Safety Assessment of Polyfluorinated Polymers as Used in Cosmetics

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All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of polyfluorinated polymers in cosmetic products, and most of these ingredients have the film former function in common. The Panel reviewed relevant data relating to the safety of these ingredients under the intended conditions of use in cosmetic formulations, and concluded that PTFE and Hexafluoropropylene/Tetrafluoroethylene Copolymer are safe in cosmetics in the present practices of use and concentration described in the safety assessment, and that the data are insufficient to determine the safety of the four fluorinated-side-chain polymers and six fluorinated polyethers.

INTRODUCTION

The Panel assessed the safety of the following 12 polyfluorinated polymers in cosmetics:

Fluoropolymers
PTFE
Hexafluoropropylene/Tetrafluoroethylene Copolymer

Fluorinated-Side-Chain Polymers
Acrylates/Perfluorohexylethyl Methacrylate Copolymer
Behenyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer
C6-14 Perfluoroalkylethyl Acrylate/HEMA Copolymer
Stearyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer

Fluorinated Polyethers
Acrylates/Methoxy PEG-23 Methacrylate/Perfluorooctyl Ethyl Acrylate Copolymer
PEG-10 Acrylate/Perfluorohexylethyl Acrylate Copolymer
Polyperfluoroethoxymethoxy Difluoroethyl PEG Diisostearate
Polyperfluoroethoxymethoxy Difluoroethyl PEG Ether
Polyfluoroethoxymethoxy Difluorohydroxyethyl Ether
Polyperfluoroethoxymethoxy Difluoromethyl Ether

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), most of these polyfluorinated polymers have the film former function in common (see Table 1).[1]

These ingredients have been grouped as a family because they share in common a fluorinated organic polymer backbone, wherein at least some of the carbon atoms in that backbone are perfluorinated. The non-fluorinated monomers utilized in the synthesis of the copolymers in this report have also been utilized in the synthesis of ingredients the Panel has previously assessed for safety. The monomers comprising these polyfluorinated polymers that have been evaluated for safety by the CIR Expert Panel are presented in Table 2.

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

CHEMISTRY

Definition and General Characterization

The definitions, structures, and functions in cosmetics of these ingredients are presented in Table 1.[1] These ingredients share in common a fluorinated organic polymer backbone, wherein at least some of the carbons in that backbone are perfluorinated. PTFE is a perfluoronated homopolymer, comprising only carbon and fluorine (Figure 1). Together with Hexafluoropropylene/Tetrafluoroethylene Copolymer, these two ingredients comprise the fluoropolymers sub-group.

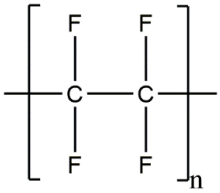


Figure 1. PTFE (Polyfluorotetraethylene)

Certain other polyfluorinated polymer ingredients can be classified as fluorinated-side-chain polymers. These ingredients comprise polyacrylates with polyfluorinated side-chains. For example, Acrylates/Perfluorohexylethyl Methacrylate Copolymer is a copolymer of acrylates and methacrylate, wherein the methacrylic acid residues are esterified with perfluorinated, branched chains (Figure 2).

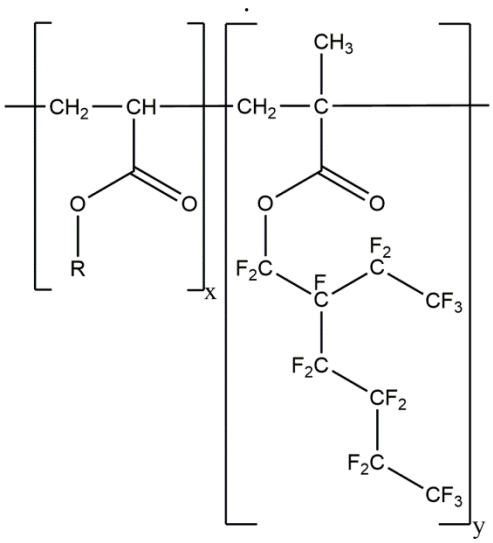


Figure 2. Acrylates/Perfluorohexylethyl Methacrylate Copolymer – wherein R is methyl, ethyl, propyl, or butyl.

The remainder of the polyfluorinated polymers in this report comprise a fluorinated polyethers sub-group. This sub-group of ingredients comprises copolymers ethers and fluorinated monomers. In some cases, Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether for example, these fluorinated polyethers also comprise end-capping units (Figure 3).

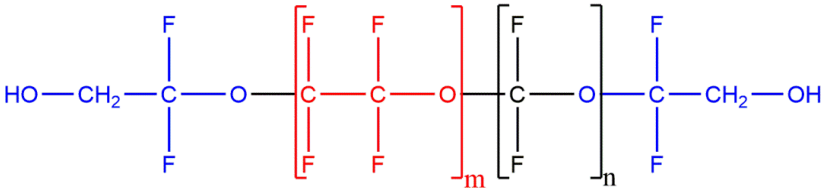


Figure 3. Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether – comprising 2 perfluorinated monomers and end-capping units

As with any polymeric ingredient, the number of monomeric repeat units (and thus polymeric size) and degree of linearity (i.e., branched or straight) have the potential to greatly impact the physical characteristics (e.g., matter phase, hardness, etc.) imbued on the moiety. Accordingly, size, distribution, and connectivity variations, as used in cosmetic ingredients, are important considerations for understanding the nature of these materials.

Chemical and Physical Properties

Polyfluorinated polymers such as PTFE are noted for high thermal stability.[2] PTFE is a white translucent to opaque solid,[3] ranging in molecular weight from 400,000 to 10,000,000 Daltons (Da).[4] The density of PTFE is 2.25 g/cm^3.[5] The melting points of polyfluorinated polymers can vary. For example, Hexafluoropropylene/Tetra-fluoroethylene Copolymer has a melting point of 270°C,[5] and PTFE has a melting point in the 320°C to 330°C range.[5] PTFE decomposes at 315 to 375°C.[6] Properties of polyfluorinated polymers are presented in Table 3.

Method of Manufacture

PTFE

PTFE is prepared by the polymerization of tetrafluoroethylene.[3] Because PTFE is poorly soluble in practically all solvents, the polymerization occurs as an emulsion in water.[7] Alternatively, polymerization may be carried out using a surfactant, such as perfluorooctanoic acid (PFOA). More recent information relating to the manufacture of PTFE is as follows:[8] "The ammonium salts (in some cases also the sodium salts) of long chain perfluoroalkyl carboxylic acids (PFCAs) such as PFOA and PFNA have been applied as processing aids (emulsifiers) at low concentrations around 0.5 wt%) in the polymerization of certain polyfluorinated polymers (i.e., PTFE, FEP, PFA, and PVDF) and fluoroelastomers. After 2006, many fluoropolymer manufacturers in China, Japan, Western Europe and the United States (U.S.) started to replace the salts of long-chain PFCAs with the salts of short-chain PCFAs (such as perfluoro-n-hexanoic acid (PFHxA)) or other nonperfluoroalkyl alternatives (such as polyfluoroalkyl ether carboxylic acids) for fluoropolymer manufacturing."

The method of manufacture of PTFE (from a supplier) is summarized below:[9]

- Virgin grade high molecular weight PTFE is the starting material.
- Molecular weight of starting material needs to be reduced in order for PTFE to be micronized into a fine powder. Electron beam irradiation used to lower molecular weight, typically into the 15,000 to 50,000 daltons range. This process is controlled via melt point reduction (starting around 341ºC and ending around 330ºC).
- Irradiated PTFE is post-baked to remove volatiles (including any trace PFOA to below 25 ppb).
- Irradiated and baked material is jet mill micronized to the particle size specification (mean particle size = 5.58 µm).

Information relating to tetrafluoroethylene monomer content of PTFE that is manufactured according to this method was also provided. Trace tetrafluoroethylene monomer in PTFE is not detected (detection limit: 75 ppb).[9]

Composition

PTFE

PTFE is composed of at least 20,000 C_2F_4 monomer units linked into very long, unbranched chains.[3] According to some of the toxicity data in this report, some of the test articles are PTFE fluorotelomers. The International Union of Pure and Applied Chemistry (IUPAC) Gold Book suggests that such telomers comprise very small polymers with between 2 and 10 repeat units.[10] For PTFE, these numbers of monomers would result in polymers with molecular weights between 238 and 1038 Da.

Impurities

According to a chemical supplier, all commercial grades of PTFE contain some trace level of PFOA and perfluorooctyl sulfonate (PFOS); levels of PFOS are fractionally lower than PFOS.[11] The incidental contentof PFOA and PLFOS is detectable in the ppb range. The supplier also noted that, in 2017, the European Union (EU) published measures to regulate PFOA and its salts and related substances under Annex XVII of Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH). The new law (EU 2017/1000) will be implemented in phases, starting July 4, 2020. Under this new law, trace content of PFOA will be regulated to < 25 ppb, and, trace content of PFOA-related substances, regulated to < 1000 ppb.

USE

Cosmetic

The safety of the polyfluorinated polymers is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[12] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[13]

According to 2018 VCRP data, PTFE is reported to be used in 365 cosmetic products (343 leave-on and 22 rinse-off products).[12] The results of a concentration of use survey conducted in 2017 indicate that PTFE is being used at concentrations up to 13% in leave-on products (mascara) and at concentrations up to 2.4% in rinse-off products (hair bleaches).[13] Further use frequency and concentration of use data are presented in Table 4.

According to VCRP and Council survey data, the remaining 11 polyfluorinated polymers in this safety assessment have no reported uses in cosmetic products in the U.S.

Cosmetic products containing PTFE may be applied to the skin and hair or, incidentally, may come in contact with the eyes (at maximum use concentrations up to 13% for PTFE in mascara) and mucous membranes (at maximum use concentrations up to 0.44% PTFE in other oral hygiene products). Ingredient use in oral hygiene products may result in incidental ingestion. Products containing PTFE may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

PTFE is reported in the VCRP as used in [fragrance] powders (dusting and talcum, excluding aftershave talcum) and in face powders, which may result in incidental inhalation exposure. Also, data from the Council's survey indicate that PTFE is used in face powders at maximum use concentrations ranging from 0.5% to 3%. According to one supplier, micronized PTFE (fine powder; mean diameter = 5.58 µm) is being used in cosmetic products.[9] This mean PTFE particle size diameter (of the raw material ingredient) is within the respirable size range of particles. Respirable fraction is defined as the mass fraction of particles that can reach the alveoli, and the median value of the distribution of particle sizes in this category is 4.25 µm (geometric standard deviation (GSD) = 1.5 µm).[14] It has been shown that 50% of the particles with an aerodynamic diameter of 4 µm will be in the respirable fraction.

The ingredients reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[15]

Non-Cosmetic

Polyfluorinated polymers (e.g., PTFE and Tetrafluoroethylene/Hexafluoropropylene Copolymer) are used in a wide variety of thermal and electrical applications because of their low heats of combustion, low rates of flame spread, high resistance to ignition and inherent chemical resistance.[16]

PTFE

PTFE is ubiquitous in materials that are commonly used in cooking (e.g., coatings for cookware), due to its thermal stability and non-stick properties.[17] PTFE membrane filters have been used in the collection of particulate matter (i.e., nano or ultrafine particulate matter fraction).[18] Diffusion cells that are used in some in vitro percutaneous absorption experiments are made of PTFE.[19] PTFE skin graft chambers have been used to isolate wounds and prevent epidermal heating from the skin edge.[20] Flexible PTFE feeding tubes have been used in oral carcinogenicity studies.[21] Other non-cosmetic uses of PTFE include: hookup and hookup-type wire in electronic equipment; computer wire, electrical tape, electrical components and spaghetti tubing; seals and piston rings, basic shapes, bearings, mechanical tapes, and coated glass fabrics; tubing and sheets for chemical laboratory and process work; lining vessels; in gaskets and pump packings, sometimes mixed with graphite or glass filters; electrical insulator, especially in high frequency applications; filtration fabrics; protective clothing; and as a prosthetic aid.[3]

PTFE is included on the list of resinous and polymeric coatings that FDA has determined may be safely used as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food (21CFR175.300). PTFE is also included on the list of polymers categorized as exemptions from the requirement of a tolerance (i.e., after meeting the criteria specified for defining a low-risk polymer), whereby this categorization relates to use as an inert ingredient in a pesticide chemical formulation (40CFR180.960).

Hexafluoropropylene/Tetrafluoroethylene Copolymer

Hexafluoropropylene/Tetrafluoroethylene Copolymer is included on the list of perfluorocarbon resins that FDA has determined may be safety used as articles or components of articles intended to contact food, subject to the provisions that are stated in the CFR (21CFR177.1550).

TOXICOKINETIC STUDIES

Dermal Penetration

Dermal penetration data on the polyfluorinated polymers reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

Absorption, Distribution, Metabolism, and Excretion

Absorption, distribution, metabolism, and excretion data on the polyfluorinated polymers reviewed in this safety assessment were not found in the published literature, nor were these data provided.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

PTFE

Results relating to the acute dermal toxicity of PTFE are presented in a study evaluating the skin irritation potential of this ingredient.[27] Skin irritation data from this study are summarized later in this report. The test substance (powder, 0.5 g) was applied to abraded and intact skin of the trunk (cm^2 area not stated) of 6 New Zealand White rabbits for 24 h. None of the animals died, and no clinical signs or behavioral alterations were observed during the study.

Oral

PTFE

The acute oral toxicity of 2 anti-cohesive coating materials containing PTFE was evaluated using 4 groups of Kunming mice (10 males and 10 females per group).[28] One of the materials contained 60% PTFE, and the other material contained 68% to 73% PTFE. Both materials were administered by gavage. The two 60% PTFE groups received doses of 12.5×10^3 mg/kg and 25×10^3 mg/kg, respectively. The two 68% to 73% PTFE groups received doses of 2.5×10^3 mg/kg and 5×10^3 mg/kg, respectively. Dosing was followed by a 1-week observation period, and LD_0 (dose at which no animals are expected to die) values were determined. The LD_0 values in mice were determined to be 12.5×10^3 mg/kg for the 60% PTFE material and 2.5×10^3 mg/kg for the 68% to 73% PTFE material.

The acute oral toxicity of 2 anti-cohesive coating materials containing PTFE was evaluated according to the same procedure (stated above) using 4 groups of Wistar rats (10 males and 10 females per group).[28] The two 60% PTFE groups received doses of 6.25×10^3 mg/kg and 18.8×10^3 mg/kg, respectively. The two 68% to 73% PTFE groups received doses of 1.25×10^3 mg/kg and 3.75×10^3 mg/kg, respectively. The LD_0 values in rats were determined to be 6.25×10^3 mg/kg for the 60% PTFE material and 1.25×10^3 mg/kg for the 68% to 73% PTFE material.[28]

A low molecular weight PTFE resin (fluorotelomer, chemical characterization data not included) was administered orally to rats (strain and dosing method not stated) at doses as high as 17 g/kg.[29] None of the animals died, and there were no clinical effects or organ changes that were related to test substance administration.

Short-Term Toxicity Study

Dermal

Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether

Results relating to the short-term dermal toxicity of Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether are presented in a guinea pig maximization test in which the test substance was injected/applied topically to 10 guinea pigs during a 7-day period.[30] Skin sensitization data from this study are summarized later in this report. No mortalities occurred and there were no signs of general toxicity in any of the animals tested.

Inhalation

PTFE

Spray inhalation experiments on a low molecular weight PTFE resin (fluorotelomer, molecular weight range and other chemical characterization data not included) were performed using 4 rats (strain not stated).[29] The rats were exposed for 9 days (3 times per day) to a 20% dispersion of the fluorotelomer in dichloro(fluoro)methyl (CCl_2F)—chlorodifluoro-methyl radical ($CClF_2$) from a pressurized container. After spraying, the jars were sealed and exposure to the dispersion was continued for 15 minutes. A total of 26 exposures were performed. During exposure, uncoordination, labored breathing, and irritation of the nose were observed. It was noted that these signs were primarily due to propellants and the dispersing agent (not stated). Recovery occurred immediately after exposure, and it was noted that there was no evidence of pathology that could have been attributed to exposure.

Subchronic Toxicity Studies

Oral

PTFE

Three types of PTFE resin (chemical characterization data not included, 25% in the diet) were fed to male and female rats (strain and number per group not stated) for 90 days.[29] After feeding with each type of PTFE resin, there were no adverse effects on growth rate or behavior and there was no microscopic evidence of tissue changes. However, a slight shift in the distribution and number of white blood cells was observed. Also, feeding with 1 of the 3 types of resin (unsintered PTFE resin) caused an increase in the size of the liver (relative to body weight). This finding was not accompanied by any histological abnormality.

Chronic Toxicity Studies

Oral

PTFE

The chronic oral toxicity of PTFE was evaluated using 6 Swiss mice.[31] The mice were fed a standard diet supplemented with PTFE (concentration not stated) for 6 months. The animals developed spotty loss of fur, skin lesions, and a 50% loss of weight. A control group (fed standard diet only) was included in the study, but results for this group were not reported.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

PTFE

The teratogenicity of 2 anti-cohesive coating materials containing PTFE (one containing 60% PTFE, and the other containing 68% to 73% PTFE) was evaluated using groups of 10 Wistar rats (5 males and 5 females per group).[28] The positive control, *N*,*N*'-methylene bis-(2-amino-1,3,4-thiadiazole), was administered to a group of 12 rats (6 males and 6 females), and the negative control (soybean oil) was administered to a group of 10 rats (5 males and 5 females). The 60% PTFE material was administered at dose of 6.25×10^3 mg/kg, and the 68% to 73% PTFE material was administered at a dose of 1.25×10^3 mg/kg. The positive and negative controls were administered at doses of 0.5 mg/kg and 5 mg/kg, respectively. All materials were administered once daily on gestation days 7 - 16. The results for both PTFE materials were classified as negative.

GENOTOXICITY STUDIES

In Vitro

PTFE

Two anti-cohesive coating materials containing PTFE (one containing 60% PTFE, and the other containing 68% to 73% PTFE) were negative in the Ames test at doses up to 10,000 µg/plate in *Salmonella typhimurium* TA98, TA100, and TA1535, with and without metabolic activation.[28]

In Vivo

PTFE

The genotoxicity of 2 anti-cohesive coating materials containing PTFE (one containing 60% PTFE, and the other containing 68% to 73% PTFE) was evaluated in the micronucleus test using groups of 10 Kunming mice (5 males and 5 females per group).[28] Cyclophosphamide served as the positive control. Doses were administered by gavage. The 60% PTFE material was administered at a dose of 12.5×10^3 mg/kg, and the 68% to 73% PTFE material was administered at a dose of 2.5×10^3 mg/kg. The positive control was administered at a dose of 60 mg/kg. Each dose was administered twice, separated by a 24-h interval. Results for both PTFE materials were classified as negative.

CARCINOGENICITY STUDIES

Inhalation

Tetrafluoroethylene (PTFE Monomer)

Because tetrafluoroethylene is used primarily in the synthesis of PTFE, it is important to note that the National Toxicology Program (NTP) has evaluated the safety of tetrafluoroethylene in inhalation carcinogenicity studies involving F344/N rats and $B6C3F_1$ mice.[4] Groups of 60 male F344 rats were exposed (inhalation) to 156, 312, or 625 ppm tetrafluoroethylene, and groups of 60 female F344 rats were exposed (in inhalation chamber) to 312, 625, or 1250 ppm tetrafluoroethylene, 5 days per week (6 h per day) for 104 weeks. Groups of 58 male and 58 female $B6C3F_1$ mice were exposed (in inhalation chamber) to 312, 625, or 1250 ppm tetrafluoroethylene 5 days per week (6 h per day) for 95 to 96 weeks. NTP's conclusion is stated as follows: "Under the conditions of these 2-year inhalation studies, there was clear evidence of carcinogenic activity of tetrafluoroethylene in male F344/N rats based on increased incidences of renal tubule neoplasms (mainly adenomas) and hepatocellular neoplasms. There was clear evidence of carcinogenic activity of tetrafluoroethylene in female F344/N rats based on increased incidences of renal tubule neoplasms, liver hemangiosarcomas, hepatocellular neoplasms, and mononuclear cell leukemia. There was clear evidence of carcinogenic activity of tetrafluoroethylene in male and female $B6C3F_1$ mice based on increased incidences of liver hemangiomas and hemangiosarcomas, hepatocellular neoplasms, and histiocytic sarcomas."

The subcutaneous (s.c.) and intraperitoneal (i.p.) carcinogenicity studies on PTFE summarized below are presented in Table 5 (size of implants tested included).

Subcutaneous

PTFE

The following results were reported in carcinogenicity studies in which various forms of PTFE (see Table 5) were implanted s.c. in mice of the following strains: 89 random-bred female Swiss mice (fibrosarcomas: 11 of 89 mice),[32,33] groups of random-bred male and female Swiss mice (fibrosarcomas: 8 of 89 mice; 1 of 61 mice; 23 of 103 mice; 10 of 53 mice; 7 of 54 mice; and 4 of 40 mice),[34,33] 19 male and 27 female inbred C5BL mice (sarcomas: 4 of 20 females and 4 of 15 females that retained implant),[33,35] 40 male and 40 female random-bred, CTM albino mice (sarcomas: 18 of 40 females; 9 of 40 males), [33,36] 38 BALB/c female mice (fibrosarcomas: 17 of 38 mice),[33,37] 38 C3Hf/Dp female mice (fibrosarcomas: 36 of 38 mice), [33,37] and 39 C57BL/He female mice (fibrosarcomas: 12 of 39 mice).[33,37]

When PTFE was implanted s.c. in carcinogenicity studies involving rats, the following results were reported: 15 rats of unknown strain (malignant sarcomas: 4 of 15 rats),[38,33] 65 male and female weanling Wistar rats (sarcomas: 2 of 65 rats),[33,39] 2 groups of Wistar rats, number per group unknown (sarcomas: 8 of 34 rats and 6 of 32 rats that survived minimum latent period),[33,40] 39 male Evans rats (no tumors),[33,41] 40 male Evans rats (no tumors).[33,41]

Intraperitoneal

PTFE

When PTFE (rod or powder form) was implanted i.p. in rats, the results were as follows: 16 weanling Wistar rats (no sarcomas; fibroadenoma: 1 of 16 rats tested with rods) and 17 weanling Wistar rats (sarcomas: 2 of 17 rats; fibroadenoma: 1 of 17 rats tested with powder; fibrosarcomas: 2 of 17 rats tested with powder).[33,42] Rats subjected to the same i.p. implantation surgical procedure (but no material was implanted) served as controls.

OTHER RELEVANT STUDIES

Muscle Necrosis

PTFE

A PTFE patch was implanted (size of implant not stated) in the muscle of rabbits.[43] Medical grade vinyl tubing served as the negative control. At specified time intervals, ranging from 24 h to 12 weeks following implantation, the rabbits were killed. The paravertebral muscles were isolated and dissected to recover the implanted material and adjacent tissue. Each site was examined grossly for signs of tissue reaction and the appropriate score was recorded. The implant and adjacent tissue were removed and prepared for microscopic examination. The initial type of necrosis exhibited by rabbit skeletal muscle in response to the physical injury of implant insertion, and the chemical injury sustained by the toxic qualities of the implant, was coagulative necrosis. Coagulative necrosis was soon followed by liquefactive necrosis. The necrotic debris was removed, partly by phagocytic macrophages and giant cells. Fibrosis immediately adjacent to and completely surrounding the

implant was observed. In addition to regenerating and encapsulating, fatty infiltration was associated with the repair process. PTFE caused an occasional to mild eosinophilic infiltrate at each time interval investigated.

Inflammatory Response

PTFE

Three populations, each consisting of two mongrel dogs, 5 New Zealand White rabbits, and 10 BALB/c mice, were injected with PTFE particulate, defined by the following particle size distribution, in a glycerine carrier: 4% of total particulate = 79.1 ± 38 nm; 24% of total particulate = 6100 ± 1000 nm; 30% of total particulate = 7000 to 25,000 nm; and 42% of total particulate = 485 ± 200 nm. The animals were observed for periods of 1 week, 3 months, 6 months, and 1 year.[44] Mice received 1 s.c. dorsal injection each, rabbits received two subareolar injections each, and dogs received 3 subareolar injections each in addition to 2 periurethral injections. There was no indication that controls were used in the study. Histologic examination of the biopsy sites revealed a persistent chronic inflammatory reaction with progressive growth of the involved tissue volume. In addition to giant cells and macrophages, lymphocytes became apparent at 3 months and comprised up to 40% of the cellular infiltrate by 1 year. Plasma cells were also noted at the 1-year period in the rabbit model.

A material consisting of 72% PTFE and 28% zinc oxide by volume was implanted (size of implant not stated) in the mandibles of 14 guinea pigs.[45] Surgical sites that had no implanted material served as negative controls. Seven animals were killed at intervals of 4 weeks and 12 weeks after surgery (i.e., total of 14 animals killed), and tissue sections were prepared. Mild-to-moderate inflammation was observed at 4 weeks, but the inflammation was predominantly moderate in intensity. In regions where the material appeared to be loosely dispersed or poorly condensed, a round cell infiltrate was present with active phagocytosis of the material by multinucleated giant cells. The inflammatory response at 12 weeks was predominantly mild. The material was surrounded by a moderately thick fibrous capsule with very few inflammatory cells, except for tissue samples in which the material appeared to be poorly condensed. In areas where the material was loosely condensed, active phagocytosis and chronic inflammation persisted and were characterized by the presence of macrophages, plasma cells, and multinucleated giant cells.

DERMAL IRRITATION AND SENSITZATION STUDIES

Irritation

Animal

PTFE

The skin irritation potential of PTFE (powder) was evaluated using 6 New Zealand White rabbits (3 males, 3 females).[27] Two areas on the trunk (cm^2 area not stated) were clipped free of hair and one area of skin was abraded. The test substance (0.5 g) was applied to occlusive patches that were applied to both intact and abraded sites for 24 h. The test sites were examined for reactions at 24 h and 72 h after patch application. Skin reactions were not observed at intact or abraded skin sites in any of the animals tested, and PTFE was classified as a non-irritant.

Human

PTFE

The skin irritation potential of a formula containing 7.6% PTFE was evaluated in a 48-h semi-occlusive patch test involving 26 subjects.[46] The dose per cm^2 was not stated. Skin irritation was not observed (primary irritation index (PII) = 0).

A single-insult (24h), semi-occlusive patch test on an eye shadow containing 12% PTFE was performed using 15 subjects.[47] The location of the patch and dose per cm^2 are not stated in this study. Skin irritation was not observed in any of the subjects tested (PII = 0).

Sensitization

Animal

PTFE

A 20% dispersion of the fluorotelomer in $CCl_2F—CClF_2$ (defined in Short-Term Inhalation toxicity section) was applied to the skin of 10 guinea pigs (strain not stated).[29] The method and duration of test substance application and dose per

cm^2 were not stated. When the CCl2F—CClF2 evaporated, the material hardened and moderate mechanical irritation was observed. There was no evidence of sensitization in any of the animals tested.

Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether

The skin sensitization potential of Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether was evaluated in a maximization test using 15 male Dunkin Hartley albino guinea pigs (10 test animals and 5 controls).[30] On day 0, the 10 test animals received the following 3 pairs of intradermal injections: Freund's complete adjuvant (FCA) emulsion (0.1 ml), Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether (concentration not stated, 0.1 ml), and Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether in FCA (0.1 ml). Similarly, the 5 control animals received the following 3 pairs of intradermal injections: FCA emulsion (0.1 ml), petrolatum oil vehicle (0.1 ml), and vehicle in FCA (0.1 ml). On day 6, the animals were treated topically with 10% sodium lauryl sulfate in petrolatum oil (0.5 ml). On day 7, the same area was treated with applications of undiluted Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether or the vehicle for 48 h using an occlusive patch. The test sites were observed for signs of skin irritation 24 h after patch removal. At challenge on day 20, an occlusive patch containing 75% Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether or the vehicle was applied for 24 h to animals of the 2 groups. Sites were observed for any reactions at 24 h after patch removal and at 24 h later.

The injection of the test substance (in vehicle) caused slight irritation (number of animals not stated). Reactions were not observed after injection of the vehicle alone. At 24 h post-removal of the 48-h occlusive patch, signs of slight irritation (erythema) were observed at sites treated with the test substance. None of the animals had a positive reaction after treatment with the test substance during the challenge phase. Also, no skin reactivity was observed in the negative control group. The authors concluded that Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether did not appear to possess sensitizing capacity in this study.[30]

Human

PTFE

The skin sensitization potential of a formula containing 2.89% PTFE was evaluated in a human repeated insult patch test (HRIPT, occlusive patches) involving 107 subjects. The dose per cm^2 and duration of patch application were not stated. There was no evidence of dermal irritation or sensitization.[46]

The skin sensitization potential of an eye shadow containing 6% PTFE was evaluated in 111 subjects. Approximately 0.01 to 0.04 g of the product was applied to an occlusive patch that was placed on the back (left side; cm^2 area not stated) of each subject.[48] The patch remained in place for 24 h. This procedure was repeated for a total of 9 induction patch applications over an approximately 3-week period. The challenge phase was initiated after a 2-week non-treatment period. An occlusive patch containing 0.2 g of the product was applied to the right side of the back (new site) for 24 h. Reactions were scored at the time of patch removal and at 48 h and 96 h after patch application. Two subjects had a low-level (±; faint minimal erythema) reaction during the induction, and the same was true for 2 other subjects during the challenge phase. It was concluded that the eye shadow did not induce skin sensitization in any of the subjects tested.

An HRIPT on a cosmetic product containing 9% PTFE (undiluted) was performed using 206 subjects.[49] During induction, the subjects received 9 consecutive 24-h patch (2 cm x 2 cm semi-occlusive patch) applications of the product (0.2 ml applied; dose per cm^2 not stated) on the infrascapular area of the back. Induction sties were evaluated at 48-h intervals. Patches applied on Friday were removed on the following Monday, i.e., 72 h after patch application. The challenge phase was initiated (during week 6) after a 10- to 15-day non-treatment period. Challenge patches were applied for 24 h to new test sites, and reactions were scored at 48 h and 72 h post-application. There was no evidence of skin sensitization in any of the subjects tested.

OCULAR IRRITATION/TOXICITY STUDIES

In Vitro

PTFE

The ocular irritation potential of a formula containing 2.89% PTFE was evaluated in the in vitro EpiOcular™ eye irritation test. An ET_{50} of > 24 h (no eye irritation potential) was reported.[46]

Animal

PTFE

To investigate the effects of focal implantation of expanded PTFE episcleral implants (i.e., explants or exoplants) on surrounding ocular tissues, an experimental and histopathological study was performed.[50] PTFE episcleral implants were inserted (for a period of 3–11 months) into the eyes of 27 Fauve de Bourgogne rabbits. A newly formed capsule constantly encased the implants. Only 2 severe complications were observed, i.e., 2 eyes had an endocapsular acute inflammation and could not be included in the study. Finally, 25 eyes were studied histopathologically. Neither intrusion nor extrusion of episcleral implants was observed. The inner surface of the capsule was often covered with numerous giant cells, i.e., a foreign-body granuloma developed against the irregular outline of the episcleral implants. The sclera was both thinned and invaginated under the episcleral implants.

In a study involving 6 New Zealand White rabbits (3 males, 3 females), PTFE (powder, 0.1 g) was instilled into the conjunctival sac of the right eye.[27] The lids were held together for ~ 3 to 4 seconds in order to prevent loss of the test substance. The eyes were rinsed at 24 h post-instillation, and observations were made for up to 72 h post-instillation. No clinical signs or behavioral alterations were observed. Conjunctival redness was observed in 4 rabbits. After 24 h, the reactions had cleared in 3 animals. The reaction had cleared after 48 h in the fourth animal. PTFE was classified as non-irritating to the eye in this study.

The ocular irritation potential of a 20% dispersion of the fluorotelomer in $CCl_2F—CClF_2$ was evaluated using rabbits (number and strain of animals and test protocol not stated).[29] The test substance caused mild conjunctival irritation, which was no longer observed in less than 72 h. Mild corneal injury was observed at 24 h, but not at 48 h. It was noted that the transient reactions observed in this study were no greater than those that were caused by $CCl_2F—CClF_2$ alone.

CLINICAL STUDIES

Other Clinical Reports

PTFE

The cellular tissue response to subcutaneously implanted PTFE (laminated to aluminum oxide; 5 x 10 mm implant blocks) was evaluated using 7 healthy volunteers.[51] PTFE was implanted s.c. in the iliac crest region. After 1 , 2, 4, 12, and 26 weeks, respectively, the implants with surrounding soft tissue were removed for histological and immunohistochemical examination using a panel of antibodies to various leukocyte markers. After 1week, there were signs of edema, slight vessel proliferation, and fibroblast proliferation. At 2 weeks, a foreign body reaction with giant cells and some decomposed microfragmented implant material dominated the peri-implant picture. At 4 weeks, there were only some giant cells seen, the reaction having been mostly lymphohistiocytic. In one specimen, eosinophils were detected. At 12 weeks, the vessel proliferation, fibroblast proliferation, and foreign body reactions were decreasing, but there was still a slight lympho-histiocytic reaction. Thus, PTFE implants primarily induced a slight foreign body reaction, leaving only a slight lympho-histiocytic reaction at 26 weeks. The authors noted that the study provided no indication of a toxic, allergic, or traditional immunological pathogenesis of the tissue reaction being elicited by PTFE.

OCCUPATIONAL EXPOSURE

PTFE

The percentage retention at 24 h of 4µm PTFE particles (aerodynamic diameter of ~6 µm) in the alveoli was studied using a total of 29 healthy male volunteers.[52] Students/workers at a university (11 total) inhaled 4.2 ± 0.7 and 4.3 ± 0.8 µm (mean ± SD) PTFE particles and the workers from a battery factory (18 workers) inhaled 3.9 ± 0.4 µm PTFE particles. Inhalation of the test particles resulted from 10 to 20 maximally deep inhalations. Radioactivity in the lungs was measured after inhalation. The 24-h retention correlated significantly with the first second of the forced expiratory volume (FEV_1) and the forced vital capacity (FVC), and persisted when the subjects were divided into different categories according to profession and smoking habits. It was noted that the results suggest that exposure to particles larger than a few microns in workers with large FEV_1 values may result in a greater risk for systemic toxic effects, when compared to workers with small FEV_1 values.

Clinical phenomena in employees exposed to fumes from the processing of PTFE have been reported.[53] After exposure to the fumes, there is a latent period of a few hours and then a feeling of general malaise, aching muscles, a sense of oppression behind the mid-chest, a dry throat, and a cough followed, by shivering and profuse sweating. The symptoms abate after 24 hours, with no after-effects. Seven cases were described, which included the 4 employees regularly working in the

PTFE section of a fabrication works. Two cases were seen during the acute phase of the illness; x-ray examination of the chest revealed no abnormalities. One case had marked conjunctival congestion. Two employees working on a "dispersion process" (process similar to paint spraying, using PTFE dispersed in 10% chromic acid) complained of skin irritation.

An investigation concerning human exposure to PTFE took place at a fabricating plant that employed 130 persons.[54] The length of employment of the workers was defined as follows: < 1 year, 1 to < 5 years, 5 to < 10 years, and ≥ 10 years. Air levels of PTFE ranging from 0 to 5.48 mg/m^3 were found. Urinary fluoride levels were investigated as an index of PTFE exposure, because carbonyl fluoride, a pyrolysis product of PTFE, is metabolized and excreted as inorganic fluoride ion. Spot urine samples and occupational histories relating to polymer fume fever were obtained from 77 workers. All urine values were below the level at which systemic effects are reported to occur. Analyses of the results (analysis of variance method) demonstrated that the mean urinary fluoride level among workers who had one or more years of exposure to PFTE (workers also had experienced 1or more reported episodes of polymer fume fever) was significantly higher ($P < 0.01$) than that among employees with less than one year or more of exposure and no history of polymer fume fever. Additional exposure beyond one year and additional polymer fume fever episodes did not result in further elevation of urine fluoride levels.

RISK ASSESSMENT

The U.S. Environmental Protection Agency (EPA) has not, to date, promulgated an enforceable drinking water standard for PFOA/PFOS under the Safe Drinking Water Act. Because of PFOA's and PFOS's extreme persistence in the environment and their toxicity, mobility, and bioaccumulation potential, these pose potential adverse effects on human health and the environment. To provide Americans, including the most sensitive populations, with a margin of protection from a lifetime of exposure to PFOA and PFOS from drinking water, EPA's Office of Water established health advisory levels at 70 parts per trillion (equal to 0.07 ppb) (81 FR 33250; May 25, 2016).[22]

Due to the adverse health effects of PFOA and PFOS, the CIR Expert Panel considered the risk from incidental ingestion of PTFE-containing cosmetic formulations. According to the Council survey, PTFE is used in oral hygiene products at a maximum reported use concentration of 0.44%.[13] Because the types of products within the "Other Oral Hygiene Products" category were not specified in the survey, and could include mouthwash, toothpaste, teeth whitening products, etc,[23] exposure from a mouthwash was used as a worst-case scenario for the estimation of oral PTFE exposure. For the purpose of this risk assessment, it is assumed that an adult uses 30 ml of mouthwash 3 times daily. (According to one study, 15 ml is perceived as the most comfortable volume.[24]) Additionally, in an abundance of caution, this scenario includes the assumption that all of the mouthwash is incidentally swallowed. (Although, it is unlikely that an adult will swallow all of the mouthwash).

- The total volume of mouthwash incidentally ingested daily = 30 mL × 3 = 90 mL = 0.09 L.
- Exposure dose of PFOA = 25 ppb highest trace content[9] x 0.44% (maximum use concentration of PTFE in oral hygiene products) = 0.11 ppb = 0.11 µg/L.
- Therefore, the total dose of PFOA exposure = 0.11 µg/L × 0.09 L = **0.0099 µg per day**.

Comparatively, the maximum dose suggested by EPA's drinking water limitation can be calculated as follows.

- EPA established a health advisory level of 70 ppt (0.07 ppb) for PFOA and PFOS (combined) in drinking water. This level was based on a lifetime of exposure to total perfluorinated compounds.[25]
- In setting this advisory level, EPA assumed a drinking water ingestion rate of 2 L/day for adults.[26]
- Therefore, based on EPA's health advisory, the maximum dose of PFOA exposure via drinking water should not exceed = 0.07 µg/L × 2 L = **0.14 µg per day**.

Accordingly, a very conservative, worst-case scenario of cosmetic usage of a mouthwash would result in a daily incidental ingestion dose of PFOA equal to 0.0099 µg/day, which is more than tenfold lower than the EPA's advisory level for drinking water (0.14 µg/day).

SUMMARY

The Panel assessed the safety of 12 polyfluorinated polymers as used in cosmetics. According to the *Dictionary*, these polyfluorinated polymers are reported to have the following functions in cosmetics: bulking agents, slip modifiers, film formers, viscosity increasing agents, dispersing agents, skin conditioning agents, skin protectants, hair conditioning agents, and solvents. Most of the ingredients have the film former function in common.

According to 2018 VCRP data, PTFE is reported to be used in 365 cosmetic products (343 leave-on and 22 rinse-off products). The results of a concentration of use survey conducted by the Council in 2017 indicate that PTFE is being used at concentrations up to 13% in leave-on products (mascara), which is the greatest use concentration that is being reported for PTFE, and at concentrations up to 2.4% in rinse-off products (hair bleaches). Use of the remaining 11 polyfluorinated polymers in cosmetics is not reported in VCRP or Council survey data.

A PTFE production method was provided by a supplier of this material. Using electron beam irradiation, the molecular weight of virgin grade, high molecular weight PTFE (as supplied) is reduced to a range of 15,000 to 50,000 daltons. The irradiated PTFE is then post-baked to remove volatiles (including any trace PFOA to < 25 ppb) and micronized into a fine powder (mean diameter = 5.58 µ). Trace tetrafluoroethylene monomer in PTFE is not detected (75 ppb detection limit). According to another supplier, all commercial grades of PTFE contain some trace level of PFOA (and fractionally lower levels of PFOS); this incidental content is detectable (if present) in the ppb range.

PTFE (powder, 0.5 g) was applied to abraded and intact skin of the trunk of 6 New Zealand White rabbits for 24 h. None of the animals died, and no clinical signs or behavioral alterations were observed.

A low molecular weight PTFE resin (fluorotelomer, chemical characterization data not included) was administered orally to rats at doses as high as 17 g/kg in an acute oral toxicity study. None of the animals died, and there were no test substance-related clinical effects or organ changes. In other acute toxicity tests, oral LD_0 values were determined to be 12.5 x 10^3 mg/kg for an anti-cohesive coating material containing 60% PTFE and 2.5 x 10^3 mg/kg for an anti-cohesive coating material containing 68% to 73% PTFE) in Kunming mice. Oral LD_0 values were determined to be 6.25 x 10^3 mg/kg (for 60% PTFE material) and 1.25 x 10^3 mg/kg (for 68% to 73% PTFE material) in Wistar rats.

Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether was injected/applied topically to 10 guinea pigs during a 7-day period. No mortalities occurred, and there were no signs of general toxicity.

In spray inhalation experiments, 4 rats were exposed for 9 days (3 times per day) to a 20% dispersion of a low molecular weight PTFE resin in dichloro(fluoro)methyl (CCl_2F)—chlorodifluoromethyl radical ($CClF_2$). Uncoordination, labored breathing, and irritation of the nose were observed, but there was no evidence of exposure-related pathology. It was noted that these signs were primarily due to propellants and the dispersing agent (not stated).

Three types of PTFE resin were fed to rats (25% in the diet) for 90 days. There were no adverse effects on growth rate or behavior, and there was no microscopic evidence of tissue changes. Feeding with 1 of the 3 types of resin (unsintered PTFE resin) caused an increase in the relative size of the liver.

No toxic effects or abnormalities were observed during macroscopic or microscopic examination of male and female weanling rats (number and strain not stated) fed diets containing finely ground 25% PTFE resin for 90 days. In a chronic oral toxicity study involving 6 Swiss mice fed a standard diet supplemented with PTFE (concentration not stated) for 6 months, growth was normal, but the animals developed spotty loss of fur, skin lesions, and a 50% loss of weight.

Two anti-cohesive coating materials containing PTFE (60% PTFE and 68% to 73% PTFE) were not teratogenic in Wistar rats. The materials were administered once daily on gestation days 7 - 16.

Results for the two anti-cohesive coating materials were negative in the Ames test at doses up to 10,000 µg/plate in the *S. typhimurium* TA98, TA100, and TA1535, with and without metabolic activation. The two materials were also negative for genotoxicity in the micronucleus test.

When PTFE was implanted s.c. or i.p. in rats of different strains, tumor formation around the implantation site was observed. The same was true for PTFE implanted s.c. in mice of different strains. The tetrafluoroethylene monomer, used in the synthesis of PTFE, was found to be carcinogenic in mice and rats in an NTP inhalation carcinogenicity study.

In a study in which PTFE particulate in a glycerine carrier was injected into 2 mongrel dogs, 5 New Zealand White rabbits, and 10 BALB/c mice, histologic examination of the biopsy sites revealed a persistent chronic inflammatory reaction. Mild to moderate inflammation was observed in a group of 13 guinea pigs after implantation of a material consisting of 72% PTFE and 28% zinc oxide.

After an occlusive patch containing PTFE powder (0.5 g) was applied to abraded and intact skin of 6 rabbits for 24 h, skin irritation was not observed. A 20% dispersion of a low molecular weight PTFE resin in dichloro(fluoro)methyl (CCl_2F) — chlorodifluoromethyl radical ($CClF_2$) was applied to the skin of 10 guinea pigs. There was evidence of what was described as mechanical irritation, but no evidence of sensitization. The skin sensitization potential of Polyperfluoroethoxy-

methoxy Difluorohydroxyethyl Ether in 10 guinea pigs was evaluated using the maximization test. Slight skin irritation, but no sensitization reaction, was observed.

A formula containing 7.6% PTFE was classified as non-irritating to the skin in a 48-h patch test involving 26 subjects. An eye shadow containing 12% PTFE was not irritating to the skin of 15 subjects in a 24-h patch test.

In an HRIPT involving 107 subjects, a formula containing 2.89% PTFE did not cause dermal irritation or sensitization. An eye shadow containing 6% PTFE did not induce skin sensitization in an HRIPT involving 111 subjects. There also was no evidence of skin sensitization in the 206 subjects patch tested with 9% PTFE. A foreign-body reaction (slight lymphohistiocytic reaction) was observed in 7 healthy volunteers implanted s.c. with PTFE.

A formula containing 2.89% PTFE was classified as having no ocular irritation potential in the in vitro EpiOcular™ eye irritation test. PTFE powder (0.1 g) was classified as non-irritating to the eyes of 6 rabbits. The eyes were rinsed after instillation. Also, in rabbits, a 20% dispersion of a low molecular weight PTFE resin in dichloro(fluoro)methyl (CCl_2F) — chlorodifluoromethyl radical ($CClF_2$) caused transient mild conjunctival irritation and corneal injury. The reactions observed were no greater than those that were caused by CCl_2F—$CClF_2$ alone.

DISCUSSION

The Panel noted that the EPA has established a health advisory level of 70 ppt (0.07 ppb) for PFOA and PFOS (combined) in drinking water to provide Americans, including the most sensitive populations, with a margin of protection from a lifetime of exposure to PFOA and PFOS. Accordingly, it was determined that a very conservative, worst-case scenario of cosmetic usage of a mouthwash would result in a daily incidental ingestion dose of PFOA equal to 0.0099 µg/day, which is more than ten-fold lower than the EPA's advisory level for drinking water of 0.14 µg/day (dose based on the advisory level and 2L/day consumption).

The Panel discussed the issue of incidental inhalation exposure from powders. PTFE is reported in the VCRP data as used in [fragrance] powders (dusting and talcum, excluding aftershave talcum) and in face powders, which may result in incidental inhalation exposure. Also, the Council's survey results indicate that PTFE is used in face powders at maximum use concentrations ranging from 0.5% to 3%. The Panel noted that, according to one supplier, a raw material micronized PTFE ingredient (fine powder; mean diameter = 5.58 µm) is being used in final cosmetic formulations, and that this mean PTFE particle size diameter, before formulation, appears to be within the range of respirable particles. Respirable fraction is defined as the mass fraction of particles that can reach the alveoli, and the median value of the distribution of particle sizes in this category is 4.25 µm (geometric standard deviation (GSD) = 1.5 µm). However, the Panel's concern over potential PTFE-induced inhalation toxicity was mitigated after results from a short-term inhalation toxicity study (4 rats; twenty-six 15-minute exposures total) on a low molecular weight PTFE resin were reviewed. There was no evidence of pathology that could have been attributed to PTFE resin exposure in this study.

The Panel noted that this safety assessment contains data from several subcutaneous implantation carcinogenicity studies on PTFE in various forms (e.g., disks, films, surgical mesh), the results of which indicated the formation of fibrosarcomas, fibroadenomas, and sarcomas (some of which were malignant) in mice/rats. However, taking into consideration the various types of cosmetic products in which PTFE is being used, the Panel determined that these studies are not relevant to determining safety for cosmetic use. The Panel also reviewed data from an NTP inhalation carcinogenicity study indicating that the tetrafluoroethylene monomer was carcinogenic in rats and mice. However, the Panel noted that, according to the production method that was received from one supplier of PTFE, residual tetrafluoroethylene monomer in PTFE is not detected (detection limit: 75 ppb).

Finally, the Panel determined that additional data are needed for completion of the safety assessment of only the fluorinated side-chain polymers and fluorinated polyethers that are being reviewed. None of these ten ingredients is reported to be in use. The complete list of data needs includes:

- Method of manufacture and impurities data
- Skin sensitization data at the highest maximum use concentration

The need for skin sensitization at the highest maximum use concentration of PTFE (13%) was previously requested by the Panel. In response to that request, a negative HRIPT on a lower concentration of PTFE, 9%, was received. The Panel agreed that these data at a lower concentration of PTFE are sufficient for determining that PTFE is not a skin sensitizer at use concentrations in cosmetics, and that the same would be true if Hexafluoropropylene/Tetrafluoroethylene Copolymer was used in cosmetic products.

CONCLUSION

The CIR Expert Panel concluded that the following two fluoropolymers are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Fluoropolymers

PTFE
Hexafluoropropylene/Tetrafluoroethylene Copolymer*

**Not reported to be in current use. If this ingredient not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to PTFE.*

The Panel also concluded that the data are insufficient to determine the safety of the following 10 ingredients:

Fluorinated-Side-Chain Polymers

Acrylates/Perfluorohexylethyl Methacrylate Copolymer
Behenyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer
C6-14 Perfluoroalkylethyl Acrylate/HEMA Copolymer
Stearyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer

Fluorinated Polyethers

Acrylates/Methoxy PEG-23 Methacrylate/Perfluorooctyl Ethyl Acrylate Copolymer
PEG-10 Acrylate/Perfluorohexylethyl Acrylate Copolymer
Polyperfluoroethoxymethoxy Difluoroethyl PEG Diisostearate
Polyperfluoroethoxymethoxy Difluoroethyl PEG Ether
Polyfluoroethoxymethoxy Difluorohydroxyethyl Ether
Polyperfluoroethoxymethoxy Difluoromethyl Ether

TABLES

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[1; *CIR Staff*]

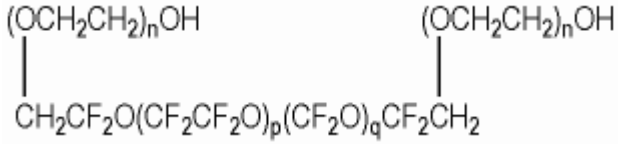
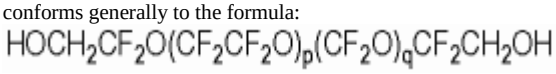
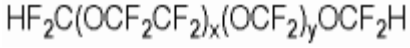
Ingredient CAS No.	Definition & Structures	Function(s)
Fluoropolymers		
PTFE 9002-84-0	PTFE is the polymer of tetrafluoroethylene that conforms to the formula: 	Bulking Agents; Slip Modifiers
Hexafluoropropylene/Tetrafluoroethylene Copolymer 25067-11-2	Hexafluoropropylene/Tetrafluoroethylene Copolymer is a copolymer of hexafluoropropylene and tetrafluoroethylene monomers.	Film Formers; Skin-Conditioning Agents - Emollient; Slip Modifiers
Fluorinated-Side-Chain Polymers		
Acrylates/Perfluorohexylethyl Methacrylate Copolymer 1557087-30-5	Acrylates/Perfluorohexylethyl Methacrylate Copolymer is a copolymer of perfluorohexylethyl methacrylate, and one or more monomers consisting of acrylic acid, methacrylic acid, or one of their simple esters.	Film Formers
Behenyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer	Behenyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer is a copolymer of behenyl methacrylate and perfluorooctylethyl methacrylate monomers.	Film Formers; Viscosity Increasing Agents – Nonaqueous
C6-14 Perfluoroalkylethyl Acrylate/HEMA Copolymer	C6-14 Perfluoroalkylethyl Acrylate/HEMA Copolymer is a copolymer of 2-(perfluoro(C6-14 alkyl)) ethyl acrylate and 2-hydroxyethyl methacrylate monomers.	Dispersing Agents - Nonsurfactant; Film Formers; Viscosity Increasing Agents – Nonaqueous
Stearyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer	Stearyl Methacrylate/Perfluorooctylethyl Methacrylate Copolymer is a copolymer of stearyl methacrylate and perfluorooctylethyl methacrylate monomers.	Film Formers; Viscosity Increasing Agents – Nonaqueous
Fluorinated Polyethers		
Acrylates/Methoxy PEG-23 Methacrylate/Perfluorooctyl Ethyl Acrylate Copolymer	Acrylates/Methoxy PEG-23 Methacrylate/Perfluorooctyl Ethyl Acrylate Copolymer is a copolymer of methoxy PEG-23 methacrylate, perfluorooctyl ethyl acrylate, and one or more monomers of acrylic acid, methacrylic acid or one of their simple esters.	Film Formers
PEG-10 Acrylate/Perfluorohexylethyl Acrylate Copolymer	PEG-10 Acrylate/Perfluorohexylethyl Acrylate Copolymer is a copolymer of PEG-10 acrylate and perfluorohexylethyl acrylate monomers.	Film Formers
Polyperfluoroethoxymethoxy Difluoroethyl PEG Diisostearate	Polyperfluoroethoxymethoxy Difluoroethyl PEG Diisostearate is the diester of isostearic acid and Polyperfluoroethoxymethoxy Difluoroethyl PEG Ether.	Skin Protectants; Skin-Conditioning Agents - Emollient; Slip Modifiers; Viscosity Increasing Agents – Nonaqueous
Polyperfluoroethoxymethoxy Difluoroethyl PEG Ether 162492-15-1	Polyperfluoroethoxymethoxy Difluoroethyl PEG Ether is the polymer that conforms generally to the formula:  where n has an average value of 1 and p/q has an average value of 1.	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous; Skin-Conditioning Agents – Occlusive
Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether 88645-29-8	Polyperfluoroethoxymethoxy Difluorohydroxyethyl Ether is the polymer that conforms generally to the formula:  where p/q has an average value of 1.	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Polyperfluoroethoxymethoxy Difluoromethyl Ether 161075-02-1	Polyperfluoroethoxymethoxy Difluoromethyl Ether is the polymer that conforms generally to the formula: 	Solvents

Table 2. Monomer Components of Polyfluorinated Polymers

Monomer	CIR Review Status
Acrylic Acid	Not Reviewed
Methacrylic Acid	Published Final Report – Conclusion: Safe as used as a nail primer by trained professionals, but there are insufficient data for retail use by consumers.[55]
Butyl Methacrylate	Published Final Report – Conclusion: Safe as used in nail enhancement products when skin contact is avoided. Products containing this ingredient should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates.[56]
Methyl Methacrylate	Scientific Literature Review issued on 1-13-2003 – Determined not to be an ingredient; report terminated (although data are available).[57]
Ethoxyethyl Methacrylate	Published Final Report – Conclusion: Safe as used in nail enhancement products when skin contact is avoided. Products containing this ingredient should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates.[56]
Propyl Methacrylate	Not Reviewed
Ethyl Acrylate	Not Reviewed
Butyl Acrylate	Not Reviewed
sec-Butyl Methacrylate	Not Reviewed
t-Butyl Methacrylate	Published Final Report – Conclusion: Safe as used in nail enhancement products when skin contact is avoided. Products containing this ingredient should be accompanied with directions to avoid skin contact, because of the sensitizing potential of methacrylates.[56]
Stearyl Methacrylate	Not Reviewed

Table 3. Chemical and Physical Properties of Polyfluorinated Polymers

Property	Value	Reference
Fluoropolymers		
PTFE		
Molecular weight (Daltons)	400,000 to 10,000,000	4
Physical form and/or color	White translucent to opaque solid	3
	PTFE is available in the following 3 forms: (1) granular for molded parts and for extruding thick-walled tubing and rods; (2) coagulated dispersions (also referred to as fine powders), for extruding thin sections; and (3) aqueous dispersions, for coating, impregnation and preparation of fibers and films. Filled polymers are also available; these are generally made by mixing fillers such as glass fiber, graphite, molybdenum disulfide, metal oxides or ceramics and finely-divided granular PTFE. Reprocessed scrap and off-grade material is also used.	4
Density (g/cm^3)	2.25	5
Solubility	No substance that will dissolve the polymer has been found	4
Melting point (°C)	320-330	5
Decomposes (°C)	315 to 375 and up to 500.	6,58
	When heated, depending on the temperature of thermal decomposition, a variety of oxidized products containing fluorine, carbon, and oxygen may be released. At temperatures ranging from 315 to 375 and up to 500, PTFE decomposition products are primarily the monomer tetrafluoroethylene, perfluoroisopropylene, and other C4-C5 perfluoro-compounds, and an unidentified waxy fume.	
	The burning of PTFE produced a significant amount of carbon dioxide (~6000 ppm), a small amount of carbon monoxide (~60 ppm), and some carbon tetrafluoride (amount not stated). Carbonyl fluoride was not detected in the combustion product gas. However, it was suspected that carbonyl fluoride may have been decomposed to form carbon dioxide and carbon tetrafluoride during the thermal equilibrium of the combustion product gas.	
Hexafluoropropylene/Tetrafluoroethylene Copolymer		
Melting Point (°C)	270	5

Table 4. Frequency and Concentration of Use According to Duration and Type of Exposure.[12,13]

	PTFE		
	# of Uses	Conc. (%)	
Totals/Conc. Range	365	0.11-13	
Duration of Use			
Leave-On	343	0.11-13	
Rinse off	22	0.15-2.4	
Diluted for (bath) Use	NR	NR	
Exposure Type			
Eye Area	229	0.11-13	
Incidental Ingestion	4	0.44	
Incidental Inhalation- Sprays	15[a]	NR	
Incidental Inhalation- Powders	31	0.6-3	
Dermal Contact	325	0.11-12	
Deodorant (underarm)	NR	NR	
Hair - Non-Coloring	NR	NR	
Hair-Coloring	NR	2.4	
Nail	NR	NR	
Mucous Membrane	4	0.44	
Baby Products	NR	NR	

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.

[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 5. Carcinogenicity of Implanted PTFE

Test Substance	Animals Tested	Test Protocol	Results
Subcutaneous Implantation			
PTFE (square sheet, 12 x 12 x 1.2 mm)	89 random-bred female Swiss mice	Implanted subcutaneously (s.c.) in left flank	First local tumor developed 25 weeks after implantation. Total of 11 (12.5%) fibrosarcomas found after average latent period of 54.5 weeks. IARC working group noted that because the implant was not retained in 9 mice and 70 mice remained alive at appearance of first tumor, the effective tumor incidence should be ~ 16%.[32,33]
PTFE	Random-bred Swiss mice: 89 females and 61 males (tested with 12 x 12 x 1.2 mm square PTFE implant); 103 females (tested with 15 mm diameter PTFE disk); 53 females (tested with PTFE fragment corresponding to 1 disk [size not specified]); and 54 females and 50 males (tested with 20 mm diameter PTFE disk)	Implanted s.c.	Tumors (all fibroadenomas) developed around the implant in all groups of mice, and incidences were as follows: 8 of 89 (10%), and 1 of 61(2%); 23 of 103 (22.3%; 10 of 53 (21.2%); 7 of 54 (15.2%); and 4 of 50 (8%). No similar tumors were observed in untreated mice (200 females, 100 males). Furthermore, of 50 female mice implanted with 12 x12 x 1.2 mm square glass coverslips, 6 developed sarcomas (13.6% incidence); of 48 females implanted with fragments of glass corresponding to 1 square, 2 developed sarcomas (4.3% incidence). The average latent period for gross palpable tumors was 55 weeks. Survival rates and when experiment was terminated not reported.[34,33]
PTFE (15 x 1.2 mm disk)	Inbred C5BL mice (27 females, 19 males)	Implanted s.c. Mice observed for 90 weeks	4 local sarcomas (20%) developed in 20 females that retained the implant and were considered to be at risk at weeks 39, 47, 52, and 58. 4 local sarcomas in 15 males considered to be at risk (26%) at weeks 49, 51, 60, and 91. The tumors always developed around the disks. In a control group of 30 male and 33 female non-implanted mice, observed for 100 weeks, no sarcomas were observed; spontaneous tumors developed in 3 females and 2 males. [33,35]
PTFE (15 x 1.2 mm disks)	Random-bred CTM albino mice (40 males, 40 females)	Implanted s.c. into right flank. Mice observed for lifespan	Sarcomas (around disks) in 18 females and 9 males. Total incidence of 38% of the 69 mice still alive at the time of appearance of first tumor. No fibrosarcomas in 99 male and 98 female control mice of same strain observed for lifespan.[33,36]

Table 5. Carcinogenicity of Implanted PTFE

Test Substance	Animals Tested	Test Protocol	Results
PTFE (15 x 1.2 mm disks)	BALB/c mice (38 females); C3Hf/Dp mice (38 females); and C57BL/He mice (39 females)	Implanted s.c. in dorsal area. Surviving mice killed at 120 weeks of age.	Fibrosarcomas (around disks) in 17 of 38 (44%) BALB/c mice, 36 of 38 (94%) C3Hf/Dp mice, and 12 of 39 (30%) C57BL/He mice; mean latent periods of 78, 61, and 82 weeks, respectively. Of the 56 tumors examined histologically, 2 were rhabdomyosarcomas and the remainder were fibrosarcomas. [33,37]
PTFE films	15 rats (strain not stated)	Implanted s.c. in 2-year study.	Malignant sarcomas in 4 of 15 rats. All 15 rats survived the study.[38,33]
PTFE implants (4 x 5 0.16 mm)	65 weanling Wistar rats (males and females)	Implanted s.c. in abdominal wall. All rats killed within 800 days	2 sarcomas induced. 45 rats alive at time of appearance of first tumor (at day 659). No tumors in in 20 control animals that received glass implants and survived for 300 days.[33,39]
PTFE disks (plain and perforated; 15 x 0.02 mm)	Wistar rats (2 groups)	Implanted s.c. in abdominal wall	34 rats implanted with plain disks and 32 rats implanted with perforated disks survived the minimum latent period. 8 of 34 rats (23.5%) and 6 of 32 rats (18.7%) had sarcomas. The implantation of surgical cotton and cotton linters (fibers from which cellophane was made) did not result in tumor formation.[33,40]
PTFE mesh surgical outflow patches (20 x 20 mm squares) or shredded material	39 male Evans rats (tested with PTFE squares); 40 rats (tested with shredded material); 41 non-implanted control rats	Implanted s.c. Experiment terminated 19 months after implantation	24 of 39 rats and 23 of 40 rats were alive when experiment was terminated. 28 of 41 controls also survived. No local tumors observed in study.[33,41]
Intraperitoneal Implantation			
PTFE rods (10 x 2 x 2 mm) or powder	16 weanling Wistar rats (tested with PTFE rods); 17 rats (tested with PTFE powder); 25 untreated controls	Implanted intraperitoneally (i.p.). Surviving animals killed 27 months after implantation	13 of 16 and 10 of 17 rats were alive after 1 year. No sarcomas in rats implanted with PTFE rods. 2 sarcomas became palpable at 354 and 476 days after implantation of PTFE powder. Extraperitoneal tumors observed after PTFE rod implantation (1 fibroadenoma in inguinal region) and after PTFE powder implantation (1 fibrosarcoma in upper leg, 1 fibrosarcoma in shoulder, and 1 inguinal fibroadenoma. In control group, 1 adenoma of testis and possible carcinoma in inguinal region observed.[33,42]

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