SCIENTIFIC OPINION

Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities\(^1\) which are both genotoxic and carcinogenic in substances added to food/feed\(^2\)

EFSA Scientific Committee\(^3,4\)

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ABSTRACT

Following a request from EFSA, the Scientific Committee was asked to deliver a statement on the applicability of the margin of exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food or feed. The Scientific Committee acknowledges that analytical methodology is continually improving, and an increasing number of impurities, including some substances which are both genotoxic and carcinogenic, can be detected at low levels in, for example, food/feed additives or food contact materials. As a result it can be foreseen that these impurities may end up in food, including products from animal origin.

The Scientific Committee is of the opinion that the MOE approach can be applied to impurities which are both genotoxic and carcinogenic, irrespective of their origin. The Scientific Committee reiterates its view expressed in 2005\(^5\) that in general a margin of exposure of 10,000 or higher, if it is based on the BMDL10 from an animal study, and taking into account overall uncertainties in the interpretation, would be of low concern from a public health point of view; the magnitude of an MOE however only indicates a level of concern and does not quantify risk.

When using the MOE approach for assessing impurities, the derivation of the MOE, its magnitude, and the uncertainties regarding its derivation should be described. A conclusion on whether the MOE is of high concern, low concern, or unlikely to be of safety concern should also be provided.

The Scientific Committee reiterates its recommendation\(^6\) that follow-up discussion should be organised with EFSA partners on the weighing of the potential health significance of the magnitude of particular MOEs and how to band MOEs with respect to conclusions that use expressions such as high concern, low concern, or unlikely to be of safety concern.

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KEY WORDS

Margin of exposure, genotoxic, carcinogenic, impurities, additives, flavourings

\(^1\) Impurities considered include for example unavoidable contaminants, residuals and by-products resulting from a production process

\(^2\) On request from EFSA, Question No EFSA-Q-2012-00233, adopted on 8 February 2012.

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BACKGROUND AS PROVIDED BY EFSA

In its opinion of 18 October 2005 on a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic (EFSA 2005), the Scientific Committee recommended use of the “margin of exposure” approach, but indicated that “substances which are both genotoxic and carcinogenic should not be approved for deliberate addition to foods or for use earlier in the food chain, if they leave residues which are both genotoxic and carcinogenic in food”.

Since then, the ANS Panel has used the margin of exposure approach in some of its scientific opinions to judge the safety of impurities, and is proposing in its new draft guidance on submission for food additive evaluations to use the margin of exposure approach for assessing the risk from impurities which are genotoxic and carcinogenic in the additive7.

Before adopting a generalised use of the margin of exposure approach for impurities, the ANS Panel asked the Scientific Committee for guidance on the acceptability and validity of such an approach in the framework of assessing the safety of food additives found to contain substances which are both genotoxic and carcinogenic.

On 9 January 2012, a preparatory meeting with members of the Scientific Committee and relevant EFSA Panels8 was organised to discuss the issue. Participants recommended the Scientific Committee to develop a statement on this issue.

TERMS OF REFERENCE AS PROVIDED BY EFSA

The European Food Safety Authority requests the Scientific Committee to consider the applicability of the margin of exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food or feed.

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8 Food Additives and Nutrient Sources Added to Food (ANS), Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), Contaminants (CONTAM)
STATEMENT

In its opinion on a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic (EFSA 2005), the Scientific Committee concluded that the margin of exposure (MOE) approach can be applied in cases where substances which are both genotoxic and carcinogenic have been found in food, irrespective of their origin, where there is a need for guidance on the possible risks to those who are, or have been, exposed.

However, in the conclusion section, the Scientific Committee also stated that “in principle substances which are both genotoxic and carcinogenic should not be deliberately added to foods or used earlier in the food chain if they leave residues which are both genotoxic and carcinogenic in food”. It is now recognised that this statement carries risk management connotations. Furthermore, it could be interpreted as applying not only to the principal component of any product added to food/feed but also to any impurities present in such a product. It should be underlined that in the 2005 opinion, no explicit consideration was given to the application of the MOE approach to impurities. The Scientific Committee has now considered this issue.

The Scientific Committee recognises that this is an important problem. Analytical methodology is continually improving, and an increasing number of impurities, including some which are both genotoxic and carcinogenic, can be detected at low levels in, for example, food/feed additives or food contact materials. As a result it can be foreseen that these impurities may end up in food, including products from animal origin.

The Scientific Committee is of the opinion that the MOE approach can be applied to impurities which are both genotoxic and carcinogenic, irrespective of their origin. The Scientific Committee notes that the wider application of the MOE would raise some scientific and risk management issues. These concern the interpretation of the magnitude of any MOE in relation to human health and the way in which conclusions in EFSA opinions on the safety of substances that will be added to food or feed are expressed.

In the 2005 opinion, the Scientific Committee gave some guidance on how to interpret the MOE. It was stated that “The Scientific Committee is of the view that in general a margin of exposure of 10,000 or higher, if it is based on the BMDL10 from an animal carcinogenicity study, and taking into account overall uncertainties in the interpretation, would be of low concern from a public health point of view and might be reasonably considered as a low priority for risk management actions. However, such a judgment is ultimately a matter for the risk managers. Moreover an MOE of that magnitude should not preclude the application of risk management measures to reduce human exposure”.

The Scientific Committee is aware that the magnitude of an MOE only indicates a level of concern and does not quantify risk. Moreover, the implications of any MOE need to be considered case-by-case, looking at both its magnitude and the uncertainties regarding its derivation. The Scientific Committee reiterates that an MOE of 10,000 or higher is considered of low concern from a public health point of view with respect to the carcinogenic effect. As a small MOE represents a higher risk than a larger MOE, it follows that a very high MOE would be very unlikely to be of safety concern. However, there is at present no international consensus on banding of MOEs and corresponding descriptive terminology.

When using the MOE approach for assessing impurities, EFSA Scientific Committee and Panels should describe the derivation of the MOE, its magnitude, and the associated uncertainties regarding its derivation. They should also give their view on whether the MOE is of high concern, low concern, or unlikely to be of safety concern. It will then be the role of the risk managers to decide whether the substance containing the impurities should be authorised.

For the purpose of risk assessment harmonisation, the Scientific Committee reiterates the recommendation made during the EFSA/WHO International Conference on risk assessment of
MOE approach for the assessment of impurities which are both genotoxic and carcinogenic compounds that are both genotoxic and carcinogenic (EFSA, 2006), that follow-up discussion is organised with EFSA partners (both risk assessors and risk managers) on the weighing of the potential health significance of the magnitude of particular MOEs and how to band MOEs with respect to conclusions that use expressions such as high concern, low concern, or unlikely to be of safety concern.

REFERENCES

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