Call for scientific and technical data on the permitted food additives propyl gallate (E 310), octyl gallate (E 311) and dodecyl gallate (E 312)

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Deadline for step 1 (Registration of the contact details of business operators interested in submitting data): 7 July 2017

Deadline for step 2 (Confirmation of data submission, deadlines and milestones): 30 November 2017

Background

According to Article 32 of Regulation (EC) No 1333/2008[1], food additives permitted in the EU before 20 January 2009 should be subject to a new risk assessment by the European Food Safety Authority (EFSA). The programme for the re-evaluation of these permitted food additives has been set up by Commission Regulation (EU) No 257/2010[2].

So far EFSA has not identified a major safety concern (such as a proven carcinogenic or genotoxic activity) for any of the re-evaluated food additives. In fact, in most cases EFSA confirms the safety of those food additives at their currently reported uses and use levels. However, for some additives EFSA has identified issues that require a follow-up. Additional specific data is needed to address those issues.

The additives whose safety re-evaluation by EFSA was hindered by limited data availability, but which are not expected to pose an immediate food safety concern, are not going to be immediately removed from the Union list of permitted additives, or their uses and/or use levels revised. Instead, business operators are requested to indicate to the Commission their interest in the continuity of approval of the additive(s) under re-evaluation and in providing, by a certain deadline, the data needed by EFSA to complete its risk assessment. In general, new toxicological studies will be needed to generate these missing data.

Once EFSA has assessed the new data, the current authorisation of the additive(s) may be revised, if needed.

If business operators do not provide the requested data (by the predefined deadline) the present authorisation will be revised based on EFSA's current scientific opinion and the additive(s) may be removed from the Union list of permitted additives. The same applies if the new data submitted is not sufficient for EFSA to conclude the risk assessment, since there will be no successive requests for additional data.

Food additives for which EFSA has identified concerns in terms of exposure or specifications will be subject to the same follow-up approach, but EFSA's assessment of the new data may not always be needed.

The Commission will undertake that the time assigned for addressing issues identified by EFSA is as short as possible and dependent on the time needed to generate and assess the required new data.

EFSA's Scientific Opinion on the re-evaluation of propyl gallate (E 310) as a food additive

The EFSA's Panel on Food Additives and Nutrient Sources added to Food (ANS) delivered a scientific opinion re-evaluating the safety of propyl gallate (E 310) when used as a food additive[3]. In 1976, the Scientific Committee on Food Additives (SCF) established a group ADI of 0-0.2 mg/kg bw

[1] OJ L 354, 31.12.2008, p. 16.
[2] OJ L 80, 26.3.2010, p. 19.
[3] https://www.efsa.europa.eu/en/efsajournal/pub/3642

for three gallates (propyl, octyl, dodecyl). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) in its last evaluation in 1996 allocated an ADI only to propyl gallate of 0-1.4 mg/kg bw and did not establish ADIs for octyl and dodecyl gallate. The Panel considered that no substantial new toxicological data have emerged since this last evaluation.

The Panel concluded that the 90-day toxicity study in rats was the key study for the evaluation of propyl gallate considering the uncertainties and lack of a no observed adverse effect level (NOAEL) in the carcinogenicity database on propyl gallate. Based on the NOAEL of 135 mg propyl gallate/kg bw/day of this study and taking account of the Opinion of the Scientific Committee of EFSA on Default values, the Panel concluded that an uncertainty factor of 300 should be applied for extrapolation from a subchronic to chronic data and due to the limitations in the reproductive toxicity database, and derived an ADI of 0.5 mg/kg bw/day for propyl gallate. The Panel also concluded that there was no longer a basis for the present group ADI and that propyl, octyl and dodecyl gallates should be evaluated separately and the present group ADI should be withdrawn.

The high level of exposure exceeded the ADI in adults and the elderly. However, given the conservatism of the exposure assessment, the Panel concluded that the use of propyl gallate as food additive at the current uses and use levels is not of safety concern.

The Panel noted that the use of hydrochloric acid in the manufacture of propyl gallate could result in chlorinated by-products and that there were limits for chlorinated organic compounds in the specifications, but no information on the identification or quantification of potential chlorinated by-products was available to the Panel.

EFSA's Scientific Opinion on the re-evaluation of octyl gallate (E 311) as a food additive

The EFSA's Panel on Food Additives and Nutrient Sources added to Food (ANS) delivered a scientific opinion re-evaluating the safety of octyl gallate (E 311) when used as a food additive[4]. The Panel considered that, whilst from theoretical considerations octyl gallate could be metabolised to octyl alcohol and gallic acid, there were insufficient data to demonstrate the rate and extent of octyl gallate metabolism *in vivo*. Having reviewed the data on the toxicokinetics (rate and extent of metabolism) of propyl, octyl and dodecyl gallate in a previous EFSA evaluation of propyl gallate, the Panel concluded that the available metabolism data on gallates were insufficient to provide a basis for the read-across of systemic toxicity data on propyl, octyl and dodecyl gallate to be valid. Therefore, there was no longer a basis for the present group ADI and the Panel concluded that propyl, octyl and dodecyl gallate should be evaluated separately and the present group ADI should be withdrawn.

No data on genotoxicity of octyl gallate were available. The Panel considered that, for the evaluation of the genotoxic hazard of intact octyl gallate, read-across from data on propyl gallate and from the *in silico* expert system was scientifically justified. Therefore, based on the available *in vitro* and *in vivo* results on propyl gallate, which provide a limited evidence of genotoxicity in some *in vitro* systems and no evidence in *in vivo* tests with adequate systemic exposure, the Panel considered that octyl gallate was unlikely to raise concern for genotoxicity. However, owing to the lack of detailed reports on carcinogenicity and chronic toxicity studies with octyl gallate and the absence of a basis for read-across for systemic toxicity from propyl gallate data, the Panel could not reach a definitive conclusion on the presence or absence of a carcinogenic potential of octyl gallate.

The Panel identified a NOAEL of 50 mg/kg bw/day in a reproductive toxicity study. Overall, the available database was too limited to either establish an ADI or serve as a basis for a margin of safety approach to be applied with confidence.

The Panel concluded that, although a safety concern was unlikely from the single use (chewing gum) for which usage and analytical data were provided, an adequate assessment of the safety of octyl gallate as a food additive in all its currently permitted uses would require a sufficient

[4] https://www.efsa.europa.eu/en/efsajournal/pub/4248

toxicological database in line with its current guidance for submission for food additive evaluations (EFSA ANS Panel, 2012)[5].

The Panel noted that, whilst the EU specifications allow for the presence of chlorinated organic compounds, these are not identified or specified, and considered that identification of possible chlorinated impurities would be needed for possible evaluation of toxicological significance. The Panel recommended that the maximum limits for the impurities of toxic elements (lead, mercury and arsenic) in the EU specifications for octyl gallate (E 311) should be revised to ensure that octyl gallate as a food additive will not be a significant source of exposure to those toxic elements in food.

EFSA's Scientific Opinion on the re-evaluation of dodecyl gallate (E 312) as a food additive

The EFSA's Panel on Food Additives and Nutrient Sources added to Food (ANS) delivered a scientific opinion re-evaluating the safety of dodecyl gallate (E 312) when used as a food additive[6]. The Panel considered that whilst from theoretical considerations dodecyl gallate could be metabolised to dodecyl alcohol and gallic acid, there were insufficient data to demonstrate the rate and extent of dodecyl gallate metabolism *in vivo.* The Panel noted that the available data demonstrated decreased hydrolysis of dodecyl gallate compared with propyl gallate. Having reviewed the data on the toxicokinetics (rate and extent of metabolism) of propyl, octyl and dodecyl gallate in the 2014 EFSA's evaluation of propyl gallate, the Panel concluded that the available metabolism data on gallates were insufficient to provide a basis for the read-across of systemic toxicity data on propyl, octyl and dodecyl gallate to be valid. Therefore, there was no longer a basis for the present group ADI and the Panel concluded that propyl, octyl and dodecyl gallate should be evaluated separately and the present group ADI should be withdrawn.

No data on genotoxicity of dodecyl gallate were available. The Panel considered that for the evaluation of the genotoxic hazard of intact dodecyl gallate, read-across from data on propyl gallate and from *in silico* expert system was scientifically justified. Therefore, based on the available *in vitro* and *in vivo* results on propyl gallate, which provide a limited evidence of genotoxicity in some *in vitro* systems and no evidence in tests *in vivo* with adequate systemic exposure, the Panel concluded that dodecyl gallate was unlikely to raise concern for genotoxicity. However, owing to the lack of detailed reports on carcinogenicity and chronic toxicity studies with dodecyl gallate and the absence of a basis for read-across for systemic toxicity from propyl gallate data, the Panel could not reach a definitive conclusion on the presence or absence of a carcinogenic potential of dodecyl gallate.

The Panel noted that there was no indication for overt toxicity in the available studies; however, owing to the limitations of these studies, the Panel was unable to identify any NOAEL. Overall, the available database was too limited to either establish an ADI or serve as a basis for a margin of safety approach to be applied with confidence.

The Panel concluded that although there was unlikely to be a safety concern from the single use for which usage and analytical data were provided, an adequate assessment of the safety of dodecyl gallate as a food additive would require a sufficient toxicological database in line with its current guidance for submission for food additives evaluations (EFSA ANS Panel, 2012).

The Panel noted that, whilst the EU specifications allow for the presence of chlorinated organic compounds, these are not identified or specified and considered that identification of possible chlorinated impurities would be needed for possible evaluation of toxicological significance. The Panel recommended that the maximum limits for the impurities of toxic elements (lead, mercury and arsenic) in the EU specifications for dodecyl gallate (E 312) should be revised to ensure that dodecyl gallate as a food additive will not be a significant source of exposure to those toxic elements in food.

[5] http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2760.pdf
[6] https://www.efsa.europa.eu/en/efsajournal/pub/4086

Overall purpose of this call for data

To give the opportunity to business operators to submit the scientific and technical data needed to address issues identified by EFSA in the re-evaluation of the safety of propyl gallate (E 310), octyl gallate (E 311) and dodecyl gallate (E 312) as food additives.

Scientific and technical data required

The data required to address the various issues identified by EFSA in the re-evaluation of the safety of propyl gallate (E 310), octyl gallate (E 311) and dodecyl gallate (E 312) as food additives are the following:

Propyl gallate (E 310)

- Data on identity and levels of chlorinated organic compounds: maximum limits for chlorinated organic compounds are laid down in the EU specifications for E 310 propyl gallate. Data on the identity and levels of these compounds is needed to assess their toxicological significance;
- Data on the lowest achievable limits for the impurities of toxic elements (arsenic, lead, and mercury): the current maximum limits for those impurities set in the EU specifications for E 310 propyl gallate are too high and therefore should be revised to ensure that food additives will not be a significant source of exposure to those toxic elements in food.

Octyl gallate (E 311)

- Toxicological data: a sufficient toxicological database in line with EFSA's current guidance for submission for food additive evaluations (EFSA ANS Panel, 2012) is required to carry out an adequate assessment of the safety of octyl gallate as a food additive in all its currently permitted uses;
- Data on identity and levels of chlorinated organic compounds: maximum limits for chlorinated organic compounds are laid down in the EU specifications for E 311 octyl gallate. Data on the identity and levels of these compounds is needed to assess their toxicological significance;
- Data on the lowest achievable limits for the impurities of toxic elements (arsenic, lead, and mercury): the current maximum limits for those impurities set in the EU specifications for E 311 octyl gallate are too high and therefore should be revised to ensure that food additives will not be a significant source of exposure to those toxic elements in food.

Dodecyl gallate (E 312)

- Toxicological data: a sufficient toxicological database in line with EFSA's current guidance for submission for food additive evaluations (EFSA ANS Panel, 2012) is required to carry out an adequate assessment of the safety of dodecyl gallate as a food additive in all its currently permitted uses;
- Data on identity and levels of chlorinated organic compounds: maximum limits for chlorinated organic compounds are laid down in the EU specifications for E 312 dodecyl gallate. Data on identity and levels of these compounds is needed to assess their toxicological significance;

- Data on the lowest achievable limits for the impurities of toxic elements (arsenic, lead, and mercury): the current maximum limits for those impurities set in the EU specifications for E 312 dodecyl gallate are too high and therefore should be revised to ensure that food additives will not be a significant source of exposure to those toxic elements in food.

As already mentioned above, EFSA's "Guidance for submission for food additive evaluations"[7] provides a description of the data requirements for the evaluation of the safety of a food additive and therefore it will be useful to clarify the nature of the data requested. Also EFSA's scientific report on "Indicative timelines for submitting additional or supplementary information to EFSA during the risk assessment process of regulated products"[8] could be useful.

Procedure of the call for data

Step 1: Registration of the contact details of business operators interested in submitting data

Business operators are requested to communicate to the Commission **by 7 July 2017** whether they are interested that propyl gallate (E 310), octyl gallate (E 311) and/or dodecyl gallate (E 312) remain permitted in the EU and therefore whether they are interested in providing the new data required. This communication should include full contact details of the business operator (name of business operator, name of contact person, postal address, telephone number and email address), as well as a clear indication of which of the requested data (including the food additive concerned) the business operator would be interested in providing. This communication should be submitted to the email address Sante-E2-Additives@ec.europa.eu.

Once the deadline for step 1 has elapsed, the Commission will make publicly available (on DG SANTE's website on food additives[9]) the list of business operators having expressed interest in submitting the data required. This aims at facilitating interactions among business operators and a possible coordinated action in the generation and submission of data.

Communication of interest to submit data would be considered as permission for the Commission to include the details of the party concerned in a list to be published online. In case a party objects to the online publication of its contact details, this should be mentioned on the first communication to the Commission.

Step 2: Confirmation of data submission, deadlines and milestones

Business operators are requested to confirm **by 30 November 2017** their intention to submit the new data required and to provide a list of the data they intend to submit, a timeline for submission of those data as well as a justification for that timeline. When appropriate, the timeline should be in line with EFSA's Scientific Report on "Indicative timelines for submitting additional or supplementary information to EFSA during the risk assessment process of regulated products". Business operators are also requested to provide a list of intermediate milestones of the data generation and when they will be achieved. This communication should be sent to the email address Sante-E2-Additives@ec.europa.eu.

The Commission will acknowledge receipt of this confirmation of data submission and will confirm the proposed timetable for data submission as well as the defined milestones and

[7] http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2760.pdf
[8] http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3553.pdf
[9] http://ec.europa.eu/food/safety/food_improvement_agents/additives/re-evaluation/index_en.htm

their time scheduling. Business operators will be requested to keep the Commission informed of the timely achievement of these milestones.

After completion of this step (step 2), the data to be submitted and both deadlines and milestones will be published on the DG SANTE's website[10].

Submission of the required data

Business operators are requested to submit the above-indicated data by the agreed deadline in one paper and two electronic copies (standard physical medium such as CD or DVD). Common electronic formats should be used (e.g. MS Office, Adobe Acrobat Reader) allowing content copying and printing (no content copy protection). The text of the files should be searchable using the search facilities of standard software packages. The submission should include a cover letter stating clearly in the subject line the food additive(s) to which it refers.

All data shall be submitted by registered post to the following contact address:

Maria Iglesia, Head of Unit E2
European Commission
Directorate-General for Health and Food Safety
Directorate E – Food and feed safety, Innovation
Unit E2 – Food Processing Technologies and Novel Foods
B-1049 Brussels

Once the new data are received, they will be submitted to EFSA for evaluation and preparation of a scientific opinion, if appropriate.

Confidential data

Business operators have the right to request a confidential treatment of certain information. They shall indicate which data they wish to be treated as confidential and give verifiable justification for each part for which a confidential treatment is required following the provisions on confidentiality as laid down in Article 12 of Regulation (EC) No 1331/2008[11]. Furthermore, the business operator shall provide the Commission with two paper and electronic versions of the dossier, namely the complete dossier and a second version of the complete dossier without confidential information.

Possibility for EFSA to use the data for the safety assessment of the same substance under other legal or regulatory frameworks

In line with Union policy objectives on animal welfare and testing on vertebrates, EFSA aims to avoid the duplication of testing on vertebrates, and to achieve an optimal use of the relevant financial and human resources by the private sector. Therefore, in anticipation of cases where EFSA may be interested in using or reusing relevant information or data (i.e. technical, toxicological data) for the evaluation of the same substance under a different legal or regulatory framework from the one mentioned above, or for the evaluation of another substance under the same or different legal framework as above, please indicate explicitly in writing, whether by participating in the voluntary submission of relevant data or information, you also give EFSA the permission to use and/or reuse these data for other EFSA safety assessments, and/or for a data sharing exercise with third parties or other international bodies.

[10] http://ec.europa.eu/food/safety/food_improvement_agents/additives/re-evaluation/index_en.htm
[11] OJ L 354, 31.12.2008, p. 1.