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European Food Safety Authority

SCIENTIFIC COMMITTEE and ADVISORY FORUM

Parma, 16 October 2008

To: **EFSA Executive Director**

Subject: **Mandate proposed to EFSA by the Scientific Committee on exploring options for providing preliminary advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC)**

Dear Dr Geslain-Lanéelle,

I am pleased to forward to you the attached note concerning an 'own-initiative' subject the Scientific Committee would like to give priority in the forthcoming period.

The Committee is proposing to prepare an opinion on "exploring options for providing preliminary advice about possible human health risks based on the concept of Threshold of Toxicological Concern". Please find attached the proposed mandate providing the background and a proposal on how the Committee would like to deal with this subject.

On behalf of the Scientific Committee, I would like to request from the EFSA the mandate to work on the above-mentioned subject with the terms of reference as specified in the Annex.

I would like to take this opportunity to convey to you my sentiments of esteem and consideration.

On behalf of the Scientific Committee,

(signed)

Professor Vittorio Silano
Chair of EFSA Scientific Committee

Draft MANDATE FOR THE EFSA SCIENTIFIC COMMITTEE

EXPLORING OPTIONS FOR PROVIDING PRELIMINARY ADVICE ABOUT POSSIBLE HUMAN HEALTH RISKS BASED ON THE CONCEPT OF THRESHOLDS OF TOXICOLOGICAL CONCERN

Background

Human health risk characterisation of chemicals is normally based on substance-specific hazard data and on estimations of the level of human exposure. Whereas the latter is often based on (conservative) assumptions and theoretical models, rather than quantitative measurements and observations, the former is generally based on extrapolation of quantitative hazard characterisation data derived from resource-intensive toxicity studies in animals. The unavoidable uncertainties and assumptions made during the risk assessment process are usually covered by applying conservative safety/uncertainty factors.

Synthetic and naturally occurring substances present in food and feed flavouring agents, food contact materials, food supplements, botanicals, and food and feed contaminants, together with their possible breakdown or reaction products, represent a very large number of substances, many of which still require risk assessment. Moreover, the continuing rapid improvements in analytical sensitivity is resulting in the detection of a growing number of chemical contaminants in food and feed at low concentrations as well as in the identification of an increasing number of poorly understood substances.

In the light of the above considerations, EFSA needs to develop, validate and apply, where possible, pragmatic and practical risk assessment approaches as priority setting tools and as a means to enable more rapid provision of advice about the possibility of health risks. Such practical approaches should not in any way compromise the high scientific quality of EFSA's output.

Reconsideration of the current concept of risk assessment can be done by promoting the evolution of hazard assessment (toxicology) from a predominantly observational science at the level of *in vivo* models to a predominantly predictive science (1) focused on broad inclusion of computational models and comparative decision trees, as for example:

- Investing in new approaches, based on scientific innovation and making use of new tools and instruments such as genomics (proteomics and metabolomics)

and other profiling techniques, systems biology, and biological pathway pertubations (2). New approaches also include concepts such as 'intelligent testing and assessment strategies'(3), 'evidence-based toxicology'(4), and 'conceptual risk assessment frameworks' (5), which are all based on step-wise risk assessment procedures defining the next step based on the outcome of the previous steps.

- Pragmatic and practical risk assessment approaches aiming at providing preliminary advice about the possibility of a human health risk. Some approaches are based on comparative analyses of hazard data from structurally - or functionally - related substances, including computational prediction of toxicity (QSAR) (6), and use of high-throughput automated screening assays. Approaches primarily based on presumed safe levels of exposure, rather than hazard data, include the tiered assessment as applied in the REACH Regulation (7), the threshold of regulation (TOR) concept as applied by the US FDA for food contact materials (8) and, the threshold of toxicological concern (TTC) concept, which can be applied using a decision-tree approach, and which is useful for substances where human exposure levels are known to be low (9).

In accordance with its mission, EFSA aims to invest in new risk assessment approaches based on scientific innovation and novel techniques such as genomics and other profiling methods. The Scientific Committee is also addressing new risk assessment approaches in the context of animal welfare considerations.

The use of pragmatic, science-based approaches in EFSA has already begun. In the area of risk assessment of micro-organisms, the Scientific Committee adopted an opinion on the use of the Qualified Presumption of Safety (QPS) approach for setting priorities within the risk assessment of microorganisms used in food/feed production referred to EFSA (10). This practical risk assessment approach meets the need of EFSA to assess the safety of large numbers of micro-organisms deliberately added to food and feed within an acceptable time frame.

In the area of food contact materials, the former Scientific Committee on Food and subsequently EFSA have applied a tiered approach to toxicity testing requirements, based on estimates of exposure to individual substances via migration from food contact materials into food and the principle that lower levels of exposure require less toxicity data for risk assessment (11).

For the assessment of the more than 2800 food flavouring substances, for which the burden of assessment is shared between EFSA and JECFA, EFSA applies, where possible

and feasible, the concept of Threshold of Toxicological Concern (TTC). This concept refers to the establishment of a generic human exposure threshold value for (groups of) chemicals below which there would be no appreciable risk to human health (12). Therefore the safety assessment of food flavourings based on very low levels of exposure becomes possible even in the absence of substance-specific hazard data.

The TTC approach is currently not applied in EFSA in areas of risk assessment other than food flavourings. It is recognised that a critical element in applying the TTC approach is the need for reliable exposure data and that estimates of exposure need to be as complete and accurate as possible, or include adequate conservatism to account for possible underestimation of exposure.

Terms of Reference

The Scientific Committee is requested to prepare a scientific opinion in which it explores options for the use by EFSA's Scientific Committee and Scientific Panels and other expert groups of the threshold of toxicological concern (TTC) approach as a formalised approach for providing scientific advice about possible human health risks.

In particular the Scientific Committee is requested to:

- Evaluate the relevance and reliability of the TTC concept for application in the food and feed area, taking into account: (i) the discriminative power of the currently available databases that underpin the concept and which have been used to define human exposure thresholds, (ii) the range and number of chemical entities represented in such databases, (iii) the routes of exposure to these chemicals, (iv) the range of reported effects following exposure, and (v) the possibilities to assess – with sufficient certainty – human exposure levels through food and feed of chemical entities for which EFSA has risk assessment responsibility;
- Advise on the application of the TTC concept in areas of chemical risk assessment addressed by EFSA other than food flavourings and define the general and specific criteria for its application as a tool to provide scientific advice on the safety/risk in these areas;
- Advise on any additional data development and/or collection needed to strengthen the underlying basis of the TTC concept and its use as a practical tool for providing scientific advice about possible human health risks related to chemical exposures via food and feed.

In developing its scientific opinion the Scientific Committee is requested to take into account the experience gained by the EFSA in applying the TTC concept in the assessment of food flavouring substances, the work currently carried out by the three non-food Scientific Committees of the Commission (SCCP, SCHER and SCENIHR) (15), and the experience gained by other agencies and international organisations/associations including: EMEA, US FDA, JECFA, WHO/IPCS, ILSI (13)(14) and COLIPA.

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EXECUTIVE DIRECTOR

Parma, 3rd November 2008
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Subject: Mandate proposed to EFSA by the Scientific Committee on exploring options for providing preliminary advice about possible human health risks based on the concept of Threshold of Toxicological Concern.

Dear Professor Silano, Dear Vittorio,

In your letter of 16 October 2008 you request a self-mandate for the Scientific Committee on "Exploring options for providing preliminary advice about possible human health risks based on the concept of Threshold of Toxicological Concern". Your letter also included the draft mandate for this task which was discussed at the recent plenary of the Committee of 25-26 September.

EFSA greatly appreciated the proposal as explained in your letter and has high expectations with respect to the outcome of the various activities. From your proposal I recognized that although the TTC approach is applied for the safety assessment of food flavouring substances, the concept is currently not applied in other areas of risk assessment in EFSA. I strongly support the initiative of the Scientific Committee to explore options for the use of the threshold of toxicological concern (TTC) concept by EFSA's Scientific Committee and Scientific Panels and other expert groups as a formalised approach for providing scientific advice about possible human health risks.

EFSA endorses your request and invites the Scientific Committee to start working on the project as described in the mandate attached to this letter. I suggest that the tasks as defined in the attached terms of reference could be completed by summer 2010.

I look forward to be regularly informed during meetings of the Scientific Committee on the progress with this challenging new task.

Yours sincerely,

Catherine Geslain-Lanéelle

Copy: Members of the Scientific Committee, Djien Liem, Bernard Bottex, David Carlander, Daniela Maurici.