TECHNICAL REPORT OF EFSA

Outcome of the public consultation on the draft guidance for submission for food additive evaluations[1]

European Food Safety Authority[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

BACKGROUND

EFSA has undertaken a public consultation on the draft guidance for submission for food additive evaluations. The draft guidance was prepared by an EFSA ANS working group and was endorsed for public consultation by the EFSA ANS Panel on 25 October 2011. The public consultation started on 15 November 2011 and closed on 15 January 2012 (8 weeks).

This report provides an overview of the comments and their consideration and includes a table with all the comments received as well as EFSA/ANS replies.

CONSIDERATION OF COMMENTS RECEIVED

1. Comments received

EFSA had received a total of 82 comments from eight interested parties including academia, industry organisations, stakeholders, European national agencies and individuals. Out of the 82 comments, two were not relevant to the draft guidance document and four were either repetitive or applicable to more than one sections. Duplicated comments appear only once and comments submitted by individuals on personal capacity are published anonymously. Comments submitted formally on behalf of an organisation appear with the name of the organisation. The comments and EFSA/ANS replies are tabulated in the appendix of this report.

[1] On request from EFSA, Question No EFSA-Q-2011-01103, approved on 7 June 2012.

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2. Screening and evaluation of comments received

All comments were subject to evaluation and assessment by the working group experts at dedicated meetings. Comments outside the risk assessment remit of EFSA were not addressed and are not included in the table of comments.

2.1. Types of comments

Most of the comments received related to the description of exposure assessment where further clarifications were necessary. Where comments applied to multiple sections e.g. summary and main text or the same point is made by different respondents, the response is given on the first occasion.

3. Incorporation of the documents in the guidance document

A meeting with the working group on Guidance for Food additives was dedicated to discuss all the comments and address how to incorporate them in the guidance. Only the relevant comments were taken into account and the guidance document was revised accordingly. These comments were appropriate and contributed to enhance the scientific quality and clarity of the guidance document. The final document on Guidance for Food additives was endorsed by the Scientific Committee at its plenary meeting (21-22 May 2012), and was presented to and adopted by the ANS Panel at its plenary meeting on 7 June 2012.

APPENDIX: TABLE OF COMMENTS RECEIVED AND EFSA/ANS REPLIES

No	ORGANISATION	SECTION	COMMENT RECEIVED	EFSA COMMENT
1a	Federation of European Specialty Food Ingredients Industries (ELC)	Summary/ General	General comments The ELC would like to comment, that in order to clarify for applicants and other stakeholders the technical requirements and evaluation process, if the EFSA could provide a flowchart describing the progression through the tiers. A diagram of the requirement within each tier is provided in Appendix A, however it is clear from the text that it is not always necessary to conduct every study specified for each tier. The requirement for a particular study is determined by the result from preceding studie(s) addressing the same end-point. For example, in assessing a single additive in the case of some end-points it may be necessary to enter tier 3, whereas for others data provided by tier 2 or 1 is sufficient. The availability of a decision-tree that enhances Appendix A and reflects the text of the document would be helpful to the overall understanding of the guidance.	The existing diagram in the document (Appendix A) has been updated to address the issues on decision making from moving to tiers. The ANS Panel would like to indicate that such a diagram is only indicative of the process involved when applying the tiered approach and that it can not accurately reflect all the possible scenarios of the testing required. Thus, a decision tree/flowchart was not produced as all the triggers and decisions to be made can not be depicted in such a flowchart. The applicants are advised to carefully read the Guidance document before finalising their testing design strategy.
1b	Federation of European Specialty Food Ingredients Industries (ELC)	Summary/ General	General comments The ELC would like to comment that although the draft Guidance is supposed to cover authorisations for new additives and extensions of use for others, the ELC notes that all of the detail covers a new additive submission. Specific guidance on requirements for, presumably, a shorter submission for extension of use for an already fully approved additive would be useful.	Applications for alteration of the use or usage conditions of existing additives can rely on data used for the original assessment; in such circumstances the ANS Panel will normally accept studies meeting the state of the art at the time of the original assessment rather than meeting current expectations for the design and conduct of these studies. Whilst the ANS Panel would prefer to have full study reports available, existing opinions on the additive may contain sufficient detail for assessment. The ANS Panel notes that there is no need for such a sentence to be added in the guidance document.

2	Federation of European Specialty Food Ingredients Industries (ELC)		In reference to the statements according to which "the safety evaluation strategy and the corresponding testing strategy should be described and justified with rationales for inclusion and exclusion of specific studies" (Annex B, p. 50) and "use of any methods differing from internationally agreed test guidelines (...) should be justified and their acceptance will be assessed on a case-by-case basis" (Chapter 4, lines 764 – 766), the ELC would like to add the following general comment that while the applicants/stakeholders should read this document as a guide, any deviation from the content requirements should be scientifically justified, according to the specificity of the product that is at stake.	The ANS Panel notes that addition of such a comment is not necessary as is already covered by text in the Guidance document.
3	University Wuppertal + BAuA Dortmund	Summary	Line 40: "applicants should base their dossier on sound science and evolving principles of risk assessment". Please substantiate this sentence, how it will be verified and appoint the consequences.	New text has been added for further clarification; the statement allows the Panel to apply new concepts as they evolve and the consequence of not basing the dossier on sound science would be its rejection and possibly a negative opinion.
4	University Wuppertal + BAuA Dortmund	Summary	Line 42-70: More, than half of the summary deals with hazard assessment, while NO sentence is dedicated to exposure assessment which shows the respect spend for the second column of risk assessment. Please, amend the summary about an equal paragraph about exposure assessment.	New text has been added in the summary to address the comment.
5	Federation of European Specialty Food Ingredients Industries (ELC)	Terms of reference as provided by EFSA	Lines 168-170: We appreciate EFSA's efforts to not only guide the applicants through the requirements to conduct the safety evaluation of a product but also to "describe additional information which might help in providing context for the risk assessment". With a view to help the applicants/stakeholders to have a good understanding of the overall process, the ELC would also suggest that the elements of context are clearly highlighted (e.g. via a different font and in italics).	The ANS Panel considers that appropriate use of font has been made to indicate elements of context, and feels that no further textual changes should be made to the document.
6a	University Wuppertal + BAuA	Introduction	Line 211: Appendix A seems to be correct (not Appendix C)	The correction has been made.

	Dortmund			
6b	Federation of European Specialty Food Ingredients Industries (ELC)	Introduction	Line 215 (and line 64 of Summary): In reference to the statement that "higher tiers will generally supersede results at lower tiers" the ELC would appreciate if the word "generally" could be qualified and if EFSA could specify, notably through examples, the circumstances under which a result at a lower tier would not be superseded by a higher tier.	The text has been modified slightly. However it was considered that providing examples could over-emphasise the few circumstances where this might occur and would potentially mislead readers. The main circumstances would be where negative tests at a higher tier (e.g. for genotoxicity) were not able for technical reasons to provide reassurance that results at the lower tier could be discounted.
7	University Wuppertal + BAuA Dortmund	Risk assessment Paradigm	If the ADI is explained by a footnote (though this is almost a dictum), than BMD, BMDL and BMDL05 and BMDL10 have to be explained, even more. Who is expected to be the target audience of this guidance: toxicologists, only? "The Panel expects to increasingly use BMDL values rather than the NOAEL for deriving an ADI" (line 250): Please, explain and give reasons for that.	These can be found in the glossary. The ANS Panel will increasingly use BMDL values for deriving an ADI as this approach has been endorsed by the Scientific Committee (EFSA, 2009a).
8	University Wuppertal + BAuA Dortmund	Risk assessment Paradigm	Line 278: Please, define "food category"	A definition is provided in the glossary.
9a	FPS Health, Food Chain Safety and Environment	Risk assessment Paradigm	272-275 indeed all EU consumers should be protected, also from small member states and all age groups. Also, high consumers of a certain food should be protected (this is extremely important for drinks). In addition, specific calculations might be needed to protect a vulnerable group (e.g. when use of an additive is requested in foods for particular nutritional uses).	The exposure assessment is intended to ensure that consumption by high level consumers is estimated for comparison with health-based guidance values in the risk assessment.
9b	FPS Health, Food Chain Safety and Environment	Risk assessment Paradigm	279-282 Exposure should ALWAYS be calculated using only proposed or existing maximum permitted levels of the additive, as this is the potential exposure. Risk managers need this information. Other calculations based on actual use levels can only be additional.	Text has been modified to address the issue.

10	University Wuppertal + BAuA Dortmund	Risk assessment Paradigm	Line 288: Please, define "second instance" as in the authorisation systems of biocides, pesticides and Reach, this term means refinement of exposure assessment. In this Guidance, Line 610 states that "refined estimates" are expected "for Scenario 2", only. Please, contradict the impression that "exposure from other source" (Line 288) will have to be considered for modification of an existing authorisation of a food additive, only.	Text has been modified to address the issue.
11	FPS Health, Food Chain Safety and Environment	1.1. Identity of substance	Additives derived from animal sources seem to have been forgotten.	Text has been modified to address the issue.
12	Federation of European Specialty Food Ingredients Industries (ELC)	1.1.5. Additives derived from botanical sources (such as steviol glycosides from Stevia, or rosemary extracts)	The ELC notes that this section refers to the active components of additives derived from botanical sources, and not to solvent residues. That is why the ELC considers that it would be necessary to include a requirement to identify and quantify any solvent residues into the Guidance.	Text has been modified to address the issue.
13	Federation of European Specialty Food Ingredients Industries (ELC)	1.1.6. Nanomaterials	Line 439: The ELC would suggest that the definition of the term ‘natural nanomaterial’ is specified.	The term 'natural nanomaterials' has been replaced by the term 'non-engineered nanomaterials used as food additives'. A definition is also provided in the glossary.
14	Federation of European Specialty Food Ingredients Industries (ELC)	1.1.7. Substances containing microorganisms or derived from microorganisms	Lines 453-456: The ELC notes that the case where an additive consists, contains or is produced from a GMO is commented only in the section on additives of microbial origin, and has not identified similar comments in relation to additives from botanical origin. With a view to help the applicants to have a good understanding of EFSA’s requirements , It is suggested to address the interplay between EC regulation Nr 1333/2008 and (EC) regulation Nr 1829/2003 in a section dedicated to gene technology in	Text has been modified to address the issue.

			the production of food additives rather than in section 1.1.7. Such a section might also be the right place to briefly summarize relevant EFSA guidance, if possible including some indications on which guidance should be considered, when an additive consists, contains, or is produced from a GMO, or when it is produced by a GMM. Therefore, this would include a comments of specific relevance for the case where an additive is produced by a GMM, which could be cross-referenced in section 1.1.7.	
15a	BEUC	1.2. Specifications	In line 460, a clear definition of "batch" should be provided as there are several ways to define a batch according to the production parameters (e.g. day, machine, raw material, shift, etc.). The desired sequence of the 5 required batches may also need to be specified (e.g. 5 batches in a raw? or should they differ in terms of the production time?).	Text has been modified to address the issue. A definition of batch is provided in the Glossary.
15b	BEUC	1.2. Specifications	Characterisation of substances (or mixtures thereof) needs to be as detailed as possible. The percentage of material stated as "unidentified" in the specifications (line 499) should be minimised (tolerable limits/criteria/guidance for "unidentified" material should possibly be considered) and the specifications should address all impurities with maximum limits. Moreover, food additives are very often not used as such but in various forms and preparations or dispersions with different composition and properties. Since these preparations are the actual substances used in food, specifications should be also provided for these preparations.	Text has been modified to address the issue.
16a	Federation of European Specialty Food Ingredients Industries (ELC)	1.2. Specifications	Line 460: According to the ELC, the requirement to provide data on 5 batches could be flexible: while the requirement should be for a maximum of 5 batches, in the case of additives produced via well-established processes with historical control data, 3 batches should be sufficient.	Text has been modified to address the issue.

16b	Federation of European Specialty Food Ingredients Industries (ELC)	1.2. Specifications	Lines 498-499: The ELC would appreciate if EFSA could elaborate further on the concept "unidentified" components that are present at low level in a product, notably on the applicable definition criteria. This could possibly take place through discussions around few examples, in order to better understand what is expected by the Panel.	Text has been modified to address the issue.
17	Federation of European Specialty Food Ingredients Industries (ELC)	1.3. Manufacturing process	Lines 505-507: The ELC would appreciate a clarification of the applicable policy regarding the management of situations where data are claimed to be confidential, including procedures applicable to protect the rights of the applicants when the eligibility of submitted data to confidentiality protection is questioned. The ELC understands that it includes aspects that are not specific to submission for authorisation of additives and acknowledges that the guidance on additives is not necessarily the most appropriate document to cover all aspect of confidentiality management.	Text has been modified to address the issue.
18a	FPS Health, Food Chain Safety and Environment	1.3. Manufacturing process	505 The generic (non-confidential) description of the manufacturing process, which should be included in the definition/specifications, should be detailed enough to allow to discriminate between acceptable manufacturing processes being authorised and those with a significant change in the production method, needing a new risk assessment. As authorizations are generic, other producers than the applicant will be allowed to produce and market the additive, as long as the additive is compliant with the specifications. Those other producers, nor control authorities, have access to confidential information in the dossier.	Text has been modified to address the issue.

18b	FPS Health, Food Chain Safety and Environment	1.3. Manufacturing process	521 to be inserted "iv) chemical or physical decontamination methods used during the production of the additive to reduce microbial risks (not including preservatives in the formulation, which are regulated in annex III of regulation 1333/2008)"	Text has been modified to address the issue.
18c	FPS Health, Food Chain Safety and Environment	1.3. Manufacturing process	524 The description of the production method in the specifications should include all relevant used chemicals and treatments which might have an influence on the identity and safety.	The ANS Panel notes that this issue is covered by the second bullet point of section 1.3 ("*For substances synthesised chemically: i) factors such as reaction sequence, side reactions, purification and preparation of the product to be commercialised, which may assist in determining likely impurities and their influence on the toxicological evaluation; ii) information on substances entering the manufacturing process, e.g. identity of the extraction solvent, reagents, special precautions (light and temperature), chemical or physical decontamination methods should be provided*.")
19	Federation of European Specialty Food Ingredients Industries (ELC)	1.4. Methods of analysis in food	Line 533: It could be clarified that a 'type' of foodstuff refers to the food category. Therefore data from matrices representative of the category in question should be sufficient to demonstrate that the analytical method is fit for purpose.	Text has been modified to address the issue.
20	BEUC	1.4. Methods of analysis in food	For stability tests, and more generally where laboratory test methods are employed/mentioned, guidance for validation criteria and uncertainty of the analytical technique/method should be provided (at least in relation to LOD, range and uncertainty).	Text has been adjusted to address the issue.
21	Federation of European Specialty Food Ingredients Industries (ELC)	1.5. Stability of the substance, and reaction and fate in food	Lines 554 – 556: The ELC suggests that it is made explicit that additives which are demonstrated to be stable within a given application should not require an assessment of the characteristics and effects in food of degradation products. Furthermore, such an assessment would only need to be conducted when it is anticipated that such degradation products are 'toxicologically relevant'.	Text has been modified to address the issue.

22	BEUC	1.5. Stability of the substance, and reaction and fate in food	For stability tests, and more generally where laboratory test methods are employed/mentioned, guidance for validation criteria and uncertainty of the analytical technique/method should be provided (at least in relation to LOD, range and uncertainty).	Text has been adjusted to address the issue.
23a	Food Standards Agency	3. Proposed uses and Exposure Assessment	Lines 230-238: The term margin of safety is ambiguous since, as noted by WHO in its Risk Assessment terminology (http://www.inchem.org/documents/harmproj/harmproj/harmproj1.pdf), "For some experts, margin of safety has the same meaning as margin of exposure, while for others, margin of safety means the margin between the reference dose (e.g. the ADI) and the actual exposure". Some might assume that if there is a MOS of 100, then the exposure could be 100-times greater before there would be any health concern. It would therefore be essential for ANS to explain what it means by "margin of safety". The term "margin of exposure" is not restricted to genotoxic carcinogens (see EHC 240).	In particular, the ANS Panel defines the Margin of Safety (MOS) as the difference between the NOAEL or LOAEL identified in the toxicological data and the estimated exposure. Determination of the adequacy of the Margin of Safety is made on a case-by-case basis based on the toxicological endpoint, available toxicological data and uncertainties. Whilst this definition could also be described as the Margin of Exposure (MOE), the ANS Panel considers restricting use of the term the Margin of Safety to threshold effects and the Margin of Exposure for compounds which are genotoxic and carcinogenic, provides a clearer distinction for risk managers of the basis for their conclusion.
23b	Food Standards Agency	3. Proposed uses and Exposure Assessment	Lines 240-251: the EFSA Scientific Committee preferred the term "Reference Point" to "Point of Departure". This also applies elsewhere in the chapter. It might also be worth noting that the BMRs referred to are default values, but others might be more scientifically justified in specific circumstances	The ANS Panel considers that Point of Departure and Reference point are to be essentially identical for the purposes of this document.
23c	Food Standards Agency	3. Proposed uses and Exposure Assessment	Lines 255 to 258 refer to the use of chemical-specific adjustment factors for interspecies extrapolation where human and animal kinetic data are available. However, some care is needed with this because the components that make up the assessment factors that are normally applied in chemical risk assessment are not always sufficient individually. This does not matter so much with the standard approach because inadequate allowance for one component of variability would normally be offset by over-conservatism in allowance for others. However,	Text has been modified to address the issue. The ANS Panel accepts the comment that this might be possible. However the ANS Panel considers that in practice this is unlikely to be an issue since all assessments are made on a case-by-case basis; the process of identifying uncertainty factors (whether default or chemical specific) would include consideration of their adequacy and applicability. Therefore as the description is of the process and the possibility of using chemical specific adjustment factors, the ANS Panel considers that no further changes to the

			when data-driven reductions are made in some components, the scope for offset is reduced. Has the chemical-specific adjustment factor approach ever been used by ANS?	text are required.
23d	Food Standards Agency	3. Proposed uses and Exposure Assessment	After line 264. It would be useful to consider other forms of the ADI (group ADI, temporary ADI, ADI not specified) that have previously been used by e.g. the Scientific Committee on Food, and to mention that for some additives an acute reference dose might also be pertinent.	Text has been modified to address the issue. Definitions are provided in the Glossary.
23e	Food Standards Agency	3. Proposed uses and Exposure Assessment	Lines 281-282: Consumption data in the EFSA Comprehensive Database are related to individual body weight. Why does ANS not use this, rather than calculating exposure per person, then dividing by population body weight?	Text has been modified to address the issue.
23f	Food Standards Agency	3. Proposed uses and Exposure Assessment	Lines 284-290: The description of the MOS approach in lines 230-233 specifies that an ADI cannot be set, e.g due to deficiencies in the database. Why would an MOS of 100 be adequate under such circumstances, rather than requiring an additional uncertainty factor?	The ANS Panel considers each MOS on a case-by case basis to determine whether the magnitude of the MOS between the anticipated exposure from the proposed uses and use levels and the NOAEL or BMDL are sufficient to conclude that there would be no safety concern given the uncertainties identified in the database as a whole.
23g	Food Standards Agency	3. Proposed uses and Exposure Assessment	Lines 293-300: This gives the impression that the Scientific Committee opinion on the MOE approach was specific to contaminants and that ANS takes a different view for residuals. But the Scientific Committee referred to all types of chemicals and also noted that "a margin of exposure of that magnitude should not preclude the application of risk management measures to reduce human exposure". Furthermore, it could be anticipated that carcinogenicity data would not be available for many impurities/residuals, and therefore an MOE approach would not be feasible. Would ANS consider using the Threshold of Toxicological Concern under such circumstances?	Following the adoption of the TTC opinion by the EFSA Scientific Committee, the Panel will use the TTC for residuals, metabolites and contaminants as described in the document.

24	Food Standards Agency	3. Proposed uses and Exposure Assessment	Line 615 and line 697 refer to mean and 95th percentiles, but it is unclear whether these are for exposures in a single day, or averaged over a longer period. The appropriate measures of potential dietary intake will depend upon whether the critical toxic effect depends on acute or longer term exposures.	Text has been modified to address the issue.
25	University Wuppertal + BAuA Dortmund	3. Proposed uses and Exposure Assessment	In studying the chapters for exposure assessment of the Draft Guidance, I am still irritated and unsure what to do when applying for authorisation of a food additive. Therefore, I analysed chapter 3 for the reasons of my irritation. What I found is that the requests for data are not structured but arranged out of order: e.g. 1.) in line 596, information is given concerning a "modification of use", but not until line 603 it is defined as "Scenario 2". Between these sentences, information is given for authorisation of new additives. 2.) In line 617, the applicant is advised to indicate the main food groups contributing to total exposure. The next but one sentence, in line 622, states that the "template will automatically calculate and identify the main food groups". Therefore, the first sentence is dispensable but irritating if one is looking for the additional request in it. In order to understand the requests for exposure assessment for food additive authorisation (which I want to compare to other authoration systems in my dissertation), I tried to formulate a structured overview of the requests for exposure assessment that you may use, if appropriate: "Generally, exposure estimates consist of two variables which have to be submitted by the applicant: • A) the particular amount in a certain food o as applied by the applicant or o actually utilized as told by the applicant or post marketing surveillance authorities) and • B) the consumption of the certain food (as taken from	Text has been modified to address the issue.

			food consumption data basis) as o mean and extreme (95th percentile) consumption o for the following age groups: toddlers (12 months up to 35 months), children (36 months to 9 years), adolescents (10-17 years), adults (18-64 years) and elderly (over 65 years). Subsequently, total exposure is calculated by summation of the multiplication of the level of use (A) multiplied with the amount of consumption (B) of all foods. Additionally, exposure from other sources (natural dietary sources, drinking water, consumer products (cosmetics), pharmaceuticals, biocides, pesticides, etc.) have to be assessed and added to total exposure." I would be glad to receive your comment if I did understand it, correcty, or correction. Thank you.	
26	University Wuppertal + BAuA Dortmund	3. Proposed uses and Exposure Assessment	I am glad to hear that 3 calculations which one can do at once are no longer called a "tiered approach". But shall epidemiologic and/or biomonitoring data no be investigated?	Text has been modified to address the issue.
27a	FPS Health, Food Chain Safety and Environment	3. Proposed uses and Exposure Assessment	580, 582 replace “normal” by “actual”	Text has been modified to address the issue.
27b	FPS Health, Food Chain Safety and Environment	3. Proposed uses and Exposure Assessment	588 Although I agree that tier 1 is not useful any more when consumption data are available, tier 2 is still the most reliable method to ensure safety for the consumer and should still be used.	The ANS Panel agrees with the comment and notes that Tier 2 is still included in both scenarios and will form the basis for risk assessment. The text has been modified to address the issue.
27c	FPS Health, Food Chain Safety and Environment	3. Proposed uses and Exposure Assessment	611 I don’t agree with the word “normal”. Exposure should ALWAYS at least be calculated using only proposed or existing maximum permitted levels of the additive, as this is the potential exposure. Risk managers need this information. Other calculations using estimated actual use levels can only be additional. There is no reliable way to obtain “normal” use levels and calculations based on so called normal use levels are only	The terms ‘typical use level’, ‘normal use level’ and ‘actual use levels’ represent the same meaning. The guidance document does not determine which data/scenario will be used for the final risk assessment, but only indicates which data have to be provided to the ANS Panel. The ANS Panel will decide in the end which data are to be used for the risk assessment. The ANS Panel will initially consider data on maximum

			indicative. If the actual maximum reported used level is much lower than the existing authorized level, and the applicant wants to avoid an exceedance of the ADI by an additional proposed use, it is an option that the applicant proposes to reduce an existing maximum permitted level (propose a lower maximum permitted level than the existing one) and the impact of the reduction on potential exposure can be calculated. Scenario 2 does not only refer to extensions of use. There is a legal basis not to set maximum use levels higher than needed and revisions of existing maximum permitted levels are possible.	proposed/permitted levels as the basis of the risk assessment for new food additives.
28	Federation of European Specialty Food Ingredients Industries (ELC)	3. Proposed uses and Exposure Assessment	Data required for the estimation of exposure in accordance with this guidance document (lines 589 to 599)It seems that applicants would be asked to provide information on "known or anticipated human exposure (...) from food (including natural dietary sources) and any other potential sources (from drinking water, consumer products (cosmetics), pharmaceuticals, etc.)". Given the wide diversity of products that may be concerned by this last category, ELC members wonder why the burden of evidence lies on producers of additives which are intended to be used in foods and drinks only. Indeed, applicants would be in the capacity to transmit such data provided that they are already available. In addition, the risk management methodologies differ according to the sectors. In this context, the ELC welcomes EFSA's oral declarations, made during the technical meeting on exposure assessment it organised on 28 November 2011 in Brussels, according to which EFSA would have to limit its risk assessment to what is known and what can be "reasonably applied". The ELC would also suggest that this important clarification appears in the Guidance.Furthermore, the draft guidance indicates that all main food groups will contribute to the total exposure. As EFSA clarified orally during the 28 November	Text has been modified to address the issue.

			technical meeting on intake assessment with stakeholders that the calculation would use the 95th percentile for the highest food group in addition to the means for all the others, the ELC suggests that this mentioned explicitly in the guidance, and should be reflected in the forthcoming 'exposure template'. We would also propose that in some circumstances of extreme variability of intake for a defined food category, median data as opposed to mean data would be much more representative of population intake.	
29	Federation of European Specialty Food Ingredients Industries (ELC)	3. Proposed uses and Exposure Assessment	General comment For clarity's sake, the ELC suggests that the Guidance provides clarifications on the following phrases, which can appear interchangeably: - food - foodstuff - food item - food category - food group	Text has been modified to address the issue.
30	BEUC	3. Proposed uses and Exposure Assessment	When assessing exposure, due consideration needs to be given to individuals that might consume much more of a certain food(s) than the average. This is all the more important when it comes to vulnerable groups such as pregnant women, children, or people suffering from allergies. For instance, some children might be unusually high consumers of a specific kind of sweets or pregnant women might consume more wine without alcohol than the normal population. Exposure estimates need to be conservative enough so as to protect all consumers by taking account of atypical food behaviours of particular population subgroups. Also, it needs to be ensured that exposure assessments reflect the different consumption patterns in the different EU Member States (smaller EU countries should be encouraged to conduct studies/surveys and provide data).	The ANS Panel agrees with the statement that smaller EU countries should be encouraged to conduct studies/surveys, but the ANS Panel also points out that the present food consumption database already includes data from smaller EU countries. However consumption data from pregnant women or people suffering from allergies are not available. The ANS Panel noted that a number of frameworks for the evaluation of mixtures are available (e.g. skinnier) and that such frameworks will be applied, where relevant, on a case-by-case basis.

			In order to account for possible "cocktail" effects, data should also be provided on other food additives typically used in the food in which the food additive under evaluation is proposed for new/modified use. Several additives are often used in a particular food (e.g. several preservatives & colours in soft drinks, or several additives in breads, etc.). It is very important that risk assessment evaluates potential synergistic effects and interactions between different food additives present in the same food (to avoid reproducing the Southampton study case).	
31	University Wuppertal + BAuA Dortmund	3. Proposed uses and Exposure Assessment	Line 595: "information should be provided on ... human exposure to ... pharmaceuticals etc.": How will you / how is the applicant expected to research which substances are used in pharmaceuticals, and at which levels? Please specify "information" and give guidance how to achieve this. And I would be glad if you tell me as I did"nt succeed in that for my dissertation, yet. Otherwise, I suppose it to be a devotional wish, only. Thank you.	The ANS Panel acknowledges that it is difficult but considers it to be essential for the risk assessment process, and therefore is the responsibility of the applicant.
32	University Wuppertal + BAuA Dortmund	3. Proposed uses and Exposure Assessment	Line 602-603: "Scenario": In the authorisation systems of biocides and pesticides as well as in the Reach-Regulation 1908/2006, "scenario" is defined, differently. Please, check if you really cannot find a less irritating designation for differentiation the procedure of authorisation of a new food additive and modification of conditions for an existing food additive - especially with regard to efforts for harmonisation of risk assessment.	The ANS Panel notes that the applicants should not confuse the word scenario used in the REACH regulation and feels that no changes should be made to the text.
33a	Federation of European Specialty Food Ingredients Industries (ELC)	3. Proposed uses and Exposure Assessment	Line 598: The ELC would respectfully suggest EFSA to make a cross reference between the concept of 'relevance' (for residues or contaminants) and the relevant sections of this Guidance. This would help the applicants to properly address the issue in a way that would likely meet EFSA's expectations.	Text has been modified to address the issue.

33b	Federation of European Specialty Food Ingredients Industries (ELC)	3. Proposed uses and Exposure Assessment	Line 607: As it is stated that a tiered approach will no longer be employed for the intake assessment, the ELC would appreciate if EFSA could clarify the concept of "first simplified calculation', its practical purpose and its context. Besides, the ELC would suggest avoiding a situation where detailed consumption data cannot be used for they may not be available, as the intake assessment constitutes an important element of a food additive risk assessment.	Text has been modified to address the issue.
34	University Wuppertal + BAuA Dortmund	3. Proposed uses and Exposure Assessment	Line 606: "template": where will the applicant find this template?	It will be published on the EFSA website under the name FAIM (Food Additives Intake Model).
35a	Federation of European Specialty Food Ingredients Industries (ELC)	3.1. Proposed uses in food and corresponding use levels	Lines 632 to 634: The ELC appreciated the dialogue on the issue of exposure assessment initiated by EFSA on 28 November 2011 and welcomes EFSA's intention to adopt a more balanced approach and use "more detailed / representative usage data" for the intake assessments. While maximum concentration data very often concern a limited number of products within a food (sub)category, the ELC encourages the use of values reflecting more precisely the reality of the market, both for the safety evaluation of new food additives and for the re-evaluation of already authorised additives.	Although the ANS Panel notes that the applicant should provide us with data on the levels (both within or across Member States), the ANS Panel will always use data based on maximum proposed/permitted levels to form the basis of the initial risk assessment.
35b	Federation of European Specialty Food Ingredients Industries (ELC)	3.1. Proposed uses in food and corresponding use levels	Lines 637 – 642: Our understanding of this section is that it is assumed that a given category within one member state will provide lower variability, in terms of usage concentration, compared to the same category across member states. Therefore we propose that in all cases (within or across member states) actual use levels are consistently reported as a range. In addition, according to the ELC, the definition of 'normal' use level provided in the Draft Guidance does not take into consideration differences in technological need for a given additive (especially colours) within a	The ANS Panel stated that mid levels are not used, but maximum reported levels.

			specific food type or between different food types within a food category. The Draft Guidance states that "In principle, a normal use level is the average level of the food additive determined in a number of samples being representative for the food in a given European Member State". Does this mean that if the additive is used in a variety of different levels, including none at all in some varieties, then the average can be taken as 'normal' for use in exposure calculations?	
36a	FPS Health, Food Chain Safety and Environment	3.1. Proposed uses in food and corresponding use levels	638 an average level should only refer to foods in which the additive is actually used. (average of positive samples). This concept of average level might only work if there seems to be a comparable use level in the large majority of products. If, for example, a mixture of sweeteners can be used to sweeten the food, variation of levels of individual sweeteners is so large, that it is not possible to have a representative level. In addition, a consumer can be brand loyal. I am in favour of using maximum reported use levels in such cases. I regret very much that EFSA does not propose any more to use maximum reported use levels.	The ANS Panel will always consider data based on maximum proposed/ permitted levels to form the basis of the risk assessment for new additives.
36b	FPS Health, Food Chain Safety and Environment	3.1. Proposed uses in food and corresponding use levels	647 conditions of use often contain restrictions within a food group of the food classification system. It should be possible to take this into account somehow. It is also possible that the applicant proposes a new food group for the classification system	This will be taken into account as far as possible based on the consumption data available. However, the ANS Panel notes that the new food group is outside the remit of the guidance.
37	University Wuppertal + BAuA Dortmund	3.1. Proposed uses in food and corresponding use levels	Please, define how "maximum permitted levels" are set and why food additive authorisation is not limited to the proposed use level, if possible according to risk assessment. Please, prove why "normal use levels are expected to be lower than the maximum permitted use level" (line 633f).	Maximum permitted levels are defined in the regulation, and foods being higher than the maximum permitted level are not allowed to be on the market.

38	Federation of European Specialty Food Ingredients Industries (ELC)	3.1. Proposed uses in food and corresponding use levels	Lines 643 to 647: Use data should be compatible both with the Food Classification System defined in Annex II of Regulation 1333/2008 and the FoodEx classification system. Although the ELC members agree with the outmost necessity to provide refined use data per well-defined food (sub)category, it is feared that providing such data on the basis of a double classification would constitute an additional complexity in this difficult exercise while the EU institutions had agreed on a harmonised classification system. The 'Correspondence Table' between the two classification systems, which is being prepared by EFSA and should be finalised by early 2012, would be welcome as it would ease this 'double exercise'. Furthermore, it is often the case that a single food category is much broader, in terms of the products encompassed, than the intended or actual usage of an additive. As this is may be a source of substantial inaccuracy, we suggest that EFSA determines methods to consider in the calculations more realistic occurrence data.	Text has been modified to address the issue.
39	Federation of European Specialty Food Ingredients Industries (ELC)	3.1.1. Authorisation of a new food additive (Scenario 1)	Lines 651 – 655: It would be needed to state clearly in the guidance "for food additives prepared by extraction from natural sources which are complex mixtures". The products mentioned in brackets (e.g. beetroot red) can be simple food additives (in the case of beetroot red, betanin) and in this case the part "ii) the corresponding concentration of the compound and other components in the mixture" is not applicable. According to the ELC, the requirement should therefore only apply to food additives that are mixtures prepared by extraction from natural sources.	Text has been modified to address the issue.

40	University Wuppertal + BAuA Dortmund	3.1.1. Authorisation of a new food additive (Scenario 1)	Please, define "food category" (line 278) and "food item" (Line 652).	The definition of 'food category' is provided in the Glossary. The term 'Food item' has been replaced by 'Food'.
41a	FPS Health, Food Chain Safety and Environment	3.1.2. Modification of an existing authorisation (Scenario 2)	665, 670, 76 and 679 please delete "in the final food product" as it doesn't make sense	Text has been modified to address the issue.
41b	FPS Health, Food Chain Safety and Environment	3.1.2. Modification of an existing authorisation (Scenario 2)	676 replace "normal use levels" by "information on actual uses and use levels"	Text has been modified to address the issue.
41c	FPS Health, Food Chain Safety and Environment	3.1.2. Modification of an existing authorisation (Scenario 2)	685-688 This paragraph should especially refer to requests for modification of annex III. Please delete "for example where a food additive is not intended to be part of the final food product, during manufacture … coating material" Proposal for a revised paragraph: "If carry over of the food additive itself or any other toxicological relevant residue may occur, (e.g. when the applicant proposes to modify annex III of regulation 1333/2008 such as for additives for the stabilization of vitamin preparations), data are requested on the carry over of the food additive and its resulting concentration in the final food product (e.g. the fortified food). Similar carry over estimates should be made when the additive is to be used in other foods which are often used as ingredients, e.g. sugar.	Text has been modified to address the issue.
42	Federation of European Specialty Food Ingredients Industries (ELC)	3.1.2. Modification of an existing authorisation (Scenario 2)	Lines 667 - 669 and 672 – 675: It would be needed to state clearly in the guidance "for food additives prepared by extraction from natural sources which are complex mixtures". The products mentioned in brackets (e.g. beetroot red) can be simple food additives (in the case of beetroot red, betanin) and in this case the part "ii) the	The ANS Panel notes the comment and since that beetroot red is not a good example, this has been replaced by rosemary extracts (EFSA, 2008).

			corresponding concentration of the compound and other components in the mixture" is not applicable. According to the ELC, the requirement should therefore only apply to food additives that are mixtures prepared by extraction from natural sources.	
43	University Wuppertal + BAuA Dortmund	3.1.2. Modification of an existing authorisation (Scenario 2)	Line 685-688: "where a food additive is not intended to be part of the final product", the substance is NO food additive but a "processing aid" according to Reg. 1333/08, art.3(2)b, "processing aids". Please, clarify if data CAN be requested on such substances which are not used as food additives as Reg. 1333/08 is valid for food additives, only (art. 2(1)).	Text has been modified to address the issue.
44	University Wuppertal + BAuA Dortmund	3.2. Exposure data	"other sources": benzoic acids, sorbic acids - e.g. - are used as biocides (and maybe pesticides, too). Please, amend "biocides, pesticides" after "pharmaceuticals".	The ANS Panel notes that only some examples are listed in the document without indicating that biocides and pesticides are not to be considered.
45	University Wuppertal + BAuA Dortmund	3.2. Exposure data	Line 698: "the population groups as indicated above": Please explain which population groups or where indicated above. In chapter 3., line 616, "age groups" are indicated which, to my mind, is not the same as "population groups".	Text has been modified to address the issue.
46	University Wuppertal + BAuA Dortmund	3.2. Exposure data	What is the difference between "combined" (line 691) and "aggregate" (line 701) exposure? Please define. 2.) How will you / how is the applicant expected to research which substances are used in pharmaceuticals, and at which levels? Please give guidance. I would be glad if you tell me as I did"nt succeed in that for my dissertation, yet. Otherwise, I suppose it to be a devotional wish, only. Thank you.	Combined and aggregate exposure have the same meaning; aggregate exposure is clearly defined in the document. In addition, the ANS Panel notes that it is difficult for the applicant to identify which substances and at what levels these additives are used in pharmaceuticals, but considers such information to be essential.
47	FPS Health, Food Chain Safety and Environment	3.2.1. Assessment of exposure to the food additive from other uses	693-695 please replace "non-additive use in food supplements" by "use as a nutrient (in fortified food, food supplements or foods for particular nutritional use), use as a novel food" Please add also "use as or in processing aids"	Text has been modified to address the issue.

48	FPS Health, Food Chain Safety and Environment	3.2.1.1. Assessment of aggregate exposure to the same compound from different sources	It can not be assumed that only the average consumer is subject to aggregate exposure. Implications of aggregate exposure should be discussed for the population as a whole.	Text has been modified to address the issue.
49a	Personal opinion (France)	3.2.1.1. Assessment of aggregate exposure to the same compound from different sources	Line 614 to 625 It is not explained how the exposure from different foods will be aggregated to estimate an overall exposure from foods. This point is critical for high percentiles because it is not valid to add high percentiles between them. It is not valid to consider only mean exposure. One can imagine that the comprehensive database will be used to estimate aggregated exposure using individual data. If it is the case, this should be explained. It should also be explained why the 95th percentile has been chosen instead of 97.5th percentile. Most of the national dietary survey have a sufficient sample size to estimate a 97.5 percentile.	Text has been modified to address the issue.
49b	Personal opinion (France)	3.2.1.1. Assessment of aggregate exposure to the same compound from different sources	Line 702 to 711 It is explained that the aggregate exposure from different sources is the sum of the mean exposures. This is confusing since it is needed to consider high percentiles. Since the exposure from different sources (food fortification, supplement...etc) will not be known from all the surveys of the comprehensive database at the individual level, there is a need to consider here some probabilistic exposure assessment.	Following discussions with EFSA's unit on Dietary and chemical monitoring (DCM), the ANS Panel can confirm that most of the national dietary surveys do not have a sufficient sample size to allow calculation of the exposure at the 97.5 percentile.

50	Federation of European Specialty Food Ingredients Industries (ELC)	3.2.1. Assessment of exposure to the food additive from other uses	Section 3.2.1 – Assessment of exposure of the food additive from other uses (lines 691 to 700) It seems that applicants would be asked to provide information on "known or anticipated human exposure (...) from food (including natural dietary sources) and any other potential sources (from drinking water, consumer products (cosmetics), pharmaceuticals, etc.)". Given the wide diversity of products that may be concerned by this last category, ELC members wonder why the burden of evidence lies on producers of additives which are intended to be used in foods and drinks only. Indeed, applicants would be in the capacity to transmit such data provided that they are already available. In addition, the risk management methodologies differ according to the sectors. In this context, the ELC welcomes EFSA's oral declarations, made during the technical meeting on exposure assessment it organised on 28 November 2011 in Brussels, according to which EFSA would have to limit its risk assessment to what is known and what can be "reasonably applied". The ELC would also suggest that this important clarification appears in the Guidance.Furthermore, the draft guidance indicates that all main food groups will contribute to the total exposure. As EFSA clarified orally during the 28 November technical meeting on intake assessment with stakeholders that the calculation would use the 95th percentile for the highest food group in addition to the means for all the others, the ELC suggests that this mentioned explicitly in the guidance, and should be reflected in the forthcoming 'exposure template'. We would also propose that in some circumstances of extreme variability of intake for a defined food category, median data as opposed to mean data would be much more representative of population intake.	The ANS Panel appreciates that it may be difficult for the applicant to provide such information, but considers it to be essential for the risk assessment. The ANS Panel intends that as much available data or information should be provided as possible. Where data on uses and use levels in other fields can not be readily obtained, the ANS Panel requires information that such uses occur and may use assumptions to provide an estimate for comparative purposes. The ANS Panel considers that the mean data is the basis of its risk assessment and not the median data, as the consequences of using median data are that such data might be lower than the mean data.

51	Federation of European Specialty Food Ingredients Industries (ELC)	3.2.1.2. Estimate of exposure to residues or contaminants	Line 713: The ELC would like to reiterate its comment made on line 598.	Text has been modified to address the issue.
52	Federation of European Specialty Food Ingredients Industries (ELC)	3.2.2. Submission of data	Lines 720 – 721: It is proposed that applicants provide data in the framework of a template. As the structure of this kind of template would necessarily have an impact on the building-up of application dossiers, which will concern a wide variety of products, the ELC welcomes EFSA's plan to submit the template to the stakeholders for their feedbacks, as it was announced during the 28 November technical meeting on exposure assessment.	The draft template (FAIM) is foreseen to be circulated in June 2012 to the stakeholders for their comments and feedback.
53	Federation of European Specialty Food Ingredients Industries (ELC)	4. Toxicological studies (Toxicokinetics and Toxicity)	General comments It is stated in various sections (including the Abstract) that progression from tier 1 to tier 2 is dependent on absorption and/or demonstrated (geno)toxicity. However, the ELC notes that it is not stated in the document that entering into tier 2 does not necessarily mean that all the tests stipulated for tier 2 are required. For example, in the case of genotoxicity, if the results from in vitro testing in tier 1 are negative, there is no requirement for the in vivo testing given in tier 2 (see lines 1030 – 1031). However even if tier 1 genotoxicity testing is negative, bioavailability and/or end-points form the 90 day study can lead to the requirement to enter tier 2. Section 4.1.1 – Toxicokinetics, General Considerations (line 868) Section 4.1.2 – Tiered Approach to Toxicokinetic Testing (lines 884-885 & 898) Section 4.4.2 – Tiered Approach to Reproductive and Developmental Toxicity Testing (lines 1268 – 1274) The following terms are used:	Text has been modified to address the issue.

			- limited bioavailability - negligible absorption - suspected to be bioavailable It is crucial that these terms are defined, as they lead to progression from tier 1 to tier 2. Presumably, 'bioavailable' means absorbed from the lumen of the gastrointestinal tract into or across epithelial cells and/or into draining lymphatics or vasculature? The ELC noted that in line 1259 the value of 1.5 µg/kg bw/day is proposed in the context of reproductive and developmental toxicity testing: can it be clarified whether this be taken as guidance in the case of progressing in general from tier 1 to tier 2 ?	
54a	Federation of European Specialty Food Ingredients Industries (ELC)	4. Toxicological studies (Toxicokinetics and Toxicity)	Line 737: The ELC suggests that it is clarified that the additive 'as manufactured' includes for practical reasons (such as stability and bioavailability) marketed preparations of the additive, unless the additive is so diluted within the preparation that the excipients are likely to unduly influence the toxicological studies.	Text has been modified to address the issue.
54b	Federation of European Specialty Food Ingredients Industries (ELC)	4. Toxicological studies (Toxicokinetics and Toxicity)	Lines 767 – 772: According to the ELC, not discounting important in vivo studies conducted post 1987 in non-GLP accredited environments, for example specialised toxicokinetic studies, is paramount. We therefore suggest that the exemption for 'historical' and 'mechanistic' studies be broadened to include 'mechanistic (ie toxicodynamic and toxicokinetic) studies', or re-phrased as 'studies important to the risk assessment that are demonstrated to be otherwise well-conducted will be considered on a case-by-case basis'.	The suggested exclusion of toxicokinetics and toxicodynamics from GLP (Good Laboratory Practice) cannot be allowed as there is an absolute requirement in the GLP legislation that "Tests and analyses must be conducted in accordance with the principles laid down in Directive 87/18/EEC where testing is done to obtain data on the properties and/or safety with respect to human health or the environment" and these areas fall into this definition as they are critical data on safety with respect to human health. In contrast the mechanistic studies we exclude are intended to elucidate mechanisms, usually to demonstrate animal observations are not relevant to humans. Crucially toxicokinetics and toxicodynamics (with the possible exception of metabolite isolation and identification) can be performed to specified predefined protocols and SOPs whereas mechanistic studies are

				iterative and experimental.
55	Food Standards Agency	4. Toxicological studies (Toxicokinetics and Toxicity)	Line 739. We suggest that not only should the scientific reasons be described, but that they also should be justified.	Text has been modified to address the issue.
56a	BEUC	4. Toxicological studies (Toxicokinetics and Toxicity)	Lines 754-766: There is a need to allow for other studies than those based on internationally agreed test guidelines to be considered. Whilst industry studies supporting the food additive under assessment should be conducted in accordance with Good Laboratory Practice (GLP), independent, contradictory studies should not necessarily be discarded even though they do not comply with internationally agreed test guidelines (criteria should be developed to guide their case-by-case acceptance for consideration by EFSA).	There is a requirement under the OECD Mutual Acceptance of Data agreement that studies should be based on internationally agreed test guidelines and comply with Good Laboratory Practice (GLP). Whilst studies conducted to support approval of the food additive under assessment should be conducted in accordance with GLP, additional studies identified from the published scientific literature (independent supporting or contradictory studies) not meeting these requirements would not be disregarded but will be assessed on a case-by-case basis for their scientific quality and relevance as part of the overall weight of evidence assessment. However it is unlikely that published studies would contain sufficient information for a full evaluation of their design and conduct due to editorial restrictions on space, therefore an application solely based on such studies would be unlikely to be adequate.

56b	BEUC	4. Toxicological studies (Toxicokinetics and Toxicity)	Lines 793-795: The scope and intent of the sentence ("For nanomaterials which exist as a permitted non-nanoform food additive, the limited additional testing on the nanoform establishes whether read-across from the non-nanoform is feasible for more complex testing") is unclear. A more detailed explanation would be necessary. Our understanding of Regulation (EC) 1333/2008 is indeed that whether or not it already exists in a non-nanoform, a food additive of which the particle size has been altered so as to reach the nanosize should be considered as a new food additive and as such should undergo a full safety assessment.	Further information can be found in the reference (EFSA, 2011a).
56c	BEUC	4. Toxicological studies (Toxicokinetics and Toxicity)	Lines 798-824: We would recommend the greatest caution when considering applying a "presumption of safety" to botanicals and botanical preparations used as food additives. As pointed out by the ANS Panel, botanical food additives' intended uses and use levels not significantly increasing exposure beyond the levels linked to the history of use is only one aspect to be considered. For instance, careful consideration also needs to be given to the production process with a view to ensuring that the substances at stake are genuinely the same as those for which a long history of use without reported adverse effects is being referred to. Another aspect to be examined when it comes to botanicals is their possible interactions with medicines: as these are not necessarily well reported, "presumption of safety" may not be a sufficient guarantee.	The ANS Panel notes that the term (presumption of safety) is used by the botanical guidance, therefore no changes will be made in the guidance document. The EFSA Scientific Committee guidance on botanicals allows the presumption of safety to be applied in certain conditions and we are bound to accept these for food additives when these conditions are met.
57	Federation of European Specialty Food Ingredients Industries (ELC)	4. Toxicological studies (Toxicokinetics and Toxicity)	Lines 820 – 824: According to the ELC, it would be reasonable to take into consideration the long-term use and high levels of use in countries outside the EU in the presumption of safety and history of use.	In agreement with the EFSA Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements (EFSA, 2009b), only the use/use levels known from European Member States can be taken into consideration. This seems also to be reasonable regarding the high standards of (nutri- and) pharmacovigilance and surveillance systems monitoring adverse effects

				established in Europe which e.g. cannot be presumed for less developed countries.
58a	French agency for food, environmental and occupational health & safety	4.1.1. General considerations	lines 842-845: Anses believes that the acceptance of in vitro models to pre-assess metabolism of food additives is an important point in the document on which more emphasis should be put on. Anses suggest that the document should systematically ask to compare human cell in vitro models to animal cell in vitro models. This comparison would allow characterise differences in terms of metabolism between the animal models used to assess toxicity of a food additive and the human consumer. Furthermore, the comparison between human cells and animal cell models would allow identifying the main metabolite which might of concern and those who should deserve further assessment given their similarity or abundance in both models. The document should also considers how to deal with situations like in which different metabolites are identified in both models, suggesting that the animal model tested in further toxicity studies might not represent human metabolism thus not allowing risk characterisation. Results from this comparison would be useful to better characterise genotoxicity potential of a food additive since it will give hints on the relevance to apply S9 activation in genotoxicity testing to characterise the human situation.	The ANS Panel considers that there is already considerable emphasis in the guidance on ensuring that the animal species used for testing is appropriate. The need for all testing should be determined on a case-by-case basis. The ANS Panel does not consider mandatory metabolism studies relevant in all circumstances.
58b	French agency for food, environmental and occupational health & safety	4.1.1. General considerations	Lines 848-856: Anses suggest that it might be of interest to extent the demand in the document concerning determination of the area on the curve (AUC) to the dose tested in a toxicity study or at least in more than one dose. A extended view of the AUC at different doses would allow confirming acceptable exposure to the additive at different doses, confirming a real dose-related exposure inside the body and confirming that linearity kinetics assumptions of	Kinetic parameters should be determined after single administration at different dose levels and following repeated dosing at relevant dose levels, the relevance of these kinetic parameters for those at dose levels causing toxicity should be established. (This may allow toxic effects due to saturation of kinetic processes that would not occur at anticipated exposure levels to be discounted).

			exposure .	
59	Federation of European Specialty Food Ingredients Industries (ELC)	4.1.1. General considerations	Line 872: the ELC would appreciate if "relevant constituents" could be defined as it is questioned how these can be determined.	Relevant constituents are generally considered to be the major components and those other components with known or demonstrable biological or toxicological activity.
60a	BEUC	4.1.1. General considerations	Lines 846-850: Measuring plasma, whole blood or serum is indeed relevant to assess systemic exposure. But urine, as biological matrix, would also be worthwhile analysing as it contains higher concentrations of so-called phase I (hepatic) and/or phase II (conjugation products) metabolites. This is important as it cannot be excluded a priori that metabolites be possibly more toxic than the food additive itself. Also, the residence time - and thus detection as a function of time - is often significantly higher in urine as compared to that in blood / serum / plasma.	Text has been adjusted to address the issue.
60b	BEUC	4.1.1. General considerations	Lines 857-861: Mention of "ex vivo" studies would be useful as it might bring an added value. "Ex vivo" means an experiment or analysis on a living tissue or material, but executed outside the body. The term "in vitro" is more restrictive because it stipulates only that the experiment/analysis does not take place in a living organism but in a test tube. For studies concerning ADME toxicokinetics in which subcellular organelles, perfused organs, etc. are used, the mentioning of "ex vivo" studies would be interesting.	The term in vitro is generally considered to cover all studies not carried out in intact or anaesthetised animals including ex vivo organ perfusion studies. As in situ perfusion studies such as intestinal loops are conducted in anaesthetised animals, these are considered in vivo studies.
61a	BEUC	4.1.2. Tiered approach to toxicokinetics testing	Lines 884-885: "Demonstration of negligible absorption from theoretical considerations" is very questionable especially if concluding on negligible absorption results in not undertaking higher tiered toxicological studies. Better guidance/criteria on when to conclude on negligible absorption should be provided.	Text has been adjusted to address the issue.

61b	BEUC	4.1.2. Tiered approach to toxicokinetics testing	Lines 916-917:The text refers to "subcellular fractions and/or cells", in contradiction with lines 857 where "subcellular organelles" is mentioned. An organelle is a part of a living cell (and thus smaller). Fractions are mostly obtained in a non-biological way, unlike organelles. Texts of pp. 26 and 27 should be harmonized.	The text has been harmonised.
62a	Food Standards Agency	4.2. Genotoxicty	Lines 1101 to 1104. It is unclear how a risk assessment would be carried out where there was clear evidence of genotoxicity in somatic cells in vivo. From what is said, it appears that demonstration of a large margin of safety for any possible carcinogenicity would not provide adequate reassurance of safety because of the possibility of adverse effects also on germ cells. Does this mean that no additive may ever contain an in vivo genotoxin at any detectable concentration?	The TTC concept would provide a suitable basis for decisions on the risks of genotoxic residuals and contaminants. The ANS Panel considers that if the margin of exposure is sufficient to conclude that a carcinogenic risk would not be significant, the risk of heritable effects is also likely to be negligible.
62b	Food Standards Agency	4.2. Genotoxicty	Line 1003: needs to refer to "potentially carcinogenic, and also mutagenic in germ cells". Otherwise it appears that the concern for germ cells relates only to carcinogenicity.	Text has been modified to address the comment.
63a	BEUC	4.2.1. General considerations	Line 972:The reasons for excluding "indicator tests" from the "basic battery" should be explained.	Text has been modified to address the comment. Further details can be found in the EFSA Scientific Committee guidance document on genotoxicity testing (EFSA, 2011d).

63b	BEUC	4.2.1. General considerations	Lines 987-993: Reference is made to the EFSA Scientific Committee (SC)'s Opinion on genotoxicity testing strategies applicable to food and feed safety assessment, which contemplates the use of the "Threshold of Toxicological Concern (TTC)" approach in assessing the likelihood of carcinogenic or transmissible genotoxic effects of low-exposure substances such as impurities, metabolites and degradation products of food additives. We note however that in the same opinion, the SC also states that "genetic alterations in somatic and germ cells are associated with serious health effects, which in principle may occur even at low exposure levels". Moreover, still according to the SC opinion, "application of the TTC approach requires reliable information on human exposure". A recent technical meeting hosted by EFSA to discuss exposure assessment of food additives has shown that reliable and representative data on food additive usage (hence on potential exposure to food additives' impurities or degradation products) is not always available. In view of the severity of the adverse effects at stake, the acceptability of the TTC concept seems therefore highly questionable.	In line with the opinion of the EFSA Scientific Committee on TTC it would be possible to use the TTC for residuals, contaminants and metabolites in/of food additives; however for the additive itself testing would be mandatory since the SC state.
64	Federation of European Specialty Food Ingredients Industries (ELC)	4.2.2. Tiered approach to genotoxicity testing	Line 997: "Testing is mandatory for all additives": it may be possible that an additive by its nature (high viscosity) is not suitable for this kind of testing.	All compounds can be formulated in a manner that is suitable for testing, therefore all additives require tier 1 testing.
65a	Food Standards Agency	4.3. Toxicity testing (subchronic, chronic and carcinogenicity)	Line 1118. An NOAEL might be identified even when adverse effects were not found at higher dose levels (i.e. when there was no effect at the highest dose).	The ANS Panel acknowledges the comment but feels that no textual changes should be made in the guidance document. When the highest dose tested has been used as the NOAEL, the ANS Panel will note it in its opinion since this is a source of uncertainty.

65b	Food Standards Agency	4.3. Toxicity testing (subchronic, chronic and carcinogenicity)	Line 1131. We suggest adding "normally" after "should". As explained further down the paragraph, there are exceptions.	Text has been adjusted to address the comment.
66	BEUC	4.3.1. General considerations	Lines 1168-1171: There has been some controversy about the ability of studies conducted according to the OECD test guidelines to capture the impact of early exposures to carcinogenic substances (e.g. aspartame). Concerns have also been expressed that these studies might miss some late effects of such exposures. We would therefore encourage EFSA, when evaluating the safety of food additives, to consider all available scientific evidence, including from relevant non-OECD/non-GLP compliant independent research (e.g. lifetime toxicity studies) as it might serve as an 'early warning' for potential hazards that current testing practices might otherwise overlook.	The ANS Panel considers all the data on a case-by-case basis and evaluates the quality and significance of such data.
67a	BEUC	4.3.1. General considerations	Lines 1122-1126: The meaning/intent of the language "significant toxicokinetic differences" is unclear. Differences between rodents and humans are known. This paragraph and conditions could be formulated more accurately.	This should be evaluated on a case by case basis and it is not feasible to provide detailed criteria.
67b	BEUC	4.3.1. General considerations	Lines 1127-1130: The text stipulates that "suffering, severe toxicity, morbidity, or death" should be avoided. However, this seems difficult in case of cardiac toxicity, i.e. for a substance that has the heart as a target organ.	The guidance document describes the intention, which is reflected in animal welfare legislation and test guidelines, but can not preclude suffering due to unpredictable effects or dose-response relationships in a particular study.

68	Ajinomoto Europe Sas	4.3.1. Toxicity testing (subchronic, chronic and carcinogenicity) General considerations	line 1182-1192, Chronic toxicity and carcinogenicity We strongly support that the draft guidance describes unnecessity of the routine conduct of two long-term rodent carcinogenicity studies using mouse as the second species, and clearly state that the carcinogenicity study using one species, the rat, is appropriate. Hopefully, it may be even more desirable to describe that the second carcinogenicity test using mouse in addition to the first test using rats, shouldn't be performed if there is no clear reason to perform the second test, from the aspect of animal welfare.	The ANS Panel supports this position (i.e. that there is no need to use 2 species) and considers that it is appropriate to perform the carcinogenicity study in one species, preferably the rat.
69	BEUC	4.4.2. Tiered approach to reproductive and developmental toxicity testing	Lines 1258-1262: We are not fully clear with the intention behind the provisions contained in lines 1258-1262. They seem to imply that reproductive and developmental toxicity studies would not be needed where intakes are below a certain value (TTC for Cramer Class III). Should it be the intention, we would be extremely concerned with such a "TTC-like" approach as TTC fails to capture endocrine-disruptive modes of action which can trigger adverse effects even at very low levels of exposure. Indeed, TTC ignores the fact that when it comes to endocrine-disruptive chemicals (EDCs), the key factor to consider is not that much the level of exposure but rather its timing. When occurring at critical windows of development, even low-level exposure to EDCs can indeed result in life-long health problems. Moreover, TTC values have been derived from databases of test studies of which the design was not appropriate for the identification of endocrine disrupters. It is widely recognised that current testing practices (incl. complying with OECD test guidelines) largely fail to capture endocrine-disrupting modes of action. Given these limitations, we would be extremely wary of setting a threshold below which potential EDC-induced developmental adverse effects would not be further investigated.	The ANS Panel notes that this point is addressed and supported in the revised SC opinion on TTC.

70	FPS Health, Food Chain Safety and Environment	4.5. Additional Tier 3 studies	Why is food intolerance and hypersensitivity linked to tier 3? I propose to delete "tier 3" in the title of 4.5. If data exist on this matter, it should always be taken into account. EFSA should ensure that literature data of effects in consumers are always taken into account (e.g hypersensitivity and food intolerance, laxative effects), even when the applicant does not include it in the dossier. EFSA could elaborate more on laxative effects/gastrointestinal discomfort. Are human tolerance studies not systematically needed for polyols and for undigestable additives derived from fatty acids and maybe other groups of additives? Will EFSA take this into account for establishing an ADI?	Text has been modified to address the issue.
71	Ajinomoto Europe Sas	4.5.1. Human studies	line 1337-1373, 4.5.1. Human studies In case of pharmaceuticals, ICH guideline clearly determines which non-clinical safety studies has to be done before the conduct of human clinical trials, and also determines the necessary period of animal toxicological test for each period of human trials. When we plan a human study of unauthorized candidate substance for a food additive, it is sometimes interrupted due to the absence of clear rule about the necessary non-clinical safety studies which must be done before the human study. Therefore, it is desirable that the essential non-clinical safety tests before human study are clearly described in the guideline.	Prior to the commencement of human studies, there should be both sufficient data for safety assessment and ethical approval. The ICH guideline for clinical trials on pharmaceuticals describes the duration of non-clinical safety studies required before the conduct of human clinical trials of a specified duration. A complete package of tier 1 testing (kinetics, 90-day study and genotoxicity) would probably be sufficient data for safety assessment for single or short-term repeated administration human studies under clinically controlled conditions.

72a	Federation of European Specialty Food Ingredients Industries (ELC)	4.5.2. Immunotoxicity, Hypersensitivity /allergy and Food Intolerance	Lines 1427 – 1431: With regard to allergy, safety evaluations should use scientifically sound and relevant studies. Although the ELC acknowledges that new methods can be used, we would suggest that any reference to studies of which the methods are not established or of which the relevance remains unclear is carefully assessed beforehand, in the light of their potential scientific outcome and significance.	The introductory section on allergy is only supposed to provide the reader with general background information. Thus, in the draft guidance document, performing "double blind placebo controlled oral food challenges or prick testing in humans" is only cited as an example and a possibility, and is not a requirement. Clearly, the use of human data must be restricted to specific cases where they may be already available because e.g. the safety of the food additive has already been assessed for other uses such as in medicines. In that case, the existing data can be useful and have to be taken into consideration. Also, case reports of human sensitisation (including other route of exposure than oral) can be informative.
72b	Federation of European Specialty Food Ingredients Industries (ELC)	4.5.2. Immunotoxicity, Hypersensitivity /allergy and Food Intolerance	Lines 1431 – 1432 ("oral food challenge or prick testing"): These techniques are used to identify for which food a person is allergic. They are not suitable to research whether or not a substance is a potential cause for an allergic reaction. It is unethical to put a test-person through a test which purpose is to intentionally inflict an allergenic response on that test-person on the test substance. A stepped approach also in relation to allergenicity would be more advisable rather than to start with suggesting these tests (e.g. check for known allergenicity of the source, check for known allergenicity of the protein, check for homology of part), as it is described in lines 1436 - 1438.	The same rationale, as in the previous response (see answer above), applies.

73	BEUC	4.5.2. Immunotoxicity, Hypersensitivity /allergy and Food Intolerance	Lines 1446-1455: Intolerance reactions are only explained by pharmacological effects and "other still undefined mechanisms" but the text does not mention alternative explanations like the known genetic differences in enzymatic activity (e.g. the presence or absence of the enzyme lactase in some individuals).	Lactose is not a food additive per se but it may be present in traces in some food additives that are derived from lactose (e.g. lactitol). In that case, the amount of residual lactose is so low that it could not be considered of safety concern even for individuals intolerant to lactose. Phenylketonuria is a well known metabolic genetic disorder where individuals lacking the enzyme phenylalanine hydroxylase cannot metabolise the amino acid phenylalanine and are therefore at risk if they are exposed to food additives containing high levels of phenylalanine (aspartame and derived sweeteners). In order to warn this population, foods containing additives with high levels of this amino acid are labelled as such. Therefore, genetic differences in enzymatic activity can be an explanation for the origin of intolerance reactions. However, in the guidance document the text does not regard the origin of the intolerance but the mechanisms/molecules responsible for the onset of symptoms. In this connection the reaction is not immunologically mediated but results from the release of bioactive amines and other still undefined mechanisms, that can be the consequence of a genetic peculiarity, indeed.
74	Food Standards Agency	4.5.2 Immunotoxicity, Hypersensitivity /allergy and Food Intolerance	Line 1454 motes that post-marketing surveillance is essential – does ANS propose to give any guidance on how this should be conducted? Should it be mentioned in Appendix A?	The ANS Panel notes that it is not EFSA's (in particular ANS Panel/FIP unit) remit to provide any guidance on post-marketing surveillance which may be an element of risk management; however, the ANS Panel acknowledges the possible contribution of post-marketing surveillance in the risk assessment process.
75	University Wuppertal + BAuA Dortmund	5.1. Integrated (alternative) testing strategies	Are "integrated testing strategies" a synonym of "alternative methods"? If so, please state, if not, please define both in order to avoid irritation. Instead of just pointing to the Cosmetics Directive, could you include a brief summary / description of the "alternative methods" in order to make the chapter more comprehensible. What	The Adler et al. (2011) review is very extensive and comprehensible, outlining all the latest developments in the field. Taking into account that this is a guidance document and not a guideline, the ANS Panel feels that as this section is only supplementary to the core studies, a brief summary/description on the alternative methods is

			about epidemiology or biomonitoring?	not feasible as it wouldn't accurately reflect the area. Nor does the ANS Panel consider necessary guidance on epidemiology or biomonitoring, which can only be conducted as part of post-marketing surveillance.
76	Food Standards Agency	5.4. Reporting and referencing of studies	Line 1515: BMDL10 value for quantal data (words need reordering)	Text has been adjusted.

* Please note that the line numbers included in the comments refer to the draft guidance document published for the public consultation