Assessment of new Flavouring Substance 3-(1-((3,5-dimethylisoxazol-4-yl)methyl)-1H-pyrazol-4-yl)-1-(3-hydroxybenzyl)imidazolidine-2,4-dione

Area of research interest: Novel and non-traditional foods, additives and processes
Project status: Completed
Project code: RP 1382
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Conducted by: Food Standards Agency and Food Standards Scotland
Date published: 13 October 2022

1. Executive summary

The FSA/FSS have undertaken an assessment of application RP 1382 for the authorisation of a new flavouring substance: 3-(1-((3,5-dimethylisoxazol-4-yl)methyl)-1H-pyrazol-4-yl)-1-(3-hydroxybenzyl)imidazolidine-2,4-dione flavour modifier of the bitter taste in various food categories. An alternative name is 2,4-Imidazolidinedione, 3-[1-[(3,5-dimethyl-4-isoxazolyl)methyl]-1H-pyrazol-4-yl]-1-[(3-hydroxy phenyl) methyl (synonymous to S6821) by Firmenich Belgium SA and Firmenich (UK).

A food additive application has been received by Great Britain (GB) where the European Food Safety Authority (EFSA), prior to the end of the transition period, evaluated an application for the product. FSA/FSS has reviewed the EFSA opinion EFSA Journal 2016;14(7):4334) for this flavouring substance and confirmed that it is adequate and relevant for GB risk analysis. Therefore, the EFSA opinion was used to form the basis of the GB opinion.

The FSA/FSS risk assessors concluded that the EFSA opinion is adequate and relevant for the risk analysis and therefore accepts the EFSA conclusion that 3-(1-((3,5-dimethylisoxazol-4-yl)methyl)-1H-pyrazol-4-yl)-1-(3-hydroxybenzyl)imidazolidine-2,4-dione, as described in this application, is not expected to be of concern at the intended levels of use.

2. Background and purpose of review

EFSA Journal 2016;14(7):4334

Question number: EFSA-Q-2012-00871

In accordance with Retained EU Regulations (EC) No.1331/2008, (EC) No. 1334/2008 and No. 2232/96, the application RP 1382 for the authorisation of 3-(1-((3,5-dimethylisoxazol-4-yl)methyl)-1H-pyrazol-4-yl)-1-(3-hydroxybenzyl)imidazolidine-2,4-dione as a flavouring substance to be used as a flavour modifier of the bitter taste in various food categories, Firmenich Belgium SA and Firmenich (UK) has been submitted for authorisation in each nation of Great Britain (GB). Whilst it was a Member State of the EU, the UK accepted the assessments of the European Food Safety Authority (EFSA) in respect of authorisations for regulated food and feed products. Since the end of the transition period, FSA/FSS has adopted equivalent technical guidance and quality

assurance processes to be able to undertake GB risk assessments for regulated product applications. Where EFSA, prior to the end of the transition period, evaluated an application for a product for which an application is now made to GB, FSA/FSS has decided to make use of the EFSA risk assessment, where this is appropriate, in forming its own independent opinion. Therefore, FSA/FSS risk assessors have reviewed the EFSA opinions for the application below in the context of intended GB use and have concluded that the intended uses are safe.

In reviewing the output of the EFSA risk assessment the reviewers have verified that the standard approach as outlined in the relevant guidance has been followed and the arguments made are consistent with the data summarised. Consideration has been given to the processes undertaken by EFSA to ensure the outcome is robust and whether there are any aspects that would require further review such as specific issues for the countries of the GB The result of the assessment is that the EFSA scientific opinion is adequate GB risk analysis.

3. Details of the EFSA assessment

3.1 Methodology applied in the EFSA opinion

At the time of submission, the EFSA Guidance on the data required for the risk assessment of flavourings to be used in or on foods (EFSA CEF Panel, 2010) was used.

In Section 2.5 (Structural/Metabolic similarities in an existing Flavouring Group Evaluation) of the EFSA Opinion the CEF Panel indicated that the candidate substance has a number of structural elements common to different chemical groups listed in Annex I to Commission Regulation (EC) No 1565/2000, however EFSA noted that the structure of the substance does not allow it to be integrated in any of the existing Flavouring Group Evaluations.

Similarly, studies on its metabolism suggest that it is not transformed into substances that fit within existing Flavouring Group Evaluations; although information on the metabolic fate of the substance was incomplete.

It was concluded that, given the above and according to the EFSA CEF Guidance (2010); evaluation of the candidate substance followed the procedure for individual compounds.

3.2 Source/organism

The candidate substance is chemically synthesised. Information on the source materials has been provided to the FSA as it has been classified as confidential in the EFSA Opinion.

3.3 Genetic modification step

Not applicable.

3.4 Production process

Information on the production process has been provided and the EFSA CEF Panel concluded that the manufacturing process would not raise safety concerns. This information was classified as confidential. The Applicant has provided the full technical dossier containing this information (as submitted in the EU) to the FSA.

3.5 Specification

Information provided on the specifications of the substance are presented in the EFSA Opinion (Table 1).

No impurities were detected by HPLC (limit of detection: 0.1%). Analytical data were provided on the levels of ethanol (0.15–0.17% by weight) and ethyl acetate (0.15% by weight) in three commercial batches. No other impurities (byproducts or intermediates, reagents and solvents used in the production process) were observed.

3.6 Exposure assessment

The Applicant has provided information on the proposed Maximum Levels of use for the candidate substance in the various food categories (Appendix C of EFSA, 2016). There is an extensive list of proposed food categories therefore the full tables are not included in this document.

Based on the information provided and using the chronic added portions exposure technique (APET) estimate (EFSA CEF Panel, 2010) chronic exposures were calculated at 0.014 mg/kg bw/d in adults and 0.036 mg/kg bw/d in children from the proposed uses. The CEF Panel noted that although this flavouring is not intended to be added in foods specifically intended for infants and young children, they could be exposed to the substance from its use in general food categories.

With regards to acute exposures, and using the acute APET estimate, acute exposures were calculated at 0.12 mg/kg bw/d in adults and 0.30 mg/kg bw/d in children.

3.7 Toxicological data

Information on the absorption, distribution, metabolism and excretion of the candidate substance was provided, indicating a bioavailability following oral administration of 2-4%. The CEF Panel noted that the in vivo mass balance and metabolic fate of the compound is incomplete, thus the extent of absorption could not be estimated. In blood, mainly some conjugates and a minor number of oxidised metabolites were observed. In vitro studies with microsomes (rat and human) indicate very limited phase I metabolism of the candidate substance.

Based on information on structural alerts, in vivo and in vitro tests on both the candidate substance and its amine hydrolysis product the CEF Panel concluded that there were no concerns with regards to genotoxicity.

A 90-day systemic toxicity study in rats as well as a developmental toxicity study in rats were conducted by the applicant. For the 90-day systemic toxicity study, a No Observed Adverse Effect Level (NOAEL) of 100 mg/kg bw/d (the highest dose tested) was established (in both sexes).

From the developmental toxicity study, no differences were observed between treated and control animals therefore it was concluded that there were no concerns for developmental toxicity in rats at dose levels up to 1,000 mg/kg bw/d (highest dose tested).

4. EFSA assessment and conclusions

Based on the NOAEL from the 90 day study (100mg/kg bw/d) and the chronic APET exposure calculations presented in Section 3.5 of the current document, the EFSA CEF Panel calculated Margins of Safety of >7000 for adults and >2000 for children, concluding that there is no safety concern for the use of 3-(1-((3,5-dimethylisoxazol-4-yl)methyl)-1H-pyrazol-4-yl)-1-(3-hydroxybenzyl)imidazolidine-2,4-dione as a flavour modifier at the proposed levels of use.

5. FSA Conclusion on reliability and applicability

The application has been assessed in line with the applicable guidance. The conclusions are appropriate and consistent within the identified caveats and uncertainties outlined in the EFSA opinion and would be applicable to the GB.

6. Outcome of assessment

FSA/FSS has reviewed the EFSA opinion and consider it adequate also for GB considerations. FSA/FSS had access to the full dossier of information for the application supplied by the applicant but have used the EFSA opinion as the basis of their assessment. FSA/FSS agree with the safety conclusions outlined in the EFSA opinion.

The FSA/FSS opinion is 3-(1-((3,5-dimethylisoxazol-4-yl)methyl)-1H-pyrazol-4-yl)-1-(3-hydroxybenzyl)imidazolidine-2,4-dione, is not expected to be of concern at the intended levels of use.

7. References

EFSA CEF Panel (Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2010. Guidance on the data required for the risk assessment of flavourings to be used in or on foods. EFSA Journal 2010;8(6):1623. doi:10.2093/j.efsa.2010.1623.

EFSA CEF Panel (Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2016. Scientific opinion on Flavouring Group Evaluation 400(FGE.400): 3-(1-((3,5-dimethylisoxazol-4-yl)methyl)-1H-pyrazol-4-yl)-1-(3-hydroxybenzyl)imidazolidine-2,4-dione. EFSA Journal 2016;14(7):4334. doi: 10.2903/j.efsa.2016.4334