CODEX ALIMENTARIUS COMMISSION

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World Health Organization

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**Agenda Item 3(a)** **CX/FA 21/52/3 Add.1**
**April 2021**

**JOINT FAO/WHO FOOD STANDARDS PROGRAMME**

**CODEX COMMITTEE ON FOOD ADDITIVES**

**Fifty-second Session**

# MATTERS OF INTEREST ARISING FROM FAO/WHO AND FROM THE 89TH MEETING OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)

***Matters for information from the 89th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)***

The results of the 89th meeting of JECFA (virtual online platform, on 1–12 June 2020) on certain food additives will be available as follows: the meeting report (WHO Technical Report Series) and the toxicological and dietary exposure monographs (WHO Food Additive Series No 80) will be accessible through the WHO JECFA publications website: http://www.who.int/foodsafety/publications/jecfa/en/. The specification monographs resulting from the 89th JECFA meeting will be published as FAO JECFA Monographs 25, FAO, Rome, 2021. The publication will become available on the FAO JECFA website at: http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-publications/en/

**Requests for scientific advice**

1. Both organizations continue to jointly prioritize the requests for scientific advice taking into consideration the criteria proposed by Codex as well as the requests for advice from Member Countries and the availability of resources. A list of all pending requests for scientific advice by JECFA will be posted on the respective FAO and WHO websites

2. In scheduling the JECFA meetings and developing the agenda, the Joint Secretaries have to take into account the priorities requested by CCFA, CCCF, and CCRVDF. Due to the increasing requests for scientific advice to JECFA, not all requests can be addressed in the subsequent meeting. In prioritizing the work, the JECFA Secretariat takes into account existing criteria, on-going Codex work and available resources.

3. To facilitate provision of extra-budgetary financial and human resources for scientific advice activities, please contact Dr Markus Lipp, FAO Food Safety and Quality Unit (jecfa@fao.org) and Kim Petersen, Department of Nutrition and Food Safety, WHO (jecfa@who.int).

***Procedural matters***

4. The 89th meeting of JECFA was originally scheduled for 2–11 June 2020 at WHO headquarters in Geneva, Switzerland. Because of the travel restrictions and lock-downs due to the COVID-19 pandemic in many countries, the joint FAO/WHO JECFA secretariat was unable to convene the meeting as scheduled. Therefore, the meeting was held as a video-conference. In view of the countries of origin of the invited experts, the only possible time for a video-conference was restricted to a 4-h time slot (12:00–16:00 CET) a day. This allowed approximately 40% of the usual daily time (8–10 h) of a JECFA 8-day face-to-face meeting.

5. As under the circumstances less meeting time had been available, compared to an normal JECFA meeting, the food additives nisin (INS 234), natamycin (INS 235), β-glucanase from *Streptomyces violaceoruber* expressed in *S. violaceoruber*, collagenase from *S. violaceoruber* expressed in *S. violaceoruber*, phosphodiesterase from *Penicillium citrinum* and phospholipase A2 from *S. violaceoruber* expressed in *S.* violaceoruber, which were originally scheduled for discussion, had therefore not been considered.

6. Furthermore, it became quickly apparent early in the meeting that the experts of the 89th JECFA would not have been able to complete the evaluations for alicyclic ketones, secondary alcohols and related esters and a toxicological evaluation of riboflavin from *Ashbya gossypii*. Therefore, these two evaluations have also been deleted from the meeting agenda. All compounds that had been deleted from the agenda of the 89th JECFA meeting will be re-scheduled for evaluation at future JECFA meetings.

***Actions required as a result of changes in acceptable daily intake (ADI) status and other toxicological recommendations from JECFA***

7. At its 89th meeting, JECFA evaluated the safety of six food additives, and conducted an exposure assessment for one group of food additives. Toxicological recommendations or other scientific advice for these food additives are provided in the attached Table 1 and Table 2 (exposure assessment). CCFA52 **is invited** to consider the recommended actions (presented in Table 1 and Table 2) which might be required following the evaluations of these food additives.

8. At its 89th meeting, JECFA also evaluated the safety of 13 flavouring agents using the revised Procedure for the Safety Evaluation of Flavouring Agents. The results of the evaluations are summarized in the attached Table 3.

9. At its 89th meeting, JECFA noted when evaluating lipase from *Mucor javanicus* that the specifications for lipase from *Aspergillus oryzae, var.* had been withdrawn by JECFA at its 55th meeting but that it had not addressed the consequences of the withdrawal of specifications on its acceptable daily intake (ADI). At its 89th meeting, JECFA decided to withdraw the ADI "not specified" for lipase from *Aspergillus oryzae,* var.

10. At its 89th meeting, JECFA noted that specifications for other food additives had been withdrawn at the 55th meeting without addressing the consequences for the respective ADIs. At its 89th meeting, JECFA recommends reconsideration of the ADIs concerned at a future meeting.

11. At its 89th meeting, JECFA recommend that a new call for data be issued in order to proceed with an updated safety evaluation and specifications for the five sorbitan esters of fatty acids (INS 491, INS 492, INS 493, INS 494, and INS 495) at the same time.

12. At its 89th meeting, JECFA noted that five polyoxyethylene sorbitan esters (polysorbates) were evaluated by JECFA at its 17th meeting and specifications were established. JECFA at its 89th meeting recommends that a new call for data be issued for their full evaluation.

***Update of guidance on evaluation of genotoxicity of chemical substances in food (section 4.5 of EHC 240)***

13. At its 89th meeting, JECFA was informed about activities of a joint FAO/WHO expert working group established in 2018 to update and extend the guidance on evaluation of genotoxicity of chemical substances in food. Since the last update provided to JECFA in June 2019, a draft of the section was sent for public consultation in December 2019. In response, the Secretariat received about 300 comments from 14 organizations or individuals, indicating a high level of interest. The comments included many helpful suggestions for further revision and clarification of the text. The comments have now been considered and addressed, and the draft has been updated.

14. Following the discussion of the guidance on genotoxicity of chemical substances in food at the 89th JECFA meeting, the updated guideline has been finalized and published on WHO homepage (Section 4.5. Genotoxicity: https://www.who.int/docs/default-source/food-safety/publications/section4-5-genotoxicity.pdf?sfvrsn=8ec3434_2

***Update of guidance on dose–response assessment and derivation of health-based guidance values (Chapter 5 of EHC 240)***

15. At its 89th meeting, JECFA was informed about the progress made by an expert working group established in 2017 with the aim to update and extend the guidance on dose–response assessment and derivation of health-based guidance values. This activity is being undertaken within the context of a joint FAO/WHO project to update various chapters of EHC 240.

16. At its 89th meeting, JECFA was informed that since the last update in June 2019, the revision of Chapter 5 of EHC 240, on dose–response assessment and derivation of health-based guidance values, has continued, and a draft of the chapter was sent for public consultation in December 2019. In response, the Secretariat received about 300 comments from 14 organizations or individuals, indicating a high level of interest. The comments included many helpful suggestions for further revision and clarification of the text. The comments have now been considered and addressed and the updated Chapter 5 is in the publication phase.

***Update of guidance on evaluation of enzyme preparations (EHC 240)***

17. At its 89th meeting, JECFA was given an update on progress made in revising guidance on the evaluation of enzymes for use in food. An expert working group was established in 2018 to discuss the available information on the safety of enzymes used in food and current practices of the food enzyme industry. Several documents and definitions were amended and submitted for public comment late in 2019. The comments received were evaluated, and the text of a revised version of Section 9.1.4.2 of EHC 240 was edited further as necessary.

18. The working group made a series of recommendations to JECFA, which came to the following consensus:

*1a.* At its 89th meeting, JECFA adopted the proposed definitions of "safe food enzyme production strain" and "presumed safe progeny strain" (Annex 2) with minor editorial changes.

*1b.* At its 89th meeting, JECFA adopted the proposed revisions to Chapter 9.1.4.2 of EHC 240 pertaining to enzymes, including a revision of the classification of enzymes and their definitions. The text for Class I Type iii and Class II enzymes was modified to state that "an ADI may be established."

*1c*. At its 89th meeting, JECFA approved the proposed checklist of data requirements for the risk assessment of enzyme preparations in submissions for review by JECFA, with a change to one of the test requirements. JECFA debated the value of including on the checklist a request for information on "Bioinformatic analysis of the amino acid sequence for potential matches with known toxins" (checklist item #29). JECFA decided that it should remain on the checklist, and the usefulness of such information should be evaluated once sufficient experience has been gained.

*1d.* At its 89th meeting, JECFA adopted the proposed list of terms and definitions related to submissions on enzyme preparations for use in food and added a definition of "total organic solids".

*2.* At its 89th meeting, JECFA recommended that allergenicity should be assessed only for enzyme preparations proposed for inclusion in Class I Type iii or Class II.

*3*. At its 89th meeting, JECFA debated whether it would be appropriate to combine consideration of immobilized enzyme preparations that are in contact with foods only during processing with consideration of enzyme preparations added to foods but removed from the final products. Differing points of view were expressed, and JECFA was reminded that such consideration did not apply to other situations in which food-grade carriers and formulation ingredients are used. Furthermore, JECFA considered that the levels of residues of immobilizing agents in the final product would be extremely low; the levels of these substances or their contaminants permitted in the final product should be at the lowest levels that are technologically feasible. JECFA decided that the wider issue of food contact materials was not one of their current terms of reference, and their Summary report of the eighty-ninth meeting of JECFA JECFA/89/SC 10 consideration would have to be initiated by the Codex Alimentarius Commission or others before it could be taken up.

*4*. At its 89th meeting, JECFA supported establishment of a separate online database for toxicological data and specifications for enzyme preparations for use in food evaluated by JECFA in order to simplify presentation of the data to users (similar to that currently used for flavourings).

*5*. At its 89th meeting, JECFA supported establishment of a separate JECFA numbering system for identifying enzyme preparations for which JECFA had completed safety evaluations (similar to that used for flavourings).

*6.* At its 89th meeting, JECFA supported development of an enzyme-specific template for the submission of information on analytical methods, including method performance characteristics (method validation data) and quality control data.

19. Following the discussion of the guidance on evaluation of enzymes at the 89th JECFA meeting, the updated guideline has been finalized and published on WHO homepage (Section 9.1.4.2. Enzymes: https://www.who.int/docs/default-source/food-safety/publications/section9-1-4-2-enzymes.pdf?sfvrsn=e238e86e_2)

**Table 1. Food additives evaluated toxicologically and/or considered for specifications at the 89th JECFA meeting**

| INS Number | Food additive | Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information | Recommended action by CCFA |
|---|---|---|---|
| | Adenosine 5´-monophosphate deaminase from *Streptomyces murinus* | The 89th JECFA concluded that the **adenosine 5´-monophosphate (AMP) deaminase from *Streptomyces murinus* would not pose a health concern** when used in the applications specified, at the levels specified and in accordance with good manufacturing practice**.**<br><br>The 89th JECFA noted that negative results were observed in genotoxicity tests, and a NOAEL of 500 mg/kg bw per day (equal to 69 mg TOS/kg bw per day) was identified in a 13-week oral toxicity study. Comparison of the dietary exposure estimate of 0.075 mg TOS/kg bw per day with the NOAEL of 69 mg TOS/kg bw per day gives a margin of exposure (MOE) of 920.<br><br>New specifications and a Chemical and Technical Assessment were prepared. | Note the JECFA conclusion that the use of AMP deaminase from *Streptomyces murinus* would not pose a health concern.<br><br>Note the new JECFA specifications for AMP deaminase from *Streptomyces murinus* (see CX/FA 21/52/4 Add.1). |
| | D-Allulose 3-epimerase from *Arthrobacter globiformis* expressed in *Escherichia coli* | The 89th JECFA established an **ADI "not specified" for D-allulose 3-epimerase from *A. globiformis* M30 expressed in E. coli** K-12 W3110 when the enzyme is used in the applications specified, at the levels specified and in accordance with good manufacturing practice.<br><br>The 89th JECFA considered the negative results observed with D-allulose in genotoxicity tests. A NOAEL of 1100 mg TOS/kg bw per day was identified, the highest dose tested, in a short-term (90-day) oral toxicity study in rats. When the dietary exposure estimate for the highest consumers (90th percentile for infants and children) of 0.38 mg TOS/kg bw per day was compared with the NOAEL of 1100 mg TOS/kg bw per day, an MOE of nearly 3000 was calculated.<br><br>New specifications and a Chemical and Technical Assessment were prepared. | Note that JECFA established an ADI "not specified" for D-allulose 3-epimerase from *A. globiformis.*<br><br>Note the new JECFA specifications for AMP deaminase from *Streptomyces murinus* (see CX/FA 21/52/4 Add.1). |
| | Carbohydrate-derived fulvic acid (CHD-FA) | The 89th JECFA concluded that **the available data are inadequate for an evaluation of the safety of CHD-FA**.<br><br>Given the deficiencies of the toxicological database, JECFA recommends that the following studies be conducted. The test protocols should be in accordance with the relevant current guidelines, and the test materials should be well characterized in relation to the article(s) of commerce:<br><br>• absorption, distribution, metabolism and excretion;<br><br>• repeated-dose 90-day oral toxicity in rodents; • two-generation reproductive toxicity or extended one-generation reproductive toxicity;<br><br>• prenatal developmental toxicity; | Note that JECFA concluded that the available data are inadequate for an evaluation of the safety of CHD-FA.<br><br>Note the JECFA recommendation for additional toxicological studies.<br><br>Note that JECFA concluded that the chemical and technical information was insufficient to prepare specifications for CHD-FA. |

| INS Number | Food additive | Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information | Recommended action by CCFA |
|---|---|---|---|
| | | • additional studies, including an in vitro micronucleus test in mammalian cells, might be required, depending on elucidation of the article(s) of commerce and the provision of full information on their composition; and<br>• information on the potential of the material to induce antimicrobial resistance. In addition, use levels should be provided for estimating dietary exposure.<br>The 89th JECFA assessed the chemical and technical information received and concluded that there **was insufficient information to prepare specifications for CHD-FA.**<br>The 89th JECFA required data to characterize the products of commerce in order to evaluate the product for use as a preservative. The required information includes a detailed description of the manufacturing processes and thorough chemical characterization of the commercial products. The following information is required:<br>• the full composition of the products;<br>• a detailed description of the manufacturing process;<br>• analytical methods and data on method validation; and<br>• analytical data for five non-consecutive batches of commercial products, including information on impurities.<br>The 89th JECFA encouraged sponsors to offer a rationale for whether a single monograph covering all products or individual monographs should be prepared. | Note the JECFA request for data on manufacturing processes and thorough chemical characterization of the commercial products. |
| | Jagua (genipin-glycine) blue (Jagua blue) | The 89th JECFA **established an ADI of 0–11 mg/kg bw for Jagua blue, on a blue-polymer basis.** This ADI was based on the absence of treatment-related long-term toxicity and of reproductive and developmental toxicity in the 12-month rat dietary study with in-utero exposure, in which the NOAEL was identified as 1127 mg/kg bw per day of the blue polymer, the highest dose tested. The ADI was established by applying an uncertainty factor of 100 to the NOAEL.<br>The 89th JECFA considered that the new toxicological data and additional characterization of the test compound provided adequate information for completing the safety evaluation of Jagua blue. The new 12-month study of rats exposed in utero was conducted for a longer exposure time and at higher doses of Jagua blue, as recommended by JECFA at its 84th meeting.<br>The 89th JECFA noted that although no new toxicokinetics study was available, newly developed analytical methods for the dimers | Note that JECFA established an ADI of 0–11 mg/kg bw for Jagua blue, on a blue-polymer basis. |

| INS Number | Food additive | Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information | Recommended action by CCFA |
|---|---|---|---|
| | | provided acceptable characterization of the test article, thus reducing the uncertainty of the safety assessment due to limited biochemical information.<br><br>The 89th JECFA noted that the upper end of the high-level dietary exposure estimate for Jagua blue, on a blue-polymer basis, for infants and toddlers of 11.5 mg/kg bw per day is in the region of the upper bound of the ADI. In view of the conservative nature of the dietary exposure assessments, in which it was assumed that all foods contained Jagua blue on a blue-polymer basis at the maximum use level, and because the ADI was based on a NOAEL that was the highest dose tested, JECFA concluded that the estimated dietary exposure to Jagua blue, on a blue-polymer basis, does not represent a health concern.<br><br>The existing specifications for Jagua (genipin-glycine) blue (Jagua blue) were revised. A Chemical and Technical Assessment was prepared. | Note that JECFA noted that the upper end of the high-level dietary exposure estimate for Jagua blue, for infants and toddlers is in the region of the upper bound of the ADI. However, JECFA noted that in view of the conservative nature of the dietary exposure assessments the estimated dietary exposure to Jagua blue, does not represent a health concern.<br><br>Note the existing specifications for Jagua (genipin-glycine) blue (Jagua blue) extract were revised (see CX/FA 21/52/4 Add.1). |
| | Lipase from *Mucor javanicus* | The 89th JECFA established an **ADI "not specified" for the lipase enzyme preparation from *M. javanicus*,** used in the applications specified and in accordance with good manufacturing practice.<br><br>The 89th JECFA noted negative results were obtained in genotoxicity tests, and no treatment-related adverse effects were seen at the highest dose tested (800 mg TOS/kg bw per day) in a 13-week study of oral toxicity in rats. A comparison of the estimated dietary exposure of 0.84 mg TOS/kg bw per day with the highest dose tested of 800 mg TOS/kg bw per day gives an MOE of at least 900.<br><br>New specifications and a Chemical and Technical Assessment were prepared. | Note that JECFA established an ADI "not specified" for the lipase enzyme preparation from *M. javanicus.*<br><br>Note the new JECFA specifications for lipase from *Mucor javanicus* (see CX/FA 21/52/4 Add.1). |
| | Phosphatidylinositolspecific phospholipase C expressed in *Pseudomonas fluorescens* (PI-PLC) | The 89th JECFA established an **ADI "not specified" for the PI-PLC enzyme preparation expressed in *P. fluorescens*,** used in the applications specified and in accordance with good manufacturing practice.<br><br>The 89th JECFA noted negative results were obtained in genotoxicity tests, and no treatment-related adverse effects were seen with PI-PLC enzyme concentrate at the highest dose tested (1871 mg TOS/kg bw per day) in the 13-week study of oral toxicity in rats. A comparison of the highest estimated dietary exposure of 0.01 mg TOS/kg bw per day with the highest dose tested of 1871 mg TOS/kg bw per day gives an MOE of at least 187 100. | Note that JECFA established an ADI "not specified" for the PI-PLC enzyme preparation expressed in *P. fluorescens*.<br><br>Note the new JECFA specifications for phosphatidylinositolspecific phospholipase C expressed in *Pseudomonas fluorescens* (PI-PLC) (see CX/FA 21/52/4 Add.1). |

| INS Number | Food additive | Acceptable daily intakes (ADIs) and other toxicological or safety recommendations and dietary exposure information | Recommended action by CCFA |
|---|---|---|---|
| | | New specifications and a Chemical and Technical Assessment were prepared. | |
| | Riboflavin from *Ashbya gossypii* | The 89th JECFA **assessments of safety and dietary exposure were not completed due to time constraints.**<br><br>The 89th JECFA drafted a chemical and technical assessment and new specifications for riboflavin from *A. gossypii* from the data submitted by the sponsor but did not finalize them for publication.<br><br>The 89th JECFA recognized the benefits of simultaneous review and harmonization of new specifications with existing specifications for riboflavin as a synthetic product and as a product of *B. subtilis* and recommended that this work be undertaken at a future meeting. | Note that JECFA has postponed the evaluation of riboflavin from *Ashbya gossypii.* |

**Table 2. Food additives assessed only for dietary exposure at the 89th JECFA meeting**

| INS Number | Food additive | Dietary exposure information | Recommended action by CCFA |
|---|---|---|---|
| 473<br>473a | Sucrose esters of fatty acids (INS 473) (SEFs) and sucrose oligoesters type I and type II (INS 473a) (SOEs) | **The 89th JECFA considered that more refined dietary exposure estimates should be provided.**<br><br>At its 49th meeting, the JECFA established a group ADI of 0–30 mg/kg bw for SEFs and sucroglycerides on the basis of their potential to induce laxative effects in adult volunteers at doses > 30 mg/kg bw per day, without applying an uncertainty factor. At its 71st meeting, JECFA noted that some of the components of SEFs may be present in significant amounts in SOEs and established a group ADI of 0–30 mg/kg bw for SEFs, SOEs and sucroglycerides.<br><br>At its 89th meeting, JECFA noted the high dietary exposure estimate of the sum of SEFs and SOEs of 113 mg/kg bw per day for children aged 3–9 years exceeds the group ADI of 0–30 mg/kg bw per day by a factor of about 4. JECFA also noted that the dietary exposure estimates for some other age groups also exceeded the ADI. JECFA noted that the high dietary exposure estimates are conservative, predominantly due to the assumptions that<br><br>• all foods that could contain SOEs and SEFs do in fact contain these food additives, whereas other food additives with the same functions in foods are available; and<br><br>• when SEFs or SOEs are used, they are always present at the reported use levels.<br><br>Therefore, JECFA considered at its 89th meeting that more refined dietary exposure estimates | Note that JECFA considered that more refined dietary exposure estimates should be provided.<br><br>Note that JECFA requests data in order to refine the dietary exposure estimates.<br><br>Note the JECFA deadline of 2 years for submitting refined data on use and use levels. |

| INS Number | Food additive | Dietary exposure information | Recommended action by CCFA |
|---|---|---|---|
| | | should be provided. To refine the dietary exposure estimates of SEFs and SOEs, either alone or summed, JECFA recommends that sponsors submit information on:<br>• typical or mean and high use levels for foods in which the food additives are used; and<br>• foods (or food categories) in which the use of SEFs and/or SOEs is permitted but in which they are never used.<br>In both cases, the information should be as specific as possible, and the foods should be classified according to the FoodEx2 classification system, which is that used for the CIFOCOss and GIFT food consumption databases, or another appropriate system.<br>The 89th JECFA noted that it did not use the CIFOCOss and GIFT databases to assess dietary exposure to SEFs and SOEs, partly because calculations of exposure would have been laborious in view of the number of broad food categories for which use levels were provided. In order to use these data for dietary exposure assessment of food additives that are present in large numbers of food categories, a table should be developed to map the foods recorded in both databases according to the FoodEx2 classification to the food categories of the GSFA. That will also ensure that mapping is consistent for all meetings.<br>The 89th JECFA recommends that more detailed information on the use of SEFs and SOEs in foods and a mapping table be made available within 2 years. | |

**Table 3. Flavouring agents evaluated at the 89th JECFA meeting**

The flavouring agents were evaluated by the revised Procedure for the Safety Evaluation of Flavouring Agents.

***A. Amino acids and related substances***

| Flavouring agent | No. | Specifications | Conclusion based on current estimated dietary exposure |
|---|---|---|---|
| **Structural class I** | | | |
| Betaine | 2265 | N | No safety concern |
| *N*-Acetyl-glutamate | 2269 | N | No safety concern |
| L-Cysteine methyl ester hydrochloride | 2270 | N | No safety concern |
| Glutamyl-2-aminobutyric acid | 2266 | N | No safety concern |
| Glutamyl-norvaline | 2268 | N | No safety concern |
| Glutamyl-norvalyl-glycine | 2267 | N | No safety concern |

***B. Phenol and phenol derivatives***

| Flavouring agent | No. | Specifications | Conclusion based on current estimated dietary exposure |
|---|---|---|---|
| **Structural class I** | | | |
| (±)-Homoeriodictyol sodium salt | 2256 | N | No safety concern |
| (±)-Naringenin | 2257 | N | No safety concern |
| (2*R*)-3´,5-Dihydroxy-4´-methoxyflavanone | 2258 | N | No safety concern |
| 7,8-Dihydroxyflavone | 2259 | N | No safety concern |
| (2*S*)-3´,7-Dihydroxy-8-methyl-4´-methoxyflavan | 2260 | N | Genotoxicity data for (2*S*)-3´,7-Dihydroxy-8-methyl-4´-methoxyflavan raise concerns for potential genotoxicity |
| (*R*)-5-Hydroxy-4-(4´-hydroxy-3´-methoxyphenyl)-7-methylchroman-2-one | 2261 | N | No safety concern |
| 3-(3-Hydroxy-4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl)propan-1-one | 2262 | N | No safety concern |