Comparison of the evaluations performed on sulfur dioxide-sulfites (E220-228) as food additives by EFSA and sulfur dioxide as biocide by ECHA

Joint EFSA – ECHA document December 2022

Executive Summary

In 2022, EFSA's Scientific Panel on Food Additives and Flavourings (FAF) re-assessed the safety of sulfur dioxide-sulfites (E 220-228) as food additives.
In parallel, the evaluation of sulfur dioxide as a biocidal active substance was finalised, with the adoption of two opinions by ECHA's Biocidal Products Committee (BPC) supporting the approval of sulphur dioxide for disinfection of wine barrels and for preservation of packaging.

In line with the Memorandum of Understanding and Rules of Procedure of the two agencies, the European Commission requires ECHA and EFSA to ensure consistency in their assessments and, in case of diverging views, to address the reasons for such divergence. The two agencies worked in close cooperation and put in place measures to support information sharing and to seek agreements on critical steps of their respective evaluations. They provide here jointly the conclusions regarding the alignment of their scientific evaluations.

ECHA and EFSA note that the EFSA assessment, in the context of the Food Additives Regulation, and the assessment in the context of the Biocidal Products Regulation, have been performed in agreement with their standard procedures and are consistent within their respective regulatory frameworks.

Some differences are apparent in the two assessments, mainly: partially different evidence used from open literature; different critical hazard effect considered (neurotoxic effects in food additives and mainly developmental toxicity effects in biocides); different approach for identification of a Reference Point (selection of no-observed-adverse effect level (NOAEL) in biocides and the use of the benchmark dose analysis (BMD) in food additives); different approach for the conclusion of the risk assessment (setting of an ADI with default assessment factor of 100 in biocides and using Margin of Exposure and considering a specific assessment factor of 80 in food additives). These divergences stem from different methodologies and approaches, from the timing of the open literature search and from the expert judgment of different working groups.

In spite of the differences on the approach followed for the assessments, and given the difference in the exposure to sulfur dioxide as a biocide and sulfur dioxide-sulfites (E220-228) as food additives, the outcome of the risk assessment by one agency will not change when applying the approach followed by the other agency.

1. Introduction

The European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA) are asked to cooperate and align views when they work on the same substances. The two agencies cooperate based on a Memorandum of Understanding[1]. Furthermore, ECHA and EFSA have established Rules of Procedure for their cooperation[2].

In 2022, EFSA's Scientific Panel on Food Additives and Flavourings (FAF) re-assessed the safety of sulfur dioxide-sulfites (E 220-228) as food additives following an earlier EFSA opinion on the re-evaluation of these food additives under Regulation (EC) No 257/2010. In parallel, the evaluation of sulfur dioxide as a biocidal active substance was finalised[3], following an assessment by Germany as the evaluating Member State (eCA). ECHA's Biocidal Products Committee (BPC) adopted two opinions supporting the approvals of:

- sulphur dioxide generated from sulphur by combustion as an active substance used for disinfection of wine barrels (product-type 4); and
- sulfur dioxide released from sodium metabisulfite as a preservative to prevent microbial growth in shoe boxes during storage and transport (product-type 9).

In line with the Memorandum of Understanding and Rules of Procedure of the two agencies, the European Commission requires ECHA and EFSA to ensure consistency and, in case of diverging views, to address the reasons of such divergence.

ECHA and EFSA worked in close cooperation during the evaluation of sulfur dioxide as a biocide by the German Authorities and of sulfur dioxide-sulfites as food additives by the Working Group of the EFSA FAF Panel. ECHA and representatives of the eCA participated at the EFSA FAF Panel Working Group meetings.[4] The cooperation continued during the peer review in biocides with participation of EFSA's FAF WG Panel Members at a biocides Human Health Working Group meeting. EFSA representatives also followed the discussion at the Biocidal Products Committee meeting where the ECHA opinions were adopted. ECHA participated at the FAF Panel meeting where the EFSA Opinion on sulfur dioxide-sulfites (E 220-228) as food additives was adopted.[5] Both agencies followed the development of each other's assessments by making available their draft assessments.

Following this cooperation, the two agencies provide this joint document with the ECHA/EFSA conclusions regarding the alignment of their scientific evaluations, taking account of their respective regulatory frameworks.

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[1] https://www.efsa.europa.eu/sites/default/files/assets/mouecha.pdf and https://echa.europa.eu/documents/10162/17206/echa_efsa_mou_20171129_en.pdf

[2] https://echa.europa.eu/documents/10162/17208/final_mb_30_2013_rop_efsa_echa_en.pdf

[3] The biocides evaluations started in 2013 for sulphur dioxide generated from sulphur by combustion and in 2015 for sulfur dioxide released from sodium metabisulfite.

[4] https://www.efsa.europa.eu/sites/default/files/2021-09/sulphur-dioxide-sulphites-minutes.pdf

[5] https://www.efsa.europa.eu/sites/default/files/2022-10/270922-m.pdf

2. Summary of differences

Detailed information on the differences in the assessment is presented in the Annex.

The major differences consist of:

a) Partially different datasets taken from the publicly available literature: the biocidal assessment is based on an older literature review compared to the more recent literature review of sulfur dioxide-sulfites in food additives.

b) Different critical hazard effect: neurotoxic effects in food additives and developmental toxicity effects in biocides.

c) Different Reference Point or Point of Departure identified, BMDL of 38 mg SO2 equivalents/kg bw per day in food additives and a NOAEL of 20 mg SO2 equivalents/kg bw per day in biocides.

d) A Standard Assessment Factor of 100 was used to set the ADI in biocides, whereas in food additives a specific Assessment Factor of 80 was applied for the assessment of the MOE.

e) Setting of an ADI in biocides and using MoE approach in food additives.

f) Dietary exposure assessment based only on the intended use of sulfur dioxide in biocides and calculated dietary exposure to sulfur dioxide–sulfites (E 220–228) based on reported uses and use levels and occurrence data in food.

g) Different risk characterisation: based on comparison with the ADI set in biocides and on comparison with MoEs calculated in food additives.

h) Different outcome of risk assessment: acceptable in biocides and of concern in food additives as a result of the difference in the exposure to sulfur dioxide as a biocide and sulfur dioxide-sulfites (E220-228) as food additives.

Regarding the impact of the (a)-(d) differences on the outcome of risk assessment, it is noted that using the same approach followed by EFSA in its assessment of sulfur dioxide-sulfites (E220-228) and concluded on a RP of 38 mg SO2 equivalents/kg bw per day, the MOE calculated from the chronic consumer exposure to sulfur dioxide via wine from intended PT4 use, would be higher than the EFSA assessment factor of 80. Therefore, the outcome of the risk characterisation for biocides would remain acceptable.

Similarly, had EFSA used the Reference Point of 20 mg SO2 equivalents/kg bw per day identified in the ECHA assessment and implemented the default assessment factor of 100, then the conclusion regarding the safety concern for the dietary sulfur dioxide-sulfites (E220-228) exposure scenarios would remain valid.

Thus, using the approach of one regulatory agency does not change the outcome of the risk assessment by the other agency.

3. Conclusions

ECHA and EFSA cooperated closely on their assessments of sulfur dioxide as a biocide and sulfur dioxide-sulfites (E220-228) as food additives, according to the Memorandum of Understanding and Rules of Procedure of the two agencies.

In line with their respective legislations, data requirements and guidance documents[6],[7]and the datasets available for the assessment, EFSA and ECHA performed separate evaluations with different objectives and datasets, applying differing methodologies.

ECHA and EFSA conclude that the EFSA assessment in the context of the Food Additives Regulation and the assessment in the context of the BPR have been performed in agreement with their standard procedures and are consistent within their respective regulatory framework.

ECHA and EFSA note that for better alignment of their assessments a number of actions are being discussed in the context of the chemical strategy for sustainability/One substance-one assessment in order to enable a better coordination and harmonisation in the assessments.[8]

Despite the divergencies outlined in this document, the outcome of the risk assessment by one agency will not change when applying the approach followed by the other agency.

[6] Guidance on BPR: Volume III: Human Health; Part A: information requirements, ver.2, March 2022; Parts B+C: Assessment and Evaluation, ver.4, Dec. 2017.

[7] EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2012. Guidance for submission for food additive evaluations. EFSA Journal 2012;10(7):2760. [53pp.]doi:10.2903/j.efsa.2012.2760

[8] https://echa.europa.eu/documents/10162/21877836/efsa-echa-position-paper-osoa_en.pdf/74b1ae31-290b-a608-85e9-05b340840b34

ANNEX

Differences in the assessments

ECHA and EFSA acknowledge the following main differences in their assessment:

Toxicological assessment based on a different dataset leading to differences in hazard assessment

The assessment of sulfur dioxide as a biocide was based on the dossiers submitted by applicants in:

- 2012[9] for PT4 (sulfur dioxide generated from sulfur by combustion).
- 2013[9] for PT9 (sulfur dioxide released from sodium metabisulfite)

The dataset for biocides dossiers is comprised mainly of open literature studies[10]. The literature search was adopted from the REACH registration dossier of sulfur dioxide submitted in 2010. Targeted literature searches were performed by the eCA in 2013, 2015 and 2019.

The updated assessment of sulfur dioxide-sulfites (E 220–228) as food additives was based on the data provided by IBOs and additional evidence identified in the new literature search conducted in 2022 in order to update the previous assessment of 2016. The dataset for food additives is comprised, as in biocides, mainly of studies available in the open literature, but includes a more updated database than the one considered in the biocides assessment. The more comprehensive open literature review enabled a complete re-assessment of published data. In the EFSA 2016 assessment, it was noted that numerous in vitro and animal studies reported that sulfites had a neurotoxic potential, however it was indicated that more data would be needed before a clear conclusion on the possible neurotoxic effects of sulfites could be made, when used as food additives. The new evidence from the literature search, performed by EFSA for its 2022 assessment, supports sulfite-induced neurotoxic effects (e.g. prolonged visual evoked potential - VEP latency) and justifies using data reporting prolonged VEP latency as a reference point to perform the risk assessment.

The literature review in the biocides assessment also identified neurotoxic effects in a limited number of studies but these were not regarded as suitable for setting a Point of Departure for risk assessment. Furthermore, it was concluded that potential neurotoxic effects would be covered by reference values derived in biocides. The identification of a

[9] the suflur dioxide approval as biocide was delayed due to concern for possible classification for mutagenicity which was resolved in Nov. 2021 with the RAC opinion on suflur dioxide concluding on no classification.

[10] The only proprietary studies were studies on: (i) sulfur (acute toxicity, skin/eye irritation, skin sensitisation, genotoxicity, repeated dose toxicity), (ii) sodium metabisulfite (ADME, acute toxicity, eye irritation, skin sensitisation, genotoxicity) and (iii) suflur dioxide and sulfites (genotoxicity).

reference point based on neurotoxic effects in food additives was confirmed when the peer review phase in biocides was close to finalisation and it was not possible to re-open the ECHA assessment of hazard identification.

Studies with different dose-response

In the assessment of sulfur dioxide as biocidal active substance, the following NOAEL values were identified from the developmental toxicity studies conducted with sodium bisulphite in mice and rats (Morgareidge, 1972a,b):

- 20 mg/kg bw/day for the study in mice,
- 15 mg/mg bw/day for the study in rats.

The NOAEL values were based on statistically significant increases in the number of dead foetuses and resorptions seen in the highest dose group in the absence of maternal toxicity. The additional benchmark dose (BMD) analysis of each individual study with 10% benchmark response (BMR) value, confirmed the adverse effects at the highest dose tested.

EFSA's FAF Panel re-assessed six oral prenatal developmental toxicity studies with sodium bisulfite, sodium metabisulfite and potassium metabisulfite that were conducted in 1972 and 1975 in rats and mice (FDRL (or Morgareidge) 1972a, 1972b, 1972c[11], 1972d[12], 1975a[13], 1975b[14]) and were evaluated during the re-evaluation in 2016. The EFSA FAF Panel conducted BMD analyses of the combined data for the endpoint post implantation loss from the different sulfites after conversion of the sulfite doses to SO2 equivalents and selected a BMR of 20% based on biological considerations. This BMD analysis indicated no developmental effects in the dose range tested.

The use of single study data in biocides versus combined study data in food additives along with the use of different BMR resulted in the different outcomes of the BMD analyses.

Characterisation of hazard and Assessment Factors

In the assessment of sulfur dioxide as biocide, the usual reference values, i.e. AELs, ADI and ARfD were set at 0.2 mg SO2 equivalents/kg bw/day.
The point of departure[15] (PoD) is the NOAEL of 20 mg SO2 equivalents/kg bw/day in the

[11] FDRL (Food and Drug Research Laboratories), 1972b. Teratology evaluation of FDA 71–22 in rats. FDA 71–22 (Sodium meta-bisulfite). Laboratory No. 0894 k
[12] FDRL (Food and Drug Research Laboratories), 1972d. Teratology evaluation of FDA 71–22 in mice. FDA 71–22 (Sodium meta-bisulfite). Laboratory No. 0893 k
[13] FDRL (Food and Drug Research Laboratories), 1975a. Teratology evaluation of FDA 71–21 in rats. FDA 71–20 (Potassium metabisulfite). Laboratory No. 2143
[14] FDRL (Food and Drug Research Laboratories), 1975b. Teratology evaluation of FDA 71–21 in rats. FDA 71–20 (Potassium metabisulfite). Laboratory No. 2143
[15] Or reference point (RP) under EFSA's terminology.

mouse developmental toxicity study, by oral route, with sodium bisulfite (Morgareidge 1972a). This NOAEL is supported by the similar NOAEL values of:

- 15 mg SO2 equivalents/kg bw/day from the developmental toxicity study in rats, with sodium bisulfite (Morgareidge 1972b)
- 28 mg SO2 equivalents/kg bw/d from the subchronic-chronic toxicity study in pigs, with sodium metabisulfite (Til et al., 1972a).

Notably, all the studies identified as potential PoD for the setting of reference values had limitations in their study design and reporting of results. To address the weaknesses of the dataset, it was decided to set the PoD at 20 mg SO2 equivalents/kg bw/day based on a set of NOAELs from the above-mentioned relevant studies rather one "key" study alone. The standard assessment factor of 100 was used for the inter- and intraspecies variability.

In the EFSA assessment as food additives, following a call for data from European Commission[6], no new biological and toxicological data specifically addressing the data gaps described in the re-evaluation of sulfur dioxide-sulfites (E 220–228) were received from IBOs. Following an assessment of the literature database, EFSA's FAF Panel concluded that the available toxicity database was not adequate to derive an ADI, and consequently withdrew the temporary group ADI for these food additives.

EFSA's FAF Panel considered a margin of exposure (MoE) approach appropriate to assess the risk for these food additives at the current exposure levels.

EFSA's FAF Panel considered that the new evidence from the literature search support sulfite-induced neurotoxic effects that were already noted during the re-evaluation in 2016, but at that time it was indicated that more data would be needed to reach a clear conclusion. A BMDL of 38 mg sulfur dioxide equivalents/kg bw/day, which is lower than the previous reference point of 70 mg sulfur dioxide equivalents/kg bw/day, was estimated based on prolonged VEP latency reported in the Ozturk et al. (2011) study and used as reference point to calculate the MoEs.

In line with the recommendation of EFSA's Scientific Committee,[16] in recent years, EFSA Panels use a benchmark dose (BMD) approach to identify a reference point. Biocides assessments use the NOAEL value[17]; BMDL values and MoE have been used only exceptionally, e.g. in the semi-quantitative risk assessment of genotoxic carcinogens.

Given the endpoint used for deriving a reference point and the available data, EFSA's FAF Panel considered that an overall assessment factor of 80 should be applied for the assessment of the MoE, instead of the default assessment factor of 100. Overall, EFSA's FAF Panel concluded that the MoE calculated based on the dietary exposure to sulfur dioxide-sulfites (E 220-228) as food additives should be at least 80 for no safety concern

[16] https://www.efsa.europa.eu/en/efsajournal/pub/7584
[17] The NOAEL approach is used also in pesticides assessment under Regulation 1107/2009.

to be raised.

Exposure assessment

The FAF Panel used different scenarios for the estimation of dietary exposure to sulfur dioxide-sulfites (E 220-228) from the use as food additives in line with the approach described EFSA's ANS Panel statement[18] and considering the reported use, use levels and analytical data.

In biocides assessments, the dietary assessment is only a part of the exposure assessment and only the dietary exposure resulting from the intended use is assessed. In case of sulfur dioxide PT4, dietary exposure was considered only via consumption of wine containing sulfur dioxide residues from the disinfection of wine barrels, whereas for PT9 there was no potential for residues in food and feed from the intended use for preservation of leather shoes during storage and transport.

Outcome of the dietary risk assessment

For sulfur dioxide as a biocide, the chronic dietary risk assessment is acceptable. The chronic consumer exposure via wine from intended PT4 use is well below the ADI of 0.2 mg/kg bw/day.

Moreover, the Reference Point of 20 mg/kg bw/day in biocides is almost two times lower than the BMDL of 38 mg/kg bw/day identified in food additives and therefore is protective for neurotoxic effects reported in the open literature.

For sulfur dioxide-sulfites (E 220-228) as food additives, it was noted that:

- when using the refined exposure scenario, MOEs at the maximum of the 95th percentile ranges were below 80 for all population groups except for adolescents.
- when using the maximum permitted levels scenario, MOEs were below 80 in all population groups at the maximum of the ranges of the mean, and for most of the population groups at both minimum and maximum of the ranges at the 95th percentile of exposure.

This raises a safety concern for both dietary exposure scenarios.

[18] EFSA ANS Panel (EFSA Panel on Food Additives and Nutrients Sources added to Food), 2017. Approach followed for the refined exposure assessment as part of the safety assessment of food additives under re-evaluation. EFSA Journal 2017; 15 (10): 5042, 9 pp002E