ANSES Opinion
Request No 2015-SA-0176
Related Request Nos 2012-SA-0235 and 2014-SA-0124

The General Directorate

Maisons-Alfort, 19 January 2016

OPINION
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 coming into contact with drinking water

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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.
This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 19 January 2016 shall prevail.

On 29 July 2015 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.

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.

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.*"

This request was made as a result of the stay of proceedings issued by ANSES on 22 April 2013 (Opinion No. 2012-SA-0235) asking for:

- 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;
- 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 metabolism (the liver for example, or the kidney, which has been 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 monitored and evidence of systemic exposure of animals should be provided.

In addition, on 26 June 2014, the Agency issued comments on the draft testing protocol for the comet assay submitted by the applicant (Scientific and Technical Support Note No. 2014-SA-0124 not published on the Agency's website). It ascertained that the draft test protocol followed the latest recommendations relating to the implementation of the comet assay (OECD guidelines not published at the time) and that the study would be conducted in accordance with good laboratory practices.

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 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 5 January 2016.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals. The experts' declarations of interests are made public on ANSES's website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE CES ON WATER

The technical dossier received from the applicant contained the information asked for in the opinion request n°2012-SA-0235:

- full analysis report 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),
- the publication describing the analytical method used to determine the impurities of the two substances (Larsen et al. 2006),
- the test report assessing the genotoxic potential of perfluorohexylethyl sulfonic acid according to the comet assay carried out by the Covance laboratory.

3.1. Analysis of documents received

Identity:

- Analysis Report of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctanesulphonic acid (and its potassium salt

The purity of perfluorohexylethyl sulfonic acid and its potassium salt is greater than 95%.

As perfluorohexylethyl sulfonic acid and its potassium salt are usually synthesised from a telomerisation reaction leading to the production of a molecule with formula $C_6F_{13}CH_2CH_2I$ (6:2 fluorotelomer iodide), it is therefore surprising that only C8 impurities and not C6 impurities are mentioned in the analysis bulletin (Buck *et al.* 2011; Kissa 2001).

However, C8 compounds are deemed more bioaccumulative than C6.

Genotoxicity:

- *In vivo* Comet assay (Covance study No.8298990. 01 July 2015 – United Kingdom, potassium salt of perfluorohexylethyl sulfonic acid purity: (97.6 %)

The in vivo alkaline Comet Assay was performed on rats' liver and stomach following the OECD test guideline No.489 (OECD, 2014) and EFSA recommendations (EFSA, 2012). This study was conducted in accordance with the OECD principles on Good Laboratory Practices (OECD, 1998; MHRA, 1999; MHRA, 2004).
The assay was performed exclusively by oral route on Sprague-Dawley male rats (6 animals/group). The potassium salt of sulfonic acid perfluorohexylethyl was diluted in water and the solution was administered at the highest dose of 2000 mg/kg/day (2 daily treatments at 21-hour intervals) at a dose volume of 10 mL/kg. The test compound was hydrolytically stable (mean from 85 to 100% and 89.5 to 120.4% for day 1 and day 2, respectively).

As perfluorohexylethyl sulfonic acid has shown genotoxic effects in *in vitro* assays, both in the presence and absence of metabolic action (see Opinion 2012-SA-0235), the choice of organs studied is appropriate. The liver is the most active organ in the metabolism of chemical substances (systemic organ) and the stomach is the first site of contact for chemical substances after oral exposure (local organ).

Prior toxicity tests helped determine that the maximum tolerated dose (MTD) of perfluorohexylethyl sulfonic acid by the oral route in Sprague Dawley rats was higher than 2000 mg/kg/d. The main genotoxicity test was therefore conducted using doses of 2000 (MTD), 1000 (MTD/2) and 500 (MTD/4) mg/kg/d (x2). The animals were sacrificed 3 hours after the second treatment.

Both negative (excipient, i.e. water) and positive (Ethyl Methane Sulfonate, EMS at 150 mg/kg) controls were tested during the main assay, specific data generated in the current study for negative and positive controls were in the range of historical data allowing validating the study. Indeed, the laboratory in charge of the realization of the Comet assay demonstrated its proficiency at performing the Comet on both the liver and the stomach from male rats.

No control of concentration in plasmas (proof of systemic exposure) was performed. However, independent data confirmed that the test article is biologically available from the rat digestive tract and that the liver of male rats is exposed.

No significant increase in the percentage of severely damaged cells was observed, either for the liver or the stomach, confirming that perfluorohexylethyl sulfonic acid administered by the oral route did not cause any excessive toxicity liable to interfere with the assessment of genotoxic activity (percentages of "ghost" cells clearly < 30%).

The assessment of genotoxic activity was conducted by examining 900 cells per group.

In the liver and the stomach, no statistically significant increase in the rate of DNA fragmentation was observed in the three groups of male rats treated with the doses of 2000, 1000 and 500 mg/kg/d (x2). Indeed, the proportions of DNA present in the tail, or tail intensity, and the olive tail moment percentages were similar to the negative controls and were of the same order of magnitude as the values of the historical controls: In the liver, the average percentages of tail DNA ranged from 0.25 ± 0.06 to 0.48 ± 0.13 *versus* 0.37 ± 0.09 for the negative control. In the stomach, the average percentages of tail DNA ranged from 0.47 ± 0.05 to 1.18 ± 0.27 *versus* 1.31 ± 0.26 for the negative control.

- Conclusion

The current study was performed following the OECD Principles of Good Laboratory Practice by a Contract Research Organization that demonstrated its proficiency at performing the Comet Assay on both the liver and the stomach from male rats. Under these experimental conditions, sulfonic acid perfluorohexylethyl did not induce DNA damage in the liver and stomach of rats treated up to 2000 mg/kg/day (X2). As a result, sulfonic acid perfluorohexylethyl is considered having no *in vivo* genotoxic activity in both these organs.

3.2. Conclusions

In light of the dossier submitted by the applicant, the CES on Water is issuing a favourable opinion on the application for authorisation to use perfluorohexylethyl sulfonic acid (CAS No: 27619-97-2) in the manufacture of organic materials coming into contact with drinking water (DW), with a maximum tolerable concentration in the consumer's tap (MTC_{tap}) of 2.5 µg/L.

Its potassium salt (CAS No: 59587-38-1) is therefore authorised under Regulation (EU) No 10/2011 and does not need to be mentioned in the positive lists of authorised substances.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the CES on Water's conclusions.

Perfluorohexylethyl sulfonic acid belongs to the family of per- and polyfluorinated alkyl substances (PFASs). The Agency therefore notes that expert appraisal work and studies on this family of substances are continuing with regard to their bioaccumulation potential, their presence in water and their possible endocrine disrupting effects (Request Nos 2009-SA-0331 and 2015-SA-0105). In light of the knowledge gained during this work, the above conclusions may possibly be reassessed and give rise to a new opinion.

KEYWORDS

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

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