



European Food Safety Authority

Public consultation on Draft EFSA statement “Genotoxicity assessment of chemical mixtures”

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General Information

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Public consultation on EFSA Statement on "Genotoxicity assessment of chemical mixtures"

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General comments

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The Council for Responsible Nutrition (CRN), the leading trade association that represents dietary supplement and functional food manufacturers and ingredient suppliers in the United States, appreciates the opportunity to provide input on the draft EFSA statement, "Genotoxicity assessment of chemical mixtures." Many CRN members market foods and/or food supplements in the EU, including botanical mixtures such as powders, tinctures, and extracts. Therefore, our perspectives on this issue are relevant. Many food supplements contain ingredients derived from foods, such as fruits, vegetables, herbs, spices, and other plants that have undergone safety testing in line with expected human exposure. We are concerned that the overly simplistic extrapolation from one (or more) compound(s) within a mixture to make a judgement on the genotoxicity of the entire mixture without reviewing the context of other relevant data such that the weight of evidence is fully considered.

For example, the very common and widely-consumed green vegetable, broccoli (*Brassica oleracea* var. *italica*) is touted as a health-promoting and in many cases a disease-preventing desirable addition to our diet. However, when intrinsic constituents are isolated and tested, for example, indole carbinol and allyl isothiocyanate, they are found to be potent mutagens. Allyl isothiocyanate is also found in many other common foods, notably cabbage, cauliflower, Brussels sprouts, mustard, and horseradish. Two other mutagens that are found in a large variety of fruits and vegetables are caffeic acid and chlorogenic acid, yet the foods they are found in are plentiful and recommended by our regulatory agencies as a major part of a healthy diet and include fruits, such as apples, grapes, cherries, peaches, pears, apricots, and plums, and the vegetables, carrots, celery, eggplant, lettuce, potatoes, and at even much higher concentrations in herbs and spices such as anise, basil, caraway, dill, rosemary, sage, and thyme. All of these concentrations are dwarfed by the concentrations of these two acids in roasted coffee beans (*Coffea arabica*), which are used to make a beverage that is widely consumed and associated with many health benefits including lower risks for metabolic syndrome, diabetes, and some types of cancer. As such, even though the offending substance may be present in appreciable levels within a mixture, the overall mixture may not be genotoxic. Therefore, positive genotoxicity data must be ameliorated by considerations of the concentration of the offending constituent within a mixture, the matrix in which the constituent is contained, and the potential anti-genotoxic constituents within the same mixture. All of these factors may impact whether the whole mixture is genotoxic. It is important to note that when a compound(s) is found to be positive (or negative) when tested in a validated in vitro or in vivo test system, that it needs to be made clear that the compound is positive (or negative) under the experimental conditions used. This may explain why at times the same compound(s) are reported in the literature as positive, negative, and equivocal, as the sensitivity of the test system, as well as the overt and subliminal variances of the procedure and/or the experimenter may influence the test results. Therefore, when assessing genotoxicity data to inform human risk assessment, it is necessary to consider the data in the context of other available information, including toxicokinetics, mechanism of action, and exposure, and evaluate the totality of evidence.

REFERENCES ARE IN THE ATTACHED

Abstract

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Abstract

Please see our comments regarding Sections 2.2 and 2.3, and modify the relevant parts of the Abstract accordingly.

2. Assessment

- 2.1. Chemical characterisation of simple and complex mixtures
- 2.1.1. Qualitative and quantitative analysis of the composition of a mixture
- 2.2. Genotoxicity assessment of fully characterised mixtures
- 2.3. Genotoxicity assessment of mixtures containing a substantial fraction of unidentified components

2.2. Genotoxicity assessment of fully characterised mixtures

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2.2 Genotoxicity assessment of fully characterised mixtures

p. 6 lines 130-132: "If such a mixture contains one or more substances that are assessed to be genotoxic in vivo via a relevant route of administration (i.e. in most cases after oral exposure), the whole mixture has to be considered as genotoxic." Whether the whole mixture is genotoxic may depend on the concentration of the substance(s) in the whole mixture. For example, caffeic acid is found in the aforementioned fruits and vegetables at levels of 50-200 ppm, as well as in spices and herbs at concentrations greater than 1000 ppm. The overall composition of the mixture should also be considered. CRN recommends that lines 130-132 be modified as follows: "If such a mixture contains one or more substances that are assessed to be genotoxic in vivo via a relevant route of administration (i.e. in most cases after oral exposure), additional data may be needed to assess the genotoxicity of the whole mixture."

p. 6 lines 133-141: "For mixtures that contain individual components that may indicate a concern for genotoxicity but for which the data available are not sufficient to conclude on genotoxicity, e.g. only positive results in in vitro genotoxicity tests of an individual component, additional data would be needed to complete an assessment. "For a mixture that contains a large number of substances with positive results in in vitro genotoxicity tests, the whole mixture could be considered as genotoxic as in vivo follow-up testing of a large number of substances is likely to result in one or more positive outcomes. If nevertheless further in vivo follow-up testing is considered, testing of a specific fraction of the mixture containing these substances may be considered on a case-by-case basis." Whether one or more components of a mixture indicate a concern for genotoxicity based on positive results in in vitro genotoxicity testing, additional analysis and/or data may be needed to assess whether the overall mixture is genotoxic. Further, the meaning of "a large number of substances" in line 137 is unclear and subject to interpretation. In addition to the number of substances with positive results in in vitro genotoxicity testing, other factors such as the concentration of substances with positive results within a mixture should be considered when assessing the potential genotoxicity of the overall mixture. Therefore, CRN recommends that lines 133-141 be modified as follows: "For mixtures that contain components that may indicate a concern for genotoxicity but for which the data available are not sufficient to conclude on genotoxicity, e.g. only positive results in in vitro genotoxicity test of individual components, additional analysis and/or data would be needed to complete an assessment. Factors to consider when assessing the potential genotoxicity of the mixture include the number and concentration of substances with positive results. If in vivo follow-up testing is considered, testing of a specific fraction of the mixture containing these substances may be considered on a case-by-case basis."

p. 7 line 159: "Circumstances under which these criteria are met are expected to be rare." CRN recommends that this sentence be removed because there are likely many circumstances under which the criteria described in the paragraph (p.7 lines 156-158) are met.

p. 7 lines 160-162: "If a mixture is known to contain more than one genotoxicant, both the Margin of Exposure (EFSA 2005, 2012a) and TTC approaches could potentially be applied, using the default assumption of dose addition as they would share the same mode of action (e.g. DNA reactivity)." It may not always be appropriate to assume dose addition for mixtures that contain more than one genotoxicant because genotoxic carcinogens have very different target organs. Therefore, they should not be added together unless there is evidence to support a common target organ and mode of action that are truly additive. CRN recommends that the sentence be modified as follows: "If a mixture is known to contain more than one genotoxicant, both the Margin of Exposure (EFSA 2005, 2012a) and TTC approaches could potentially be applied, using dose addition if they share the same mode of action (e.g. DNA reactivity) and target organ."

2.3. Genotoxicity assessment of mixtures containing a substantial fraction of unidentified components

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2.3 Genotoxicity assessment of mixtures containing a substantial fraction of unidentified components
p. 7, lines 186-188: The section title refers to a “substantial fraction of unidentified components” and the text refers to a “substantial fraction of compounds that have not been chemically identified.” The accompanying footnote indicates that a general definition of ‘substantial’ is not possible. We agree that a general definition of ‘substantial’ is not possible. Therefore, this term should be removed from both the section title and text.

p. 8, lines 194-196: “As described in Chapter 2.2, if the mixture contains one or more substances that are evaluated to be genotoxic in vivo via a relevant route of administration, the whole mixture raises concern regarding genotoxicity.”

Please see our comments regarding Section 2.2, p. 6, lines 130-132.

3. Conclusions

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3. Conclusions

Please see our comments regarding Sections 2.2 and 2.3, and modify the relevant parts of the Conclusions accordingly.

References

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Pottenger LH, Bus JS, Gollapudi BB. (2007) Genetic toxicity assessment: employing the best science for human safety evaluation part VI: when salt and sugar and vegetables are positive, how can genotoxicity data serve to inform risk assessment? Toxicol Sci. 2007 Aug;98(2):327-31. Epub 2007 Mar 25.

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Background Documents

[Privacy Statement on PC on Draft Statement on Genotoxicity Assessment of Chemical Mixtures.pdf](#)

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