The Director General

EXTRACT of OPINION of 22 April 2013 of the French Agency for Food, Environmental and Occupational Health & Safety

on the application for authorisation to use 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid (CAS No. 27619-97-2) and its potassium salt (CAS No. 59587-38-1) in the manufacture of organic materials intended to come into contact with drinking water

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.

On 4 December 2012 the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) received a formal request from the French Directorate General for Health (DGS) to conduct an expert appraisal in response to the application for authorisation to use 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid (CAS No. 27619-97-2) and its potassium salt (CAS No. 59587-38-1) in the manufacture of organic materials intended to come into contact with drinking water (DW).

1. BACKGROUND AND PURPOSE OF THE REQUEST

The marketing of materials and articles intended to come into contact with DW, and their use in facilities for the production, treatment and distribution of water, are subject to the regulatory provisions of Articles R. 1321-48 and 49 of the French Public Health Code (CSP).

The Ministerial Order of 29 May 1997, as amended, specifies the conditions to be met by materials and articles used in permanent facilities for the production, treatment and distribution of DW. In particular, it states that organic materials can be used in contact with DW provided that they are made from chemical constituents authorised under the regulations on materials and articles that can be placed in contact with foodstuffs, as well as those listed in Annex III of the Order. The authorised constituents appear on lists known as “positive lists of substances”.

The aim of this formal request was to assess the inclusion of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid (CAS No. 27619-97-2) and its potassium salt (CAS No.

59587-38-1) on a positive list of substances that can be used in the manufacture of organic materials coming into contact with DW (PDWs).

Chapter C of the DGS's Practical Guide (1999) on the constitution of dossiers relating to the health compliance of materials placed in contact with DW specifies which documents must be included in the dossier when applying to add a new substance to one of the positive lists annexed to the Order of 29 May 1997, as amended.

In addition, as part of the efforts to harmonise their procedures for assessing the safety of PDWs, four Member States of the European Union (known as the "4MS"[1]) agreed to converge their materials approval systems and to adopt common or directly comparable practices. The Report of December 2011 entitled "Positive Lists for Organic Materials" by the 4MS specifies the information required and describes the assessment procedure for adding a new authorised substance to the common positive list (4MS, 2011). This procedure is based on the "Note for Guidance for Food Contact Materials" issued by the European Food Safety Authority (EFSA, 2008).

Moreover, Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food, specifies that:

- "*Substances such as acids, alcohols and phenols can also occur in the form of salts. As the salts usually are transformed in the stomach to acid, alcohol or phenol the use of salts with cations that have undergone a safety evaluation should in principle be authorised together with the acid, alcohol or phenol. In certain cases, where the safety assessment indicates concerns on the use of the free acids, only the salts should be authorised by indicating in the list the name as '… acid(s), salts'*";
- *"The following substances not included in the Union list are authorised subject to the rules set out in Articles 8, 9, 10, 11 and 12: salts (including double salts and acid salts) of aluminium, ammonium, barium, calcium, cobalt, copper, iron, lithium, magnesium, manganese, potassium, sodium, and zinc of authorised acids, phenols or alcohols."*

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in expertise activities: General requirements for an expertise activity (May 2003)".

The collective expert appraisal was conducted by the Working Group on Assessing the safety of materials and articles used in permanent facilities for the production, treatment and distribution of DW (PDWs WG), on the basis of a report on the applicant's technical dossier prepared by four experts from this same WG and one expert from the Expert Committee on Assessment of physico-chemical risks in food (ERCA CES) for the toxicological part of the dossier.

The assessment was carried out according to the 4MS common approach (4MS, 2011).

The analysis conducted and the conclusions reached by the PDWs WG were presented to the Working Group on Assessment of substances and processes subject to authorisation in human food (ESPA WG) and adopted by the Expert Committee (CES) on Water on 2 April 2013.

[1] *France, Germany, United Kingdom and the Netherlands*

3. ANALYSIS AND CONCLUSIONS OF THE CES ON WATER

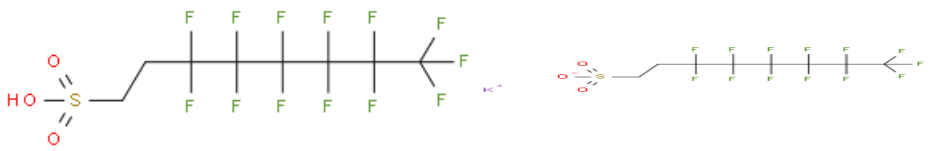
The technical dossier received from the applicant contained all the information necessary for the assessment (see Section 2.4 of the 4MS Common Approach, EFSA's "Note for Guidance" and Chapter C of the DGS Practical Guide of March 1999).

3.1. Analysis of documents received

3.1.1. Identity

Table I summarises the main data on the identity of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid (or perfluorohexylethyl sulfonic acid) and its potassium salt.

Table I: Main data on the identity of the substances

Name	3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid	Potassium salt of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid
CAS number	27619-97-2	59587-38-1
Empirical formula	$C_8H_5F_{13}O_3S$	$C_8H_4F_{13}O_3S.K$
Semi-structural formula		
Molecular weight	428 g/mol	466 g/mol
Purity	No full analysis report provided	No full analysis report provided

The dossier does not contain a full analysis report for the two substances, specifying the nature and levels of any impurities, and the analytical methods used to detect them. However, it does mention that perfluoro-n-hexanoic acid (PFHxA, CAS No. 307-24-4) may be formed during the synthesis of perfluorohexylethyl sulfonic acid, and that the technologies used in its manufacture and in that of its salts can remove traces of this impurity to achieve final concentrations of less than 0.5 ppm.

3.1.2. Physical and chemical properties

The physico-chemical properties of perfluorohexylethyl sulfonic acid and its potassium salt are presented in Table II.

Table II: Main physico-chemical properties

Name	Aqueous solution from 25 to 35% of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid	Potassium salt of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid
Decomposition temperature		>300°C
Solubility in water		3.3 g/L (20°C) 150 g/L (80°C)
Density	1.15 (20°C)	
pH	2.2 (1% solution by weight)	6 (Solution at 40 g/L)
Surface tension	22.6 mN/m (25°C)	

Sulfonic acids react with strong oxidising agents and metals. As perfluorohexylethyl sulfonic acid and its potassium salt are composed of six perfluorinated carbon atoms, they are unlikely to break down in the environment into perfluorooctanoic acid (PFOA), but may form perfluorohexanoic acid (PFHA).

3.1.3. Intended uses

Perfluorohexylethyl sulfonic acid and its potassium salt are used as auxiliaries for the production of polymers in the manufacture of fluoropolymers (FP) used for the manufacture of tubes, fittings or accessories coming into contact with DW.

This FP, according to the applicant's declaration, presents strong resistance to oxidation by water containing chlorine-based disinfectants, in particular chlorine dioxide, thereby reducing the risk of pipes breaking. It also reduces the risk of pollutants permeating through the walls when the pipes have been buried in polluted soils.

The products in question are pipes with a diameter of less than 80 mm intended to be used for the supply of cold water (branch pipes) and the distribution of water inside buildings.

This FP is also used in accessories, in particular those in contact with disinfectants at high concentrations.

Perfluorohexylethyl sulfonic acid is used at a few percent by weight in the formulation of FP.

3.1.4. Authorisations for use

Perfluorohexylethyl sulfonic acid and/or its salts have not been granted authorisation for use in the manufacture of food contact materials (FCM) or materials in contact with DW (PDWs).

3.1.5. Migration data

According to the NF EN 12873-1 Standard, applied by the applicant's laboratory

Migration tests were carried out according to the NF EN 12873-1 Standard on two samples of FP, in cold non-chlorinated water (23 ± 0.5°C) and hot non-chlorinated water (85 ± 2°C), with a surface to volume (S/V) ratio of 10 dm^{-1}. At the end of each of the three stagnation periods of 24 hours (tests in hot water) or 72 hours (tests in cold water), perfluorohexylethyl sulfonic acid was screened for in the migration water using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) in "MRM" (Multiple Reaction Monitoring) mode.

The applicant initially conducted migration tests in hot water with three successive 24-hour stagnation periods of contact at 85°C without detecting any migration of perfluorohexylethyl acid. However, since the analytical method's limit of detection (LOD) and limit of quantification (LOQ) are respectively 30 and 100 µg/L, the maximum concentration likely to be found in the consumer's tap (C_{tap}) was estimated to be quite high (less than 60 µg/L (20 x 3 (µg/dm^2/d)).

Migration tests were then carried out in cold water with three successive 72-hour stagnation periods of contact at 23°C. The LOD and LOQ of the analytical method used were respectively 0.74 and 2.5 µg/L. After 3, 6 and 9 days, no migration was detected, which corresponds to a migration rate of less than 0.025 µg/dm^2/d. Assuming the "worst

case" exposure situation corresponding to pipes with a diameter of less than 80 mm, the conversion factor (CF) of 20 (4MS, 2011) leads to a maximum estimated concentration likely to be found in the consumer's tap (C_{tap}) of less than 0.5 µg/L (20 x 0.025 (µg/dm^2/d)).

Modelled using the AKTS-SML diffusion model AKTS-SML[2] (Piringer model)
The applicant modelled the migration of perfluorohexylethyl sulfonic acid in water using AKTS-SML software (version 4.54). The approach was consistent with the one described in the CEN/TR 16364 technical report. However, the model described has yet to be validated on the basis of feedback and its reliability remains to be confirmed.

The applicant considered that the diffusion behaviour of FP could be likened to that of rigid polyvinyl chloride (PVC), whose diffusion parameters are known (JRC, 2010). It believed that this assumption was protective with regard to the degree of crystallinity (Xc) and the melting temperature (mT) of FP, which are higher than for PVC (Xc > 50% for FP and Xc = 5-10% for PVC; mT = 170-180°C for FP and mT = 125°C for PVC), and the glass transition temperature (Tg), which is lower for FP than for PVC (Tg = -40°C for FP and Tg = 80°C for PVC), thus limiting the substance's migration into water (Brandrup *et al.*, 1999). For estimating migration, it used an upper-limit diffusion coefficient (Dp*) of 10^{-4} and a partition coefficient ($K_{p,w}$) of 10^{-6}, a density of 1.25 g/cm^3, a molecular weight of 428 g/mol and a residual concentration of perfluorohexylethyl sulfonic acid in the material of 16 µg/g.

In both cold water and hot water, the concentrations in water calculated at the end of the stagnation period "n" were less than or equal to those calculated for the stagnation period "n-1". The C_{tap} values calculated by modelling after the third stagnation period were around 0.2 µg/L at 23°C and 5.5 µg/L at 85°C. As the Piringer model can only be used for temperatures below 70°C, the result for the estimated migration at 85°C should be considered with caution.

Conclusion
The specific migration tests for perfluorohexylethyl sulfonic acid according to the European standard NF EN 12873-1 show a C_{tap} of less than 0.5 µg/L at 23°C and 60 µg/L at 85°C, with the concentrations measured in the migration water remaining below the analytical methods' limits of detection.

The C_{tap} was estimated by modelling a value of about 0.2 µg/L at 23°C and 5.5 µg/L at 85°C with a conservative model.

The maximum concentration of perfluorohexylethyl sulfonic acid likely to migrate into water at a temperature of 23°C is therefore below the threshold of 2.5 µg/L, below which only genotoxicity studies are mandatory for assessing the substance (4MS, 2011).

3.1.6. Data on the residual content in the material in contact with water

The residual level of perfluorohexylethyl sulfonic acid in FP granules and tubes was determined by the applicant using liquid chromatography coupled with mass spectrometry (LC-MS) after methanol extraction by microwave heating for 15 minutes at 150°C in with LOD and LOQ of 1.1 and 3.6 µg/g respectively. Concentrations were between 15 and 16 µg/g.

This value was used for modelling migration (see Section 3.1.5).

[2] *Software developed jointly by the Swiss Federal Office of Public Health (FOPH) and the company AKTS (Advanced Kinetics Technology Solutions) www.akts.com.*

3.1.7. Microbiological properties

The applicant stated that the substance was not used as an antimicrobial agent.

3.1.8. Toxicological data

Genotoxicity

- Gene mutation in bacteria (Ames test) (Study No. 23703MMO dated 16/08/2002 conducted by the CIT Laboratory (France), 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid content: 29.8%)

The study, conducted according to OECD guideline 471, indicates a lack of mutagenic potential for perfluorohexylethyl sulfonic acid on this bacterial system.

- *In vitro* test for chromosomal aberration in mammalian cells (Study No. AC03GD.331.BTL dated 27/08/2007 conducted by the BioReliance laboratory (USA), 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid content: 35.6%)

An *in vitro* test for chromosomal aberrations in Chinese hamster ovary (CHO) cells was conducted according to OECD guideline 473. The results clearly show the *in vitro* genotoxic potential of perfluorohexylethyl sulfonic acid both in the absence and presence of metabolic activation after a short treatment time on this cell system, with the induction of predominantly structural chromosomal aberrations. This effect was not found after a long period of treatment without metabolic activation even though the maximum dose tested was very similar (300 and 250 µg/mL respectively for 4 and 20 hours of treatment) and the longer duration test is considered to be more sensitive. It is surprising to note the total lack of structural aberrations for the negative control, at the three concentrations tested on the two cultures, a total of 800 cells analysed, which is rather inconsistent with the historical data (a mean of 0.6% ± 0.9%, extreme deviations of 0 to 5.5%). Additional readings should have been taken for the longer duration test or it should have been repeated. Although the choice of the cell line is questionable given its murine origin and its genetic instability that could cause false positives (Honma and Hayashi, 2011), as the results obtained for negative controls show no significant aberration rates, this effect cannot be described as "false positive". The considerable clastogenic activity demonstrated after a short treatment time means that a localised *in vivo* genotoxic effect cannot be ruled out.

- *In vivo* test for chromosomal aberration coupled with a micronucleus test (Study No. AC03GD.331.BTL dated 07/12/2007 conducted by the BioReliance laboratory (USA), 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid level: 35.6%)

The *in vivo* test on "ICR" mouse bone marrow cells followed most of the recommendations in OECD guidelines 474 and 475. The mice were exposed orally by a single treatment. Despite the lack of inhibition of erythropoiesis (no decrease in the PCE[3]/NCE[4] ratio) and of determination of plasma concentrations, given the significant reductions in mitotic index in the three treated groups during the metaphase analysis test, it can be considered that the bone marrow was actually exposed. The substance administered orally at doses of up to 2000 mg/kg bw did not induce a statistically significant increase in the number of micronucleated cells, or in the number of numerical and structural chromosomal aberrations in "ICR" mouse bone marrow. However, chromatid type exchanges were observed in the male groups treated at 500 and 2000 mg/kg bw. These clastogenic effects that correspond to a double genetic event (breakage and rearrangement) should be regarded as biologically significant and a systemic effect cannot be totally ruled out.

[3] *PCE: polychromatic erythrocytes.*

[4] *NCE: normochromatic erythrocytes.*

- *In vivo* unscheduled DNA synthesis (UDS) test (Study No. AC03GD.381.BTL dated 11/10/2007 conducted by the BioReliance laboratory (USA), 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid level: 35.6%)

The test was conducted according to OECD guideline 486. Perfluorohexylethyl sulfonic acid did not induce unscheduled DNA synthesis in hepatocytes of male Sprague-Dawley rats treated orally with single doses of 500, 1000 and 2000 mg/kg bw. However, the lack of verification of plasma concentrations of perfluorohexylethyl sulfonic acid in treated animals makes it impossible to confirm their systemic exposure, and furthermore the lack of determination of the number of cells in phase "S" means that it is impossible to demonstrate any proliferative effect. Moreover, the relevance and weight of this second-line *in vivo* test are poor with regard to current knowledge. According to Kirkland and Speit (2008), this test does not appear to be sensitive enough to show genotoxic carcinogens *in vivo* with less than 20% sensitivity. In contrast, the comet assay can show about 90% of genotoxic carcinogens *in vivo*. Discussions are underway at international level (OECD) to archive the guideline corresponding to this test and replace it with the comet assay.

General toxicity

- ♣ Subacute oral toxicity (28 days) (Study No. DPT443/984760 dated 01/09/1999 conducted by the Huntington Life Sciences Ltd laboratory (USA), preparation tested: 25% mixture of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid and its ammonium salt in suspension in water)

A study was conducted in Crl:CD® BR rats according to OECD guideline 407. The product has proven toxicity in male and female rats exposed orally for 28 days (administered doses: 15, 50 and 150 mg/kg bw/day). Although no treatment-related mortality was observed up to the maximum dose of 150 mg/kg bw/day, significant histopathological changes in male and female rats were observed in the kidneys and to a lesser extent the liver from 50 mg/kg bw/day. These effects were corroborated by weighing the organs and by increases in plasma levels of urea, creatinine and inorganic phosphorus. Haematotoxicity at the maximum dose tested of 150 mg/kg bw/day was also observed.

The no observed adverse effect level (NOAEL) was set at 15 mg/kg bw/day for male and female CD rats, based on the results of this 28-day oral toxicity study.

Conclusion

The studies followed most of the recommendations in the corresponding OECD guidelines. Nevertheless, no control was provided for any of the studies concerning the concentrations in the treatment solutions with the solvents/excipients used, which, apart from being a deviation from good laboratory practice (GLP), means that the product's stability under the treatment conditions cannot be guaranteed. However, this limit is not likely to call into question the findings of the studies.

The genotoxicity tests conducted on perfluorohexylethyl sulfonic acid are unable to confirm the absence of *in vivo* genotoxic potential for this substance, either at the systemic level from the presence of chromatid exchanges in the metaphase analysis test *in vivo* on mouse bone marrow, or at the local level due to the strong clastogenicity observed in the metaphase analysis test on cell culture.

3.2. Conclusions

In view of the dossier submitted by the applicant, the CES on Water:

1) given the dossier as it now stands, is issuing a stay of proceedings on the application for authorisation to use 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid (CAS No. 27619-97-2) and its potassium salt (CAS No. 59587-38-1) in the manufacture of organic materials intended to come into contact with drinking water.

2) is asking for:

   a. the provision of a full analysis report for the two substances, specifying the nature and levels of any impurities and the methods used to detect them;

   b. an alkaline comet assay to be conducted, capable of showing various types of DNA damage (single- and double-strand breaks, alkali-labile sites, incomplete DNA repair sites, etc.). As effects have been demonstrated both in the absence and presence of metabolic activation, the study should focus on a systemic organ capable of metabolisation (the liver for example, or the kidney, which was found to be a target organ), but also on a local organ of interest based on the oral exposure expected in humans, for example an organ of the gastrointestinal tract (stomach and/or bowel and/or duodenum). The assay should be conducted taking into account the recent recommendations in the literature defining the optimal conditions for its implementation (Tice *et al.*, 2000; Hartmann *et al.*, 2003, 2004; Burlinson, 2007). The concentrations of acid in the treatment solutions used in this study should be verified and evidence of systemic exposure of animals should be provided.

3) reiterates that although negative results for this test conclude that perfluorohexylethyl sulfonic acid is not genotoxic *in vivo,* a 28-day subacute oral toxicity study is not acceptable for setting a maximum tolerable concentration (MTC_{tap}) higher than 2.5 µg/L.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety adopts the conclusions and recommendations of the CES on Water.

The Director General

Marc Mortureux

KEYWORDS

Drinking water, water contact materials, organic materials, positive lists, authorisation of a substance.

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4.1. Publications

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4.2. Standards

NF EN 12873-1: Influence of materials on water intended for human consumption - Influence due to migration - Part 1: Test method for non-metallic and non-cementitious factory made products.

CEN/TR 16364. Influence of materials on water intended for human consumption – Influence due to migration – Prediction of migration from organic materials using mathematical modelling.

4.3. Legislation and Regulations

Ministerial Order of 29 May 1997 on materials and products used in permanent facilities for the production, treatment and distribution of drinking water, as amended by the Orders of 24 June 1998, 13 January 2000, 22 August 2002 and 16 September 2004 (published in the Official Journals of 1 June 1997, 25 August 1998, 21 January 2000, 3 September 2002 and 23 October 2004).