

Call for scientific and technical data on the permitted food additive indigotine, indigo carmine (E 132)

Published: 9 March 2018

Deadline for step 1 (Registration of the contact details of business operators interested in submitting data): 13 April 2018

Deadline for step 2 (Confirmation of data submission, deadlines and milestones): 9 September 2018

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 indigotine/indigo carmine (E 132) 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 indigotine/indigo carmine (E 132) when used as a food

¹ OJ L 354, 31.12.2008, p. 16.

² OJ L 80, 26.3.2010, p. 19.

additive³. In this re-evaluation, only studies with indigo carmine and indigotine were taken into consideration, provided that the identity of the test material was clear. However, only the term indigo carmine is used in this opinion.

The Panel observed that indigo carmine was poorly absorbed and does not raise concern for genotoxicity. No adverse effects in subacute, chronic, reproduction and developmental toxicity studies, and no modifications of haematological and biological parameters in chronic toxicity studies have been identified at doses less than or equal to 500 mg/kg bw/day.

The only report of an adverse effect was in testis with a lowest observed adverse effect level (LOAEL) of 17 mg/kg bw/day which would give rise to a safety concern if confirmed. The Panel considered that this study has shortcomings since it is not clear to the Panel whether the adverse effects observed were due to the food additive itself or to impurities and/or contaminants present in the material tested and/or to the conduct of the study.

The Panel considered that the current acceptable daily intake (ADI) of 5 mg/kg bw/day for indigo carmine was applicable to a material with the same purity and manufacturing process as material used in studies without adverse effects on testis (93% pure colouring and 7% volatile matter) and concluded that any extension of this ADI to indigo carmine of lower purity and/or manufactured using a different process would require new data which would need to address the adverse effects on testis.

The Panel noted that at the maximum permitted level (MPL), exposure estimates of indigo carmine would exceed the ADI for toddlers and children at the high level. Exposure estimates using the available usage and analytical data did not show an exceedance of the ADI for any population groups.

The Panel noted that the three main contributing food categories for age-groups where MPL scenario estimates exceeded the ADI showed high number of analytical data far below MPL or had no use level reported combined with no detection in limited analytical data. The Panel therefore considered that it is not likely that the ADI will be exceeded.

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 indigotine/indigo carmine (E 132) as a food additive. Since indigotine and indigo carmine are synonyms, the more common term indigo carmine will be used in this call to refer to indigotine/indigo carmine, for simplicity.

Scientific and technical data required

The data required to address the various issues identified by EFSA in the re-evaluation of the safety of indigo carmine (E 132) as a food additive are the following:

- **Toxicological data for E 132:** According to EFSA the ADI of 5 mg/kg bw/day for indigo carmine is only applicable for indigo carmine of at least 93% purity, manufactured using the same or equivalent manufacturing process resulting in the material tested in Borzelleca *et al.* studies⁴. For an extension of this ADI to indigo carmine complying with the current EU specifications for E 132 indigo carmine (which allow for a lower purity of “not less than 85 % total colouring matters, calculated as the sodium salt”) new data addressing the adverse

³ <https://www.efsa.europa.eu/en/efsajournal/pub/3768>

⁴ Borzelleca JF and Hogan GK, 1985. Chronic toxicity/carcinogenicity study of FD&C Blue No. 2 in mice. Food and Chemical Toxicology, 23, 719-722; Borzelleca JF, Hogan GK and Koestner A, 1985. Chronic toxicity/carcinogenicity study of FD&C Blue No. 2 in rats. Food and Chemical Toxicology, 23, 551-558; Borzelleca JF, Goldenthal EI and Wazeter FX, 1986. Multigeneration study of FD&C Blue No. 2 in rats. Food and Chemical Toxicology, 24, 159-163; Borzelleca JF, Goldenthal EI, Wazeter FX and Schardein JL, 1987. Evaluation of the potential teratogenicity of FD&C Blue No. 2 in rats and rabbits. Food and Chemical Toxicology, 25, 495-497.

effects on testis observed in the Dixit and Goyal (2013) study⁵ should be generated. The chemical identity (identity and percentage of colouring matters and non-colouring components) of the tested food additive, including the presence of possible impurities and/or contaminants, should be investigated and reported. The manufacturing process of the tested food additive should also be described. In the absence of a commitment for the submission of the requested data, the specifications of E 132 indigo carmine will be amended, in line with EFSA's conclusions on the characteristics of the material to which the established ADI should apply.

- **Data on the lowest achievable limits for the impurities of toxic elements (arsenic, lead, mercury and cadmium) in E 132:** The current maximum limits for those impurities set in the EU specifications for indigo carmine (E 132) in Commission Regulation (EU) No 231/2012⁶ 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. Therefore data on the lowest achievable limits for arsenic, lead, mercury and cadmium in E 132 are requested.
- **Data on the identity of unsulphonated aromatic amines and their lowest achievable limits in E 132:** The current EU specifications for indigo carmine (E 132) allow for the presence of not more than 0,01 % unsulphonated aromatic amines (calculated as aniline). Data are requested on the identity of the unsulphonated aromatic amines present in the food additive E 132, as well as data on their individual lowest achievable limits.

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 13 April 2018** whether they are interested that indigo carmine (E 132) remains 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 additives⁹) 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.

⁵ Dixit A and Goyal RP, 2013. Evaluation of Reproductive toxicity caused by Indigo carmine on male swiss albino mice. *PharmacologyOnLine*, 1, 218–224.

⁶ OJ L 83, 22.3.2012, p. 1.

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

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 9 September 2018** 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 website¹⁰.

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, DVD or USB flash drive). 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:

Bruno Gautrais, 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 1331/2008¹¹. Furthermore, the business operator shall

¹⁰ https://ec.europa.eu/food/safety/food_improvement_agents/additives/re-evaluation_en

¹¹ OJ L 354, 31.12.2008, p. 1.

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.