

The Director General

Maisons-Alfort, 17 July 2013

OPINION
of the French Agency for Food, Environmental
and Occupational Health & Safety

**on the application for authorisation to use 3,7,11-trimethyldodecyn-3-ol (TMDDO),
CAS No. 1604-35-9, in silicone materials and articles intended for food contact**

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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 6 September 2012, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) received a request from the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) for an Opinion on the application for authorisation to use 3,7,11-trimethyldodecyn-3-ol (TMDDO), CAS No. 1604-35-9, in silicone materials and articles intended for food contact.

In a letter dated 15 January 2013 addressed to the DGCCRF, ANSES requested additional information on the extraction yield of TMDDO as well as on the chemical nature of any reaction products or oligomers. This information, provided by the applicant to the DGCCRF on 21 March 2013, was recorded by ANSES on 28 March 2013.

1. BACKGROUND AND PURPOSE OF THE REQUEST

At European level, all materials and articles intended to come into contact with foodstuffs are governed by Regulation (EC) No 1935/2004.

In the absence of European harmonisation, specific regulatory measures concerning silicones intended for food contact are described in the French Ministerial Order of 25 November 1992 on silicone elastomer materials and articles placed or intended to be placed in contact with foodstuffs, food products and beverages.

The current application concerns the addition of 3,7,11-trimethyldodecyn-3-ol (TMDDO) to the list of authorised substances in Annex I, Section II – Inhibitors, of the French Ministerial Order of 25 November 1992 on silicone elastomer materials and articles placed or intended to be placed in contact with foodstuffs, food products and beverages.

In accordance with the Ministerial Order of 13 November 1986, any application to use a new substance intended for the manufacture of materials and articles intended for food contact in France must be accompanied by a dossier that complies with Article 2 of this Order.

The Opinion of the French High Council for Public Health (CSHPF) of 9 December 1997 specifies the documents that must be included in applications to use substances, and the Instruction of 27 November 1986 details the physio-toxicological experimental protocols.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

The collective expert appraisal was conducted by the permanent working group on Assessment of substances and processes subject to authorisation for human food (ESPA WG), which met on 17 September and 13 December 2012, and on 18 April 2013. It examined the following items:

- Applicant's technical dossier;
- Bibliographic and scientific data sent following a request for additional information by the ESPA WG.

3. ANALYSIS AND CONCLUSIONS OF THE ESPA WG

3.1. Analysis

The applicant's dossier was prepared on the basis of the European Food Safety Authority's (EFSA) "Note for Guidance for Food Contact Materials" of 30 July 2008 and supplemented by the information requested solely by the French authorities:

- Technological function - technical justification for the use of the substance: technical or any other arguments for the use of the substance or materials, expected effects, expected benefits, potential value to the user and consumer.
- Advantages and disadvantages for the environment.

3.2. Identity

3,7,11-trimethyl-1-dodecyn-3-ol (TMDDO), also known as 3,7,11-trimethyldodec-1-yn-3-ol (IUPAC), 2,6,10-trimethyl-11-dodecyn-10-ol or 3,7,11-trimethyl-3-hydroxy-1-dodecyn is identified by CAS No. 1604-35-9.

The main data regarding the identity of TMDDO are shown in Table 1 below:

Name	3,7,11-trimethyl-1-dodecyn-3-ol (TMDDO)
CAS number	1604-35-9
Empirical formula	C ₁₅ H ₂₈ O
Semi-structural formula	$\text{HC} \equiv \text{C} - \underset{\text{OH}}{\overset{\text{Me}}{\text{C}}} - (\text{CH}_2)_3 - \underset{\text{Me}}{\text{CH}} - (\text{CH}_2)_3 - \text{CHMe}_2$
Molar mass	224.38 g/mol

Table 1: main data regarding the identity of TMDDO

The method for manufacturing TMDDO is described in US patent 9828468.

The main impurity identified by chromatographic analysis is 6,10-dimethylundecane-2-one at a concentration of less than 0.29%.

The chromatographic spectra also show three other peaks, attributed to unidentified substances, which have been quantified on the basis of the area measured for TMDDO. These analyses were used to calculate the total amount of impurities, equal to 1.07%, i.e. a purity for TMDDO of 98.93%, which is higher than the minimum value declared by the supplier of 98.5%.

The applicant's submission does not concern mixtures containing TMDDO.

3.2.1. Physico-chemical properties

TMDDO is liquid at room temperature (solid at -65°C) and its boiling point is estimated to be 290°C at a pressure of 1013 hPa. TMDDO's stability was assessed by differential scanning calorimetry (DSC) under air flow. TMDDO is stable up to a temperature in excess of 200°C, which is higher than the maximum values normally encountered when manufacturing silicone elastomers. TMDDO is immiscible in water and its octanol-water partition coefficient (Log P_{OW}) obtained by calculation is 5.21. No other information related to the lipophilicity of TMDDO was provided in the dossier.

TMDDO reacts with the Si-H groups of a silicone matrix, but is not susceptible to hydrolysis. In view of the data obtained by DSC, TMDDO is unlikely to be broken down during the silicone elastomer manufacturing process (a substance that remains stable at temperatures in excess of 200°C, which is the maximum temperature reached during the manufacture of silicone elastomer materials).

The residual TMDDO contained in the silicones is not expected to react with foodstuffs.

3.2.2. Intentional use of the substance

During the heat curing of silicone elastomers obtained by moulding (the HCE [heat-cured elastomer] method), TMDDO is used to inhibit catalysis of the hydrosilylation reaction by platinum compounds. The presence of an inhibitor prevents the reaction from occurring and enables ready-to-use mixtures to be stored for periods long enough to meet industrial requirements.

Currently, only 1-ethyl-1-cyclohexanol is authorised as an inhibitor of this reaction under French legislation (Ministerial Order of 25 November 1992). According to the applicant, this substance has disadvantages, such as mixtures evolving too quickly during storage

and a non-uniform curing rate within the material due to its vapour pressure being too high, which is not the case with TMDDO.

Using its own in-house studies, the applicant demonstrated that using TMDDO as an inhibitor improves the shelf life of ready-to-use mixtures while increasing productivity in the manufacture of silicone (Gambut et al. 2000, Karlson et al. 2001).

The maximum content of TMDDO used in the manufacture of silicone elastomers is known and expressed in terms of mass (confidential data provided in the annex to the dossier). The five samples used to analyse TMDDO were consistent with the TMDDO formulation presented by the applicant.

The silicone elastomer materials manufactured with TMDDO are intended for the cookware market, for cooking all kinds of foods in a wide variety of conditions: temperatures from -18°C to 250°C and periods of food contact ranging from a few minutes to over an hour for cooking, and up to several weeks for freezing.

3.2.3. Authorisations for the substance

An application for authorisation of TMDDO is currently being examined by the German authorities with the aim of including this substance on the list in BfR Recommendation XV, Chapter III, on silicone materials intended for contact with food.

TMDDO was notified as a new substance in the 6th amendment of Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

3.2.4. Migration data

Specific migration

No analysis of specific TMDDO migration was conducted by the applicant. This data may be omitted in the case of a monomer or starting substance if the residual amount of the substance in the finished product has been determined using a suitable analytical method (see Section 3.2.5).

Overall migration

Regarding overall migration tests, no analyses were performed on samples of silicone made with TMDDO, on the assumption that this substance had no impact on the migration of the material's other constituents. This data is generally not required for an application concerning a monomer, starting substance or additive.

Quantification and identification of oligomers and reaction products

No attempt was made to identify or quantify the reaction products or oligomers derived from the monomers, starting substances or additives, on the assumption that TMDDO had no impact on the formation of these substances during polymerisation of the silicone. This data may be omitted if suitable justification has been provided. It was therefore not requested by the ESPA WG because the applicant had provided a literature review as additional information. The findings of this review indicate that the conditions under which TMDDO is used as an inhibitor of the hydrosilylation reaction do not promote the occurrence of alternative reactions: either TMDDO reacts with the silicone material by becoming attached to it, or it does not react and remains in the finished material in its original chemical form.

3.2.5. Data on the residual amount of substance in the material in contact

Methodology

Two analytical methods (with and without standard additions) are described in the dossier provided by the applicant. However, the ESPA WG requested additional information relating to the extraction yield of TMDDO.

In order to determine the TMDDO content in the silicone elastomer sample, the applicant extracted TMDDO using dichloromethane (DCM, 40 mL). It assumed that the TMDDO was uniformly distributed between the 24 mL of DCM recovered during the extraction phase and the 16 mL of DCM remaining in the material and causing it to swell. It proposed the use of a correction factor of 1.67 (40 divided by 24) taking into account the loss of TMDDO to be determined due to the material's retention of DCM.

The use of this correction factor was validated by the ESPA WG, since the applicant had included control measures, in the additional information that enabled the efficacy of the TMDDO extraction method (measurement of the residual amount) to be verified.

Estimated migration by calculation according to a worst-case scenario

Specific TMDDO migration was calculated according to a worst-case situation (a surface area/mass of food ratio of 16.7 dm²/kg) that assumed complete migration of TMDDO into foods based on the residual amount measured as undetectable using the standard addition method (results are shown in the analysis report annexed to the dossier).

The residual amount of TMDDO was estimated at 0.042 µg/g of material, and the maximum migration in this worst-case scenario is 18.5 µg of TMDDO/kg of food.

The applicant indicated a value of 15 µg of TMDDO/kg of food due to figures rounded in the calculations being used in a different way.

3.2.6. Microbiological properties

The substance is not used as an antimicrobial agent.

3.2.7. Impact of TMDDO on the environment

In Directive 67/548/EEC and its amendments, this substance is classified as dangerous for the environment and assigned the symbol N "Toxic to aquatic organisms - may cause long-term adverse effects in the aquatic environment". In Regulation (EC) No 1272/2008, TMDDO is classified H400 "Very toxic to aquatic life" and H410 "Very toxic to aquatic life with long-lasting effects". According to OECD criteria, TMDDO is not readily biodegradable.

3.2.8. Toxicological data

Genotoxicity

- **Gene mutation assay in bacteria (Ames test)¹.**

A study of the mutagenic potential of TMDDO (purity 98.9%) was carried out on two species of bacteria: *Salmonella typhimurium* (TA 98, 100, 1535, 1537) and *Escherichia coli* (WP2 uvrA). The five doses of TMDDO tested in triplicate in two independent tests ranged from 0 to 5000 µg/plate for test 1 and 0 to 2500 µg/plate for test 2 (pre-incubation

¹ BASF Laboratory, Study nos. 40M0025/054015, January 2006.

for 60 min at 37°C). The negative controls (DMSO)² and, depending on the strain, the positive controls (MNNG, NOPD, AAC, 4-NQQ and 2AA), were performed with and without metabolic activation (S9).

The study, conducted according to OECD guideline 471, indicates a lack of mutagenic activity in TMDDO on both bacterial species.

- **Gene mutation assay in cultured mammalian cells³**

The ability of TMDDO (purity 98.9%) to induce mutations in the HPRT (hypoxanthine-guanine phosphoribosyltransferase locus) gene was tested *in vitro* on monolayer cultures of Chinese hamster ovary cells (CHO sub-strain K1). Four independent tests were conducted, respectively in the absence and presence of exogenous metabolic activation (S9 mix). The preliminary cytotoxicity assay (not GLP) on the cells was used to specify doses of TMDDO for the mutagenicity tests, with tested concentrations between 1.0 and 2300 µg/mL. The doses (in duplicate), which were analysed for 4 hours in three independent tests, were between 0.25 and 26 µg/mL. The negative and positive controls were carried out using respectively DMSO, ethyl methanesulfonate (EMS) and 3-methylcholanthrene (MCA).

In conclusion, TMDDO showed no mutagenic activity in mutagenesis tests on a specific locus of mammalian (CHO) cells (according to OECD (No. 476, 1997) and EPA (1998) guidelines, and according to Directive 2000/32/EC).

- **Chromosomal aberration assay in cultured mammalian cells⁴**

This assay is used to test whether TMDDO presents clastogenic activity (structural chromosomal aberrations) and aneugenic activity (change in the number of chromosomes) in Chinese hamster lung fibroblasts (V79 cells). The maximum TMDDO concentrations tested were between 5 and 12.5 µg/mL in the two independent experiments in the absence of metabolic activation, and between 4 and 20 µg/mL in the presence of metabolic activation (S9 mix). For the low concentrations, no conclusion could be reached from the analysis of a limited number of observable metaphases. For the high concentrations tested, the large proportion of lysed cells meant that it was not possible to determine the frequency of metaphases. The results of these tests show that TMDDO does not induce a significant increase in the number of metaphase aberrations after 4 h and 18 h of treatment followed by metaphase preparations between 10 and 24 h depending on the experiment. A significant effect in the second experiment without metabolic activation at a dose of 12.5 µg/mL on a single analysis criterion (5% aberrant cells, junctions included) was not considered biologically relevant. The significance of this criterion is not generally regarded as a criterion of clastogenicity. In addition, according to the applicant, the value of 5% is included in the laboratory's historical control values. The high cytotoxicity of TMDDO meant that it was not possible to conduct analyses at the highest concentrations.

In conclusion, under the experimental conditions presented, it can be considered that TMDDO does not induce any clastogenic or aneugenic effect in V79 cells *in vitro*.

² DMSO: Dimethyl sulfoxide; MNNG: N-methyl-N'-nitro-N-nitrosoguanidine; NOPD: 4-nitro-o-phenylenediamine; AAC: 9-aminoacridine, 4-NQO: 4-nitroquinoline-N-oxide; 2AA: 2-aminoanthracene.

³ BASF Laboratory, Study nos. 50M0025/054126, May 2006.

⁴ BASF Laboratory, Study nos. 32M0025/054127, May 2006.

- **Other toxicological information**

A safety data sheet for TMDDO (TMDDO, BASF; 11 pages dated 1/09/2011) was provided by the applicant. The toxicological information reported concerns an LD₅₀ of between 500 and 2000 mg/kg (according to OECD protocol 423), dermal irritation (dermal irritation test on rabbits carried out according to OECD protocol 404) and eye irritation (eye irritation test in rabbits performed according to OECD protocol 405). No additional information concerning toxicity and toxicology was found for TMDDO in the scientific databases studied, except for ecological data (grade 1 acute and chronic aquatic toxicity).

Conclusion relating to toxicological data

The studies followed the recommendations in the corresponding OECD guidelines and were deemed admissible by the ESPA WG. These studies did not demonstrate any mutagenic or clastogenic potential, so the ESPA WG considers them to be relevant.

3.3. CONCLUSIONS OF THE ESPA WG

The applicant's dossier complies with the specifications of EFSA's "Note for Guidance for Food Contact Materials" and was supplemented by specific information required by the French regulations on silicone elastomer materials and articles.

In view of the dossier submitted and the additional information provided by the applicant, under the conditions of use presented leading to a migration limit of no more than 0.05 mg/kg of food⁵, the ESPA WG is issuing a favourable opinion on the application for authorisation to use 3,7,11-trimethyldodecyn-3-ol (TMDDO) CAS No. 1604-35-9, with a minimum purity of 98.9%, in the manufacture of silicone materials and articles intended for food contact.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety adopts the conclusions of the ESPA WG.

The Director General

Marc Mortureux

⁵ Specific migration limit recommended in the guidelines of the European document "Note for guidance" - revision of 30 July 2008.

KEYWORDS

FCMs, TMDDO, Silicone, Ministerial Order of 25/11/1992.

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