

Call for scientific and technical data on the permitted food additives iron oxides and hydroxides (E 172)

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Deadline for step 1 (Registration of the contact details of business operators interested in submitting data): 19 January 2017

Deadline for step 2 (Confirmation of data submission, deadlines and milestones): 19 June 2017

Background

According to Article 32 of Regulation (EC) No 1333/2008¹, 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 257/2010².

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 iron oxides and hydroxides (E 172) as food additives

The EFSA'S Panel on Food Additives and Nutrient Sources added to Food (ANS) recently delivered a scientific opinion re-evaluating the safety of iron oxides and hydroxides (E 172; yellow iron oxide (FeO(OH)·H₂O), red iron oxide (Fe₂O₃) and black iron oxide (FeO·Fe₂O₃)) when used as food

¹ OJ L 354, 31.12.2008, p. 16.

² OJ L 80, 26.3.2010, p. 19.

additives³. As these substances have different physical and chemical properties, and can be used separately, the Panel recommended that a clear differentiation (e.g. by adding a, b, c to the E number) be made between the different iron oxides and hydroxides currently all included under E172. Furthermore, the Panel noted that concentration data on yellow iron oxide, red iron oxide and black iron oxide alone would be needed for the calculation of exposure estimates for each of the three single iron oxides.

Because of the potential importance of nanoparticles in toxicokinetics and toxicological effects, the Panel considered that the particle size and particle size distribution should be included in the specifications of iron oxides and hydroxides (E 172).

The Panel considered that the maximum limits for certain toxic elements (cadmium, arsenic, lead and mercury) present as impurities in the EU specification for iron oxides and hydroxides (E 172) should be revised in order to ensure that iron oxides and hydroxides as food additives will not be a significant source of exposure to these toxic elements in foods. It is also recommended that the limit specified in the EU specifications for chromium should be for the presence of chromium(III) and absence of chromium(VI). Furthermore, nickel is permitted up to a concentration of 200 mg/kg in the food additives iron oxides and hydroxides (E 172), which could markedly increase the dietary exposure and decrease the already low margin of exposure (MOE) for nickel.

In 1980, an acceptable daily intake (ADI) of 0-0.5 mg/kg bw/day was established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Absorption of iron from iron oxides is low. The acute oral toxicity of iron oxides is greater than 10 g iron oxide/kg bw. From a subacute and a subchronic toxicity study, the Panel identified a no-observed-adverse-effect level (NOAEL) for red iron oxide of 1 000 mg/kg bw/day, the highest dose tested. Red and black iron oxide, both in nano- and micro-form, were positive in *in vitro* genotoxicity assays in mammalian cells. Due to the limitations of the database, and considering the impossibility to read-across between iron oxides with different redox state, the Panel considered that the genotoxicity of iron oxides cannot be evaluated based on the available data. Concerning carcinogenicity and reproductive and developmental toxicity, no signs of toxicity were observed in unpublished studies which were not available and could not be evaluated by the Panel. The Panel concluded that an adequate assessment of the safety of E 172 could not be carried out because a sufficient biological and toxicological database was not available. Consequently the Panel recommended that additional toxicological data should be provided on these compounds.

Refined exposure estimates show that exposure to E 172 ranged from 0.03 mg/kg bw/day for infants to 3.7 mg/kg bw/day for toddlers at the mean and from 0.1 mg/kg bw/day for infants to 9.5 mg/kg bw/day for toddlers at the 95th percentile for the non-brand-loyal scenario.

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 iron oxides and hydroxides (E 172) 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 iron oxides and hydroxides (E 172) as food additives are the following:

- Toxicological data: additional toxicological data on iron oxides and hydroxides (E 172) is needed to enable an adequate assessment of the safety of these compounds as food additives. Consequently, the minimum, Tier 1 testing according to the EFSA's "Guidance for

³ <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2015.4317/epdf>

submission for food additive evaluations”⁴, should be conducted for the material as marketed as the food additive (E 172):

- red iron oxide: *in vivo* genotoxicity at the site of contact (gastrointestinal tract) and subchronic toxicity,
 - yellow iron oxide: a complete set of genotoxicity studies and subchronic toxicity,
 - black iron oxide: ADME, *in vivo* genotoxicity and subchronic toxicity.
- Data on particle size and particle size distribution for iron oxides and hydroxides (E 172): because of their potential importance in toxicokinetics and toxicological effects, particle size and particle size distribution should be included in the specifications of iron oxides and hydroxides (E 172). The determination of particle size and particle size distribution for iron oxides and hydroxides (yellow iron oxide, red iron oxide and black iron oxide) should be performed using appropriate methodologies, and at least two independent methods, as presented in the EFSA's "Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain"⁵. The characterisation of particle size distribution should include appropriate statistical descriptors (e.g. range, median, quartiles) as well as the percentage (in number and in mass) of particles in the nanoscale (particles with at least one dimension of less than 100 nm).
 - Data on the lowest achievable limits for the impurities of toxic elements (cadmium, arsenic, lead, mercury and nickel) in iron oxides and hydroxides (E 172): the current maximum limits for those impurities in the EU specifications are too high and therefore should be revised to ensure that iron oxides and hydroxides (E 172; yellow iron oxide, red iron oxide and black iron oxide) as food additives will not be a significant source of exposure to those toxic elements in food.
 - Data on actual use levels of yellow iron oxide, red iron oxide and black iron oxide: to be able to calculate exposure estimates for each of the three substances (yellow iron oxide, red iron oxide and black iron oxide), data on their actual individual use is needed (i.e., which food categories and subcategories contain each of the three substances, the proportion of foods within categories/subcategories in which they are used, and actual use levels (typical and maximum)). If a blend of iron oxides and hydroxides is used (a product marketed as “brown iron oxide”), data on the blend composition should also be provided. Food business operators interested in submitting data on actual use levels of yellow iron oxide, red iron oxide and black iron oxide should register via the step 1 procedure of the call for data explained below. A template and further instructions for data submission will be made available to them at a later stage.

EFSA's “Guidance for submission for food additive evaluations”⁶ provides a description of the data requirements for the evaluation of the safety of a food additive and could be useful to clarify the nature of the data requested above. Also EFSA's scientific report on “Indicative timelines for submitting additional or supplementary information to EFSA during the risk assessment process of regulated products”⁷ could be useful.

All studies should be performed according to recent internationally recognised guidelines of the Organisation for Economic Co-operation and Development (OECD).

⁴ <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2760/epdf>

⁵ <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2140/epdf>

⁶ <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2760/epdf>

⁷ <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3553/epdf>

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 19 January 2017** whether they are interested that iron oxide and hydroxides (E 172) 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 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 additives⁸) 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 19 June 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 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 website⁹.

It should be noted that the requested data on actual use levels of the single iron oxides is excluded from the step 2 procedure. Consequently, the Food Business Operators which indicate in step 1 interest in submitting data on actual use levels of yellow iron oxide, red iron oxide and black iron oxide will receive a template and further instructions for data submission after the completion of step 1.

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

⁸ https://ec.europa.eu/food/safety/food_improvement_agents/additives/re-evaluation_en

⁹ https://ec.europa.eu/food/safety/food_improvement_agents/additives/re-evaluation_en

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 1331/2008¹⁰. 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 OJ L 354, 31.12.2008, p. 1.