products of the fluorotelomer-based polymer (i.e., PFCAs ≥C8) is not expected to differ significantly from that of PFOA and its salts.

Environmental Toxicity Summary:

Available evidence indicates a low acute and chronic toxicity of the fluorotelomer-based polymers. The PNEC of the fluorotelomer-based polymer is based on the reported 96h IC50 for algae (*Selenastrum capricornutum*) of 36.3 mg/L. Given that the mitigation factor of 110 is applied to account for natural conditions, a smaller application factor of 10 is further applied to account for inter species variability. Therefore, the PNEC for the fluorotelomer-based polymer is 3.63 mg/L.

Toxicity data on the degradation products is lacking and toxicity data on PFCA's is restricted to effects from PFOA. Given the high bioaccumulation potential of the longer chain PFCA's and the limited toxicity data of this group, more chronic data are required to adequately assess the long term toxicity of this class of substances. Considering the concerns raised through examination of environmental fate, bioaccumulation, persistence, and increasing presence in biota, a PNEC addressing the long term exposure to the degradation products is not possible, nor deemed necessary, for characterization of risk from exposure to the degradation products. The available toxicity data demonstrates the potential for damage or adverse effects to the environment.

Reference

New Substances Evaluation Report (New Substances Notifications 13211 and 13395). *Canadian Environmental Protection Act, 1999*. Government of Canada. Available upon request: http://www.ec.gc.ca/subsnouvelles-newsubs/default.asp?lang=En&n=6F22A1D6-1

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SECTION 4 DESIGNATED NATIONAL AUTHORITY

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Definitions for the purposes of the Rotterdam Convention according to Article 2:

(a) 'Chemical' means a substance whether by itself or in a mixture or preparation and whether manufactured or obtained from nature, but does not include any living

organism. It consists of the following categories: pesticide (including severely hazardous pesticide formulations) and industrial;

(b) 'Banned chemical' means a chemical all uses of which within one or more categories have been prohibited by final regulatory action, in order to protect human health or the environment. It includes a chemical that has been refused approval for first-time use or has been withdrawn by industry either from the domestic market or from further consideration in the domestic approval process and where there is clear evidence that such action has been taken in order to protect human health or the environment;

(c) 'Severely restricted chemical' means a chemical virtually all use of which within one or more categories has been prohibited by final regulatory action in order to protect human health or the environment, but for which certain specific uses remain allowed. It includes a chemical that has, for virtually all use, been refused for approval or been withdrawn by industry either from the domestic market or from further consideration in the domestic approval process, and where there is clear evidence that such action has been taken in order to protect human health or the environment;

(d) 'Final regulatory action' means an action taken by a Party, that does not require subsequent regulatory action by that Party, the purpose of which is to ban or severely restrict a chemical.