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Follow-up of the re-evaluation of sulfur dioxide (E 220), sodium sulfite (E 221), sodium bisulfite (E 222), sodium metabisulfite (E 223), potassium metabisulfite (E 224), calcium sulfite (E 226), calcium bisulfite (E 227) and potassium bisulfite (E 228)

EFSA Panel on Food Additives and Flavourings (FAF),
Maged Younes, Gabriele Aquilina, Laurence Castle, Karl-Heinz Engel, Paul J Fowler, Maria Jose Frutos Fernandez, Peter Fürst, Ursula Gundert-Remy, Rainer Gürtler, Trine Husøy, Melania Manco, Wim Mennes, Peter Moldeus, Sabina Passamonti, Romina Shah, Ine Waalkens-Berendsen, Polly Boon, Karlien Cheyns, Riccardo Crebelli, Rex FitzGerald, Claude Lambré, Manuela Mirat, Beate Ulbrich, Christiane Vleminckx, Agnieszka Mech, Ana Maria Rincon, Alexandra Tard, Zsuzsanna Horvath and Matthew Wright

Abstract

Sulfur dioxide–sulfites (E 220–228) were re-evaluated in 2016, resulting in the setting of a temporary ADI of 0.7 mg SO_2 equivalents/kg bw per day. Following a European Commission call for data, the present follow-up opinion assesses data provided by interested business operators (IBOs) and additional evidence identified in the publicly available literature. No new biological or toxicological data addressing the data gaps described in the re-evaluation were submitted by IBOs. Taking into account data identified from the literature search, the Panel concluded that there was no substantial reduction in the uncertainties previously identified in the re-evaluation. Therefore, the Panel considered that the available toxicity database was inadequate to derive an ADI and withdrew the current temporary group acceptable daily intake (ADI). A margin of exposure (MOE) approach was considered appropriate to assess the risk for these food additives. A lower confidence limit of the benchmark dose of 38 mg SO_2 equivalents/kg bw per day, which is lower than the previous reference point of 70 mg SO_2 equivalents/kg bw per day, was estimated based on prolonged visual evoked potential latency. An assessment factor of 80 was applied for the assessment of the MoE. At the estimated dietary exposures, when using a refined exposure scenario (Data set D), MOEs at the maximum of 95th percentile ranges were below 80 for all population groups except for adolescents. The dietary exposures estimated using the maximum permitted levels would result in MOEs 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. The Panel concluded that this raises a safety concern for both dietary exposure scenarios. The Panel also performed a risk assessment for toxic elements present in sulfur dioxide–sulfites (E 220–228), based on data submitted by IBOs, and concluded that the maximum limits in the EU specifications for arsenic, lead and mercury should be lowered and a maximum limit for cadmium should be introduced.

Keywords: sulfur dioxide, E 220, CAS 7446-09-5, sodium sulfite, E 221, CAS 7757-83-7, sodium bisulfite, E 222, CAS 7631-90-5, sodium metabisulfite, E 223, CAS 7681-57-4, potassium metabisulfite, E 224, CAS 16731-55-8, calcium sulfite, E 226, CAS 10257-55-3, calcium bisulfite, E 227, CAS 13780-03-5, potassium bisulfite, E 228, CAS 7773-03-7, food additive

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Correspondence: fip@efsa.europa.eu

Panel members: Maged Younes, Gabriele Aquilina, Laurence Castle, Gisela Degen, Karl-Heinz Engel, Paul J Fowler, Maria Jose Frutos Fernandez, Peter Fürst, Ursula Gundert-Remy, Rainer Gürtler, Trine Husøy, Melania Manco, Wim Mennes, Peter Moldeus, Sabina Passamonti, Romina Shah, Ine Waalkens-Berendsen and Matthew Wright.

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Summary

Sulfur dioxide–sulfites (E 220–228) were re-evaluated by the EFSA former Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) in 2016. The ANS Panel noted several uncertainties and limitations in the database and concluded that the current group acceptable daily intake (ADI) of 0.7 mg SO_2 equivalents/kg bw per day (derived using a default uncertainty factor) would remain adequate but should be considered temporary while the database was improved.

At the request of the European Commission, the EFSA Panel on Food Additives and Flavourings (FAF Panel) provides in this opinion an updated safety assessment sulfur dioxide (E 220), sodium sulfite (E 221), sodium bisulfite (E 222), sodium metabisulfite (E 223), potassium metabisulfite (E 224), calcium sulfite (E 226), calcium bisulfite (E 227) and potassium bisulfite (E 228). The Panel was also requested to assess the data provided by interested business operators (IBOs) in support of an amendment of the EU specifications for these food additives in Commission Regulation (EU) No 231/2012. The present opinion deals with the assessment of the data provided by interested business operators (IBOs) as a response to a dedicated European Commission call for data, as well as additional evidence identified in the publicly available literature.

Dietary exposure to sulfur dioxide–sulfites (E 220–228), expressed in SO_2 equivalents, was calculated using five data sets, taking into account different considerations on the available concentration data (maximum permitted levels (MPLs), reported uses and use levels and analytical data).

Data set D considered analytical data for a food category instead of use level data, even if the use levels were higher; use levels were only included in this data set for those food categories for which no analytical data were available. These results were considered to represent the level of SO_2 equivalents in final products, because they take into account losses of sulfur dioxide during processing, storage and the preparation stages. Furthermore, this data set D includes the presence of sulfur dioxide in foods and beverages due to the addition of sulfur dioxide–sulfites (E 220–228); carry-over; and other sources, such as natural occurrence. The Panel considered Data set D to most realistically represent the dietary exposure to sulfur dioxide equivalents. Furthermore, the non-brand-loyal scenario was considered the most appropriate for risk assessment of sulfur dioxide–sulfites (E 220–228), because these food additives are added to a wide range of foods, and they do not impact on taste or flavour.

In the refined non-brand-loyal exposure assessment scenario, mean dietary exposure ranged from $<$ 0.01 mg SO_2 equivalents/kg bw per day in infants to 0.32 mg SO_2 equivalents/kg bw per day in toddlers. The 95th percentile of dietary exposure ranged from 0.05 mg SO_2 equivalents/kg bw per day in infants to 1.17 mg SO_2 equivalents/kg bw per day in adults. Overall, the Panel considered that the uncertainties identified would, in general, result in an overestimation of the dietary exposure to sulfur dioxide–sulfites (E 220–228) from their use as food additives for the refined estimated exposure scenarios considering data set D.

Analytical data on arsenic, lead, cadmium and mercury in commercial samples of E 221 E 222, E 223 and E 224 were provided by three IBOs. The potential exposure to these toxic elements from the use of sulfur dioxide–sulfites (E 220-E 280) was calculated by assuming that they may be present in the food additive up to a certain limit value and then by calculation pro-rata to the estimates of exposure to the food additive itself. Since the exposure to sulfur dioxide–sulfites (E 220–228) is expressed in mg SO_2 equivalents/kg bw per day, to calculate the exposure to impurities from the use of these food additives, the Panel converted the estimates to sulfite and considered two cases: (a) Exposure was expressed as sodium metabisulfite (E 223), that was considered to be the sulfite most typically used; (b) all the exposure expressed as sodium bisulfite (E 222) which is considered to be a worse case for these calculations due to its low yield of SO_2. Data set C, taking into account use levels and analytical data, was considered the most appropriate scenario available for estimating the exposure to toxic elements from the use of these food additives.

The Panel estimated the potential exposure (i) to Pb, Hg and As based on the maximum limits specified in Regulation (EU) No 231/2012 and (ii) to Pb, Hg, Cd and As at the highest reported limit of quantification and by applying a factor of 10. For both scenarios, in particular, the lower end of the range of calculated MOE values for As was considered to be insufficient. For Pb, Hg and Cd based on the outcome of the evaluation for the typical (E 223) and worse case (E 222), the presence of these toxic elements in sulfur dioxide–sulfites (E 220-E 228) either at the current specifications limit values or at the levels selected by the Panel would not give rise to concern.

The Panel noted that the maximum limits in the EU specifications for toxic elements should be established based on actual levels in the commercial food additive. Therefore, the Panel recommended that the maximum limits to be lowered on the basis of the information provided and on the considerations of the Panel. Moreover, the Panel recommends that the European Commission considers introducing a maximum limit for cadmium for these food additives.

An extensive literature search has been performed as requested in the European Commission mandate and genotoxicity and toxicological studies retrieved in the literature search were screened and assessed for their relevance and reliability.

No new data on absorption, distribution, metabolism and excretion (ADME) or reaction products were submitted by IBOs following the European Commission call for additional data. The Panel considered that sulfites undergo high first pass metabolism after oral exposure but that systemic exposure to sulfites may be up to around a quarter of the dose. The available data show distribution of sulfites in brain following intraperitoneal administration of sodium sulfite and both brain and heart after inhalation of sulfur dioxide.

Following the European Commission call for data, no new biological and toxicological data specifically addressing the data gaps described by the ANS Panel in the re-evaluation of sulfur dioxide–sulfites (E 220–228) in 2016 were received from IBOs. In addition, only limited new data were identified from the literature search. Overall, the Panel considered that there was no substantial reduction in the uncertainties previously identified in the re-evaluation. From the literature search, there are no new data on adverse effects following oral and inhalation exposure in the area of general toxicity. However, there were consistent reports that oral sulfite administration produced adverse effects on the central nervous system (CNS) and there were reports in studies of insufficient reliability with respect to their internal validity for adverse effects on the testis at lower doses than for CNS. The use of sulfur dioxide and sulfites (sodium sulfite, sodium bisulfite, sodium metabisulfite, potassium metabisulfite, potassium bisulfite, calcium sulfite and calcium bisulfite) as food additives does not raise a concern with respect to genotoxicity. However, the Panel considered that the available toxicity database was inadequate to derive an ADI. The Panel therefore considered a margin of exposure (MOE) approach appropriate to assess the risk for these food additives at the current exposure levels.

The temporary group ADI established in 2016 was based on gastrointestinal effects in a long-term rat study with an NOAEL of 70 mg SO_2 equivalents/kg bw per day. At that time, it was also 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 support sulfite-induced neurotoxic effects (e.g. prolonged visual evoked potential (VEP) latency) which justifies using data from Ozturk et al. (2011) study.

A lower confidence limit of the benchmark dose (BMDL) of 38 mg SO_2 equivalents/kg bw per day, which is lower than the previous reference point of departure of 70 mg SO_2 equivalents/kg bw per day, was estimated based on prolonged VEP latency reported in the Ozturk et al. (2011) study and used as reference point to calculate the MOE.

In performing the quantitative extrapolation from the rat data to humans, the Panel considered whether the available data would allow modifying the default assessment factor for the MoE approach of 100. The assessment factor for the MoE considers aspects of interspecies toxicokinetics and dynamics as well as intraspecies toxicokinetics and dynamics and also the duration of the study (WHO, 2005).

Data for the toxicodynamics were available (Dyer, 1985; Otto et al., 1988), which, however, did not allow the quantification of respective interspecies differences.

Taking into account the intra-individual human variability in toxicodynamics for the specific endpoint used to derive the reference point, a reduction of the default toxicodynamic factor of 3.2–1.23 was considered, resulting in a total assessment factor of 40. Applying the additional default extrapolation factor of 2 for subchronic to chronic exposure, an overall assessment factor of 80 has been considered for the assessment of the MoE.

The Panel considered that the shortcomings in the toxicity database highlighted by the ANS Panel at the time of the 2016 re-evaluation had not led to the generation of adequate new data that could have addressed these shortcomings. Accordingly, due to the absence of new biological and toxicological data from IBOs and following an assessment of the literature database, the Panel concluded that the available toxicity database was not adequate to derive an ADI, and consequently withdraws the current temporary group ADI for these food additives.

The 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. At the estimated dietary exposure to sulfur dioxide–sulfites (E 220–228), when using the refined exposure scenario (Data set D), MOEs at the maximum of the 95th percentile ranges were below 80 for all population groups except for adolescents. The dietary exposure estimated using the maximum permitted levels would result in MOEs 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.

Table of contents