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SUMMARY REPORT

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What's new on Novel Foods

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I INTRODUCTION

On 19-20 November 2009 EFSA organised its 13th Scientific Colloquium with international experts to discuss scientific information needed for applications on novel foods and novel food ingredients submitted for authorisation in the European Union.

Novel foods are foods and food ingredients that were not used for human consumption to a significant degree within the European Community before 15 May 1997. Regulation (EC) No 258/97 of January 1997 lays out detailed rules for the authorisation of novel foods and novel food ingredients. These rules were applicable also to foods containing or consisting of a genetically modified organism (GMO) until 2003 when the GMO Regulation came into force. The scientific aspects of information necessary to support applications for placing on the European market novel foods and novel food ingredients were addressed by recommendations of the Scientific Committee on Food (SCF).

In 2003 EFSA took over the tasks of the SCF in providing a safety assessment on novel food applications requested by the European Commission. In the light of the upcoming revision of the Novel Food Regulation and considering the significant development of emerging sciences such as nanotechnology and the proposed introduction of the evaluation of traditional foods from non-EU countries on the basis of a history of safe use, EFSA expects to be asked by the European Commission to provide scientific and technical guidance for applicants in their preparation and presentation of the application for novel food and novel food ingredients.

The objective of this Colloquium was to bring together international experts and interested parties from different sectors for an open scientific debate on key issues related to the foreseen revision of the Novel Foods Regulation that will serve as input for the preparation of an EFSA Guidance for applicants.

The Colloquium was attended by around 100 international experts in safety assessment and regulatory affairs, food manufacturers and others involved in novel foods, coming from 24 countries, including the United States, Peru and New Zealand. A briefing note had been circulated to all participants before the Colloquium raising a set of discussion points on four topics. After a short plenary session with introductory presentations the meeting broke up in small groups to enable in-depth discussions. The discussion groups (DGs) addressed the following themes:

DG 1 – History of (safe) use and traditional foods from non-EU-countries

DG 2 – Data requirements and approach for anticipated intake

DG 3 – Key issues in absorption, distribution, metabolism, and excretion (ADME) studies, toxicology and allergenicity

DG 4 – Data requirements to demonstrate safety of foods derived by nanotechnology

In a final discussion session, one rapporteur for each of the four discussion groups reported back to the plenary. Discussions on the assessment of novel foods focused in particular on the history of safe use of traditional foods from non-EU countries but which would be considered "novel" in the EU, intake assessment, and the toxicological and allergenicity assessment of novel foods. Participants also addressed the issue of nanotechnologies, in particular data requirements for demonstrating the safety of novel foods made using nanotechnologies.

II REPORTS FROM DISCUSSION GROUPS

DG1: History of (safe) use and traditional foods from non-EU-countries

Rapporteur: Clemens van Rossum - Chair: Seppo Salminen

The following seven questions on this topic were discussed:

1. Can general requirements for the food characteristics and compositional data be specified applicable to all traditional foods, to foods with novel breeding methods, to foods that are marketed to another target group and to foods that are consumed at another stage of their development?

In the EC proposal for revision of the Novel Food Regulation (EC, 2007), a separate procedure was introduced for traditional foods from non-EU countries. A number of amendments were proposed in a later version of this text, representing a common position, dated 7 September 2009 (EC, 2009). This latest proposed text includes general criteria as part of the definitions for traditional foods from non-EU countries and for the history of safe food use.

> **Article 3.2 (d)** "traditional food from a third country" means novel food, other than the novel food under sub-points (i) to (iv) of point (a), derived from primary production, with a history of food use in any third country, such that the food in question has been and continues to be part of the customary diet for at least 25 years in a large part of the population of the country;
>
> **Article 3.2 (e)** "history of safe food use in a third country" means that the safety of the food in question is confirmed with compositional data and from experience of use and continued use for at least 25 years in the customary diet of a large part of the population of a country.

From a scientific point of view, it may be challenging to translate these concepts into general requirements, valid for widely diverging types of food. Foods consumed for more than 25 years in a given country could include primary products, whole foods derived from these primary products, food ingredients, or food supplements. It has to be noted, though, that the proposed definition of traditional food refers specifically to products derived from primary products. This is addressed in more detail in recital 6 in the same document (EC, 2009), which states:

> "…. Furthermore, it should be clarified that foods from third countries which are novel in the Community can be considered as traditional only when they are derived from primary production as defined in Regulation (EC) No 178/2002[1], whether they are processed or unprocessed (e.g. fruit, jam, fruit juice). However, foods thus obtained should neither include foods produced from animals or plants to which a

[1] This source text defines the concept as follows: 'primary production' means the production, rearing or growing of primary products including harvesting, milking and farmed animal production prior to slaughter. It also includes hunting and fishing and the harvesting of wild products.

non-traditional breeding technique was applied or foods produced from the offspring of such animals, nor foods to which a new production process is applied…."

The examples given in this recital are processed whole foods derived from primary production by simple processing techniques. On the other hand, fermented products or fractions derived from primary products by simple processes may have been consumed as part of the customary diet, and satisfy other requirements set in the definitions presented above. The concepts used in the proposed definitions (including *the customary diet*) may be interpreted in different ways (Jones and Craddock, 2009). This could cause problems similar to those related to some concepts in the current Novel Food Regulation (Verhagen et al., 2009). Nevertheless, it was felt that products used as food supplements are generally not considered as part of the customary diet, and that extracts from primary products should not be assessed as traditional foods. Furthermore, the application of production techniques not used traditionally would contradict the basic concept of a separate procedure for traditional foods. So products from novel breeding techniques should not be considered as traditional foods. Similarly, marketing products to other target groups or consuming products at a different stage of their development conflicts with accepting the established history of consumption as evidence for safety.

The group concluded that compositional data should be used to characterise the traditional food, and serve as a baseline for comparison for actual products to be marketed. Both nutrients and other known substances have to be considered.

2. How detailed should data on the macronutrients and micronutrients be documented (amount and type of fat, protein, carbohydrates, or also the lipid acid profile, amino acids, vitamins, minerals, ...).

There is much experience in gathering and reporting general food composition data, both within the EU and in other countries in the world. These databases could be used to model the general requirements for characterising the traditional food by using analytical data, including macronutrients and the most relevant micronutrients. It can be envisaged that more detailed data will be relevant for specific product types, such as the fatty acid profile for oils. In these cases, useful information from other sources, such as CODEX standards, may be available.

3. What are the data requirements to establish the "specifications" of such as batch testing, methods, validations, certification and documentation?

In principle, criteria would have to be similar to those used for testing other foods, but the experience from other NF assessments is that the quality of data provided in applications varies strongly. It should therefore be emphasized that reliable data should be produced, by using up to date analytical methods and recognized international standards. The analyses should be performed by qualified laboratories. In order to apply the concept of traditional foods in a meaningful way, the identity of the traditional food should be determined beyond doubt. Together with the compositional data, this will ensure that the historical data on previous consumption is relevant for the actual product. If the traditional food is well defined, this may help to substantiate the safety of an essentially identical product with a different geographical origin.

4. Which data should be requested for the history of safe use (including possible adverse effects)?

This question was discussed together with:

5. What is the relevant information on the "experience of use and continued use in the normal diet of a large part of the population of a country", which should be provided by an applicant?

Data on known antinutrients and inherent toxicants should be provided on a case-by-case basis. Any data from literature on adverse effects, related to the traditional food, should be discussed by the applicant. This should also include any reports on possible allergenicity of the product. Data on previous use in other countries than the country of origin may also be useful.

It is important to establish that the previous consumption was not just anecdotal, and therefore reference is made to the number of consumers in the country of origin. Nevertheless, it is impossible to determine from a scientific point of view if a certain number of consumers would be sufficient to demonstrate the history of consumption. Furthermore, the definition refers to *a large part of the population of a country*, but a regional product in a large country could be consumed by more people than a product that is consumed by everyone in a very small country. It therefore seems to be more useful to compare the historical use to the intended level of use and the intended target groups. The consequences of any differences therein should be considered. This is in line with the approach for the comparative safety assessment of novel foods and foods from genetically modified organisms (Constable et al., 2007).

For a few products, that can be regarded as traditional foods, an authorisation dossier was previously assessed under the current Novel Food Regulation. One of these dossiers (regarding baobab fruit pulp) was taken as an example, showing the type of information that can be used to substantiate a history of safe use. This can include information on training people for harvesting, product specification, and sales figures by companies, as well as information from government organisations, ethnobotanists, peer reviewed publications, or patent applications. Data requirements were also discussed in publications (Jones and Craddock, 2009) and (Constable et al., 2007).

6. Discuss the data requirements and the relevance with respect to 'significant changes' related to the production process, considering composition, residuals and critical toxicants.

In principle, the product should be identical to the traditional food, for which historical data are available. However, it is to be expected that changes or improvements in production methods will be applied in the course of time. Nevertheless, the concept of a traditional food could still be applied if the product matches approved standards of identity, including compositional data.

7. Which considerations should be addressed by an applicant with regards to non-nutritive dietary constituents such as secondary plant metabolites, anti-nutritional factors and contaminants.

The presence of such substances can only be considered on a case-by-case basis. Several sources of information may be available, such as scientific literature on the species itself and related species, and expert judgement by botanical specialists. The conditions of use of the traditional food may be important, since these can reflect traditional risk management solutions.

Background documents

Constable A, Jonas D, Cockburn A, Davi A, Edwards G, Hepburn P, Herouet-Guicheney C, Knowles M, Moseley B, Oberdörfer R, Samuels F, 2007. History of safe use as applied to the safety assessment of novel foods and foods derived from genetically modified organisms. Food Chem Toxicol. 2007 Dec;45(12):2513-25. Epub 2007 Jun 21. http://www.ilsi.org/Europe/Publications/2007Hist_Safe.pdf

EC (European Commission), 2007. Proposal for a Regulation of the European Parliament and of the Council on novel foods and amending Regulation (EC) No XXX/XXXX. COM(2007) 872 final. http://ec.europa.eu/food/food/biotechnology/novelfood/COM872_novel_food_proposal_en.pdf

EC (European Commission), 2009. Common Position with a view to adopting a Regulation of the European Parliament and of the Council on novel foods, amending Regulation (EC) No 1331/2008 and repealing Regulation (EC) No 258/97 and Commission Regulation (EC) No 1852/2001. http://register.consilium.europa.eu/pdf/en/09/st11/st11261.en09.pdf

Jones, A and Craddock, N, 2009. Definitions, Concepts and History of Safe Use Assessment. Issue Paper Prepared for UNCTAD BioTrade Initiative concerning the proposed amendment to the European Novel Foods Regulation with particular reference to Traditional Foods from Third Countries, UNCTAD and GTZ. http://www.biotrade.org/BTFP/BTFP-docs/novelfoods-issue.pdf

Verhagen H, te Boekhorst J, Kamps L, van Lieshout MJ, Ploeger H, Verreth D, Salminen S., and van Loveren H, 2009. Novel Foods: an explorative study into their grey area. British Journal of Nutrition 101: 1270-1277. doi:10.1017/S0007114508184690. http://www.ncbi.nlm.nih.gov/pubmed/19175945

DG2: Data requirements and approach for anticipated intake

Rapporteur: Judith Buttriss - Chair: Karl-Heinz Engel

A proper estimate for anticipated intake (exposure assessment) for average and high consumers is a key element in risk assessment. The exposure assessment allows estimation whether the anticipated intake would be higher/lower than a specific toxicological reference value (e.g. tolerable upper intake level, acceptable daily intake). Where no such value has been derived it allows estimating the margin of safety (MOS), i.e. the anticipated intake in relation to a no-observed adverse effect level (NOAEL) from an appropriate toxicological study. The discussion group was given four questions to consider:

1. What are the requirements for a food consumption database for the purpose of intake assessment for the population in the EU?

1a. What is already available at a national level?

Discussion started on the different surveys of European populations that are already available. There are a number of high quality ones already used for novel food assessment that were designed with risk assessment in mind as well as assessment of nutrient intake. Participants referred to the new UK rolling National Diet and Nutrition Survey programme and Irish diet and nutrition survey both of which are already being used for risk assessment in Europe. A strength of both of these surveys is that data are collected for individuals. As with all surveys, there are also limitations. For example, the data are never totally up to date and there is currently no information for infants or pregnant women, and the data for ethnic groups is limited. The published data are presented in an aggregated format but the raw data can also be made available. But, regardless of the quality of the data, for the assessment of novel foods that have yet to reach market, it is necessary to use data for existing foods to estimate the likely consumption amount and frequency of the proposed novel food.

1b. EFSA's contribution

EFSA then updated the group on the work it has been undertaking to draw together the existing population survey data. Already available is the 'concise database', which provides aggregated data for around 15 food categories from 19 countries. Before the end of 2009, EFSA expects to publish a Guideline on general principles for national food consumption surveys. Available in 2010 will be a 'comprehensive database' which will provide disaggregated data for adults and children. A limitation of both of these databases is that the methodology used varies from survey to survey. Therefore EFSA is currently considering establishing a pan European survey of individuals using a consistent methodology. This would focus on a representative sample of adults plus samples of children aged 0-1, 1-3, 3-10y. EFSA is considering a minimum of 1000 adults and 1000 children per country, with larger samples in countries with larger populations. As well as dietary data, information will also be collected on physical activity and there are plans to use a food frequency questionnaire (FFQ) methodology to collect data on supplement usage and on medicines that might contain nutrients.

A number of recommendations to EFSA were made by the group. It was thought to be important to consider at-risk groups, especially children and pregnant women, and possibly also older people. It would also be useful to have information on vegetarians and other groups with particular dietary preferences. Special attention should be given to rarely consumed foods (a new statistical method has now been developed that can be used in such circumstances) and there is also a need for validation in more than one country of a combination of a FFQ and 24h dietary recalls that may be of use when collecting information on food supplements use. There is also a need for industry's support in collecting data on branded foods. The length of the survey period will be important in order to be able to extrapolate adequately, for risk assessment purposes, from the short to medium to longer term. It was agreed that at least some of the survey data should be placed in the public domain and in a form that meets the needs of applicants for novel food approvals.

There was support from the group for such a survey designed to provide data at the pan European level. Furthermore whilst it will be important to consider the requirements of such a survey from different perspectives – novel foods, additives, nutrient intakes – recognition is needed that above all the dietary survey should be as robust as possible, taking subject compliance and available funding into consideration.

In novel food assessment it is particularly important to be able to identify groups with particularly high intakes. Consumption surveys give us this sort of information. But if consumption is very low, it is far more difficult to identify the required details. It was also agreed that concentration in the product AND amount consumed AND frequency are all important metrics to establish.

It was decided that a one size fits all approach to risk assessment may not work for novel foods because the category includes different types of product. Examples discussed included replacement for a macronutrient (e.g. a type of dietary fibre), a functional ingredient where a particular amount is needed for the function to be exerted, and an ingredient linked to a health claim where again a particular amount is required to achieve the health effect. Food consumption surveys will be an appropriate approach for some but not all of these scenarios; another approach that might be used in tandem or instead was considered to be a FFQ linked to market data.

1c. Food composition data: the EuroFIR e-search facility

Having appropriate food composition data is also an important factor and the EC-funded EuroFIR Network of Excellence, that was established 5 years ago, has now established an e-search facility to enable access to electronic national food composition databases. The e-search portal currently provides access to around 20 databases which together provide harmonised data (for example, with respect to descriptions and data quality; a feature of the work of EuroFIR) on almost 50,000 foods, including branded food items. There are also specialist databases, such as a database concerning plant bioactives. Access to the e-search facility will be publicly available from July 2010 to members of the EuroFIR AISBL (details available from paul.finglas@eurofir.org). A limitation of existing food composition databases is that they provide very little information on the composition of food ingredients and food supplements. It was agreed that collection of such data should be a feature of future food composition and food consumption surveys. It was noted that the 4-year EC funded project, FACET, is collecting information on flavourings, additives and contact materials (www.ucd.ie/facet/).

2. Discuss different approaches to derive intake estimates, their advantages and disadvantages. How can "reasonable worst case" intake estimates be derived for high consumers? How to derive a reasonable intake estimate for the average consumer?

The current approach to establishing 'worst case' intake estimates requires anticipation of what the consumption of a novel food by various population groups might be several years hence. The difficulty in producing realistic estimates is a weakness that can result in gross overestimates, regardless of how good the consumption data are. In arriving at a worst case estimate, a number of assumptions have to be made, which increasingly magnify the error, especially when the ingredient may be present in a number of food formats. Those with experience in this area believe that, where the novel ingredient is available in multiple formats, real consumers do not achieve the worst case scenarios, although estimates are more reasonable where there is a single food source.

Assumptions need to be linked with the expected target group for the food, and to high consumers within this group. If real data are available, the 97^{th} or 95^{th} percentile can be used and if there are no survey data on the actual population, it may be possible to use data from another population as surrogate. Where there are multiple use options for the novel food, an approach already in use is to assume intakes at the 95^{th} or 97^{th} percentile for 2 options and then the average for the remaining options. The choice of centile should be determined by the survey size and duration (there is a need to avoid extreme outliers which may result from miscoding or from temporary atypical behaviour). For safety assessments, likely intakes by consumers of the proposed product(s) should be considered rather than intakes across the population (consumers and non-consumers).

With regard to estimates for the 'average consumer', several options were mentioned: using the mean intake of a similar food in food consumption surveys; where there is a functional ingredient, applicants could identify a specified daily intake for the target group and restrict intake by limiting the use level/ foods that can carry the ingredient, in conjunction with relevant legislation. A third approach would be to use a FFQ in conjunction with market data. The possibility, if necessary, of using a post market survey to refine estimates and to check for unintended use was also discussed; this was popular with some but not all of the discussion group.

3. Discuss uncertainties when estimating intakes, and how to address them.

There was discussion about the usefulness of attempting to derive an accurate intake estimate for a product that is not yet on sale. It was suggested that rather than deriving a worst case scenario that most likely is going to be incorrect, it is better to start with a realistic estimate, made by the applicant based on the available data, and then if necessary conduct a post-market assessment to arrive at a more secure figure. This approach would put more emphasis on the post-market stage. Producing reasonable estimates is particularly difficult when there are multiple product formats (such as with stanols/sterols that are provided via spreads, yogurts etc). Reference was made to a theoretical paper from ILSI on fortification of foods. Throughout the group's discussion, the importance of using a step wise approach to risk assessment was emphasised, with clear actions at each step. The required approach needs to be clear so that applicants understand how to apply and use the approach. In case worst case estimates are made, the applicant should clearly describe the methods and data used.

Much of the discussion related to uncertainties but there are also a few certainties. For example, it might be assumed that products enriched with stanols are all enriched up to the

functional level, making estimation relatively easy (whereas concentrations of contaminants can be far more variable). The extent of long term, regular use of supplements is an area where there is the least data, and more work is needed. It was suggested that the potential simultaneous use of a novel ingredient in both food supplements and fortified foods is one of the most challenging situations as it is difficult to predict (when estimating worst case intakes) whether or not the food and the supplement will be used in tandem or as alternatives. Therefore, the risk manager/policy maker should make an *a priori* decision how to distribute amounts over foods and food supplements (e.g. 100 : 0 or 50 : 50 or 0 : 100). Thereafter, the appropriate risk assessment procedure can take place.

4. Which approach should be followed by the applicant for his proposal of an intake estimate? What kind of data is required from the applicant?

Anticipation of intake levels is very challenging for applicants, who have to estimate in advance which food vehicles may receive both approval and uptake in the market place, which is constantly evolving. There was support from some for greater use of post-market assessment to refine estimates and to check for unintended consequences, where necessary. With regard to estimating potential intake of traditional foods from a third country, it should be possible to identify a food that is consumed in the same way as the 'new' food, to establish an order of magnitude. For traditional foods, the quantitative part of the assessment may be much less important than for other novel foods.

In general, though, a case by case approach is required in novel food assessment and the opportunity now exists to use the databases referred to above that have been compiled by EFSA using the national food consumption surveys that are already available. It was considered unfair to expect an applicant to do a detailed assessment for 27 Member States. Instead it would be more reasonable to ask for detailed data for one or two Member States plus some statements that focus on possible worst case consumption scenarios. Again, EFSA's recently collated databases may be a useful means of pinpointing countries that may have particularly high intakes (recognising the heterogeneity in the methodology used for the national surveys).

It was concluded that it was not appropriate to recommend a standard approach; the approach should be determined by the type of novel food. Above all, there is a need for common sense, supported by high quality data!

DG3: Key issues in absorption, distribution, metabolism, and excretion (ADME) studies, toxicology and allergenicity

Rapporteur: Valeria Di Giorgi - Chair: Annette Poeting

The group discussion addressed specific questions.

1. How should the different types of novel foods and food ingredients be tested? Is it possible/ appropriate to recommend standard toxicological testing programmes for specific types of products in order to derive safe intake levels for consumers?

Novel foods/novel food ingredients comprise a wide variety of different products including pure chemicals, chemical mixtures and complex food. The participants agreed with a case by case approach to identify the studies required for the safety assessment rather then establishing a defined standard program based on the classification listed in the Commission recommendation (EC, 1997). In order to decide on the testing program it is necessary to have a detailed specification of the composition, purity and origin of the novel product.

It is possible to give a general indication, as follows:

- in case of pure chemicals or defined chemical mixtures, the safety assessment should be done according to the guidance on the evaluation of food additives by the SCF (2001); this guidance is in principle also applicable to novel food ingredients with claimed specific functional properties
- for botanicals and botanical preparations it should be referred to the respective EFSA Guidance Document (2009).

2. What are the criteria to be applied in the safety assessment of complex foods? Are specific toxicological studies required and how can applicants be advised in making the respective decisions? Should a subchronic (90-day) feeding study in rodents be generally recommended?

At first the group identified the need to have a clear definition of a "complex food". The following discussion focussed on approaches for the safety assessment of novel "macro ingredients", e.g. (modified) high-molecular weight carbohydrates, as well as "whole foods", e.g. fruits or grain from novel plant sources. In order to determine the appropriate type and extent of toxicological testing or to justify the absence of specific testing there are criteria that must be considered such as the nature of product, its origin, the production process, specification, composition, in particular the presence of critical substances, history of use, previous intake as well as the intended/anticipated intake (exposure).

The 90 day rodent feeding study is considered to have sufficient sensitivity and specificity to detect toxicologically and nutritionally relevant effects and can thus be generally recommended for the testing of complex novel foods. Scientific justification for not carrying out this study has to be provided. The group found that compositional data, *in vitro* studies, mechanistic studies and the 28 day rodent study may be helpful for the design of a 90 day study but there was agreement that the 90 day study is the appropriate way to address longer term intake. Important issues to be considered in the testing of "macro ingredients" and "whole foods" are dose selection and formulation of nutritionally balanced diets. The group considered that it is important to administer the highest possible dose that may be supplemented in a balanced diet. Therefore the use of diets, which are specifically designed

according to the nutrient content of the novel products is recommended. In addition, the choice of an appropriate control food (or foods) has to be carefully considered. Testing of specific products, e.g. oils, may pose specific problems with regard to dose selection and choice of control(s).

Compared with the testing of pure chemicals and defined chemical mixtures the extrapolation of results (i.e. no-observed adverse effect level - NOAEL) from studies with "macro ingredients" and "whole foods" with regard to the human situation may require new approaches since the safety margin that may result is often low when compared to the anticipated human intake.

Regarding the assessment of "whole foods" the group also considered the possibility to use representative extracts as test materials. However, in this case possible matrix effects have to be considered for setting the appropriate study and analyzing the results.

3. In which cases should additional studies be conducted, e.g. on chronic toxicity, reproductive and developmental toxicity, neurotoxicity, immunotoxicity, endocrine activity?

The outcome of the 90 day rodent study will largely determine whether additional studies including studies in other species are required. If there are indications for specific adverse effects or inconclusive results a study on chronic toxicity may be required. From the discussion emerged that the absence of a chronic study may be justified by a high margin of safety in the 90 day study. The reversibility of effects was also considered an important issue. The group further considered that information on the nature of the novel food/food ingredient and composition data might also lead to specific testing. For example, the presence of endocrine active substances may require *in vitro* and *in vivo* screening tests on specific endocrine activity and/or *in vivo* studies on reproductive toxicity. In the case of "macro ingredients" like indigestible carbohydrates, studies on gastrointestinal effects and/or studies on the bioavailability of nutrients may be needed for the safety assessment.

The group suggested that the safety assessment should take into account the target population, and the possible consumption of the novel food by potentially sensitive population groups (at risk groups), in order to define the testing. Regarding pregnancy, animal studies on developmental toxicity may be required. If diabetics have to be considered specific animal models may be applied. For young children, tolerability studies may be required in specific cases. However, there was consensus that such studies may not always be justified for ethical reasons.

4. Should genotoxicity studies be carried out and which ones are appropriate?

The necessity of testing and the selection of the appropriate tests depend on the nature of the product and its composition. Overall, the group suggested that the approaches outlined in the relevant Guidance documents used within EFSA, i.e. the Guidance documents for the safety assessment of food additives (SCF, 2001) and botanicals (EFSA, 2009) should be followed:

First step: three *in vitro* tests covering the endpoints gene mutations and chromosome mutations - if any positive > *in vivo* genotoxicity testing.

The group discussed the problem of interpretation of results for many substances. In addition, it was pointed out that complex foods can only be tested as an extract and thus matrix effects

have to be considered. Also the issue with solubility in *in vitro* test systems was discussed, often resulting in false positive results.

It may be useful to apply specific models: e.g. enzymatic hydrolysis models to mimic digestion.

5. When are animal studies sufficient, and when are human safety studies required?

Human studies should normally be conducted:

a. if animal models are not relevant

b. for the assessment of nutritionally relevant constituents

c. to confirm the absence of specific adverse effects detected in animal studies at relevant human intake levels

d. if specific population group has to be considered, including target group

e. for metabolic investigation (ADME studies) digestion and GI tolerance

6. Can concerns on the allergenic risk of traditional foods be addressed based on "compositional data" and on "experience of continued use in the normal diet of a large part of the population of a country"? If not, how should applicants demonstrate that a food is not of concern with regards to its allergenic potential, and what kind of testing scheme can be followed? Is there a hierarchy for certain tests?

There is not a reliable test to predict the allergenicity of a food/food ingredient.

The experience gained from previous use of a food in non- EU countries is considered important, but may not be conclusive for the EU situation because of different genetic background, environment/cross reactivity and different level of exposure.

It is important to consider any phylogenic relationship of the novel food to a source known to be allergenic. In this case the cross-reactivity may be tested *in vitro* using sera from allergic persons and/or *in vivo* studies.

The composition data may give indications on the allergenic potential of the NF. The potential allergenicity of specific proteins can be assessed using the approach described in the GD of the EFSA GMO Panel (EFSA, 2006). The source of the protein, the amino acid sequence homology to known allergens, the digestibility by proteases and potential cross-reactivity are relevant issues to be considered.

Overall, the group agreed that allergenicity should not be a reason for negative outcome, in fact it may be addressed by labelling at the risk management level.

7. What are the key issues for ADME studies in the safety testing of food ingredients (i.e. single substances and chemical mixtures) and complex novel foods?

Starting from the consideration that the NF GD 1997 had no specific recommendation, the group considered that in case of simple chemical substances / chemical mixtures it has to be considered obligatory (as stated in GD Food Additives).

The group noticed that the GD on Botanicals normally requires information on toxicokinetics, so it may be useful in this specific case, to evaluate different bioavailability of substances from different matrices.

For "complex food" it is difficult to make a general recommendation, because of the composition, the case by case approach is recommended.

Under specific scenarios, it may be important to have this data in order to evaluate any interaction with nutrients or drugs, or to collect human digestion and absorbtion data.

Background documents

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DG4: Data requirements to demonstrate safety of foods derived by nanotechnology

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Introduction

The special characteristics and properties of engineered nanomaterials (ENMs), such as the small size, surface reactivity and translocation across biological membranes as well as interactions of ENMs with the surrounding matrix and unexpected effects resulting from this may require generation of specific data for risk assessment purposes. There is a need for proper identification (including physico-chemical characterisation) of ENMs used in the food and feed sector. There are at present difficulties detecting ENMs in food and feed matrices and consequently exposure assessment is difficult. Generic data requirements and guidance for risk assessment of ENMs have been presented in various reports over the last five years, including OECD documents and the recent EFSA Opinion. Whilst EFSA has recently been asked by the Commission to prepare a guidance document to provide practical recommendations for the risk assessment of ENMs for use in food, today there remains a lack of detailed description of data requirements to demonstrate the safety of foods and feeds comprising ENMs.

1. In addition to the OECD endpoints, are there other appropriate endpoints for food risk assessment?

Although current OECD standard endpoints for the risk assessment of ENM's[2] are viewed to be acceptable, it is reassuring that the OECD Stewardship Programme is reviewing this aspect in some detail and will report shortly. However, the relative lack of published studies investigating the safety of ENM's as foods and feeds is problematic and there is a need for an tailored programme of testing in the short to medium term to build up a body of scientific evidence, identify areas of possible concern, and determine whether these apply to all or to which forms of ENMs. Food materials with larger particle sizes have been tested through rigorous safety assessments for at least 70 years and it is important that a greater understanding of the safety implications related to the use of ENM's in the food chain is achieved soon.

The use of ENMs in food and feed will generally be at low level and it is likely therefore that any adverse effects would be chronic rather than acute. In view of this, as an absolute minimum an ENM should undergo a 90 day chronic study including full histopathology, but given the relative paucity of data, lifetime studies (with appropriate endpoints) should be considered. Consideration should also be given to immunotoxicity and neurotoxicity data as there are published reports of ENM's passing the blood-brain barrier. Although of indirect relevance in the context of food and feed safety, environmental and occupational risk assessments would also be required.

2. Can food groups be grouped for ENM risk assessment, and if so, what criteria could be applied?

[2] http://www.olis.oecd.org/olis/2008doc.nsf/LinkTo/NT000034C6/$FILE/JT03248749.PDF

Given the current approach to the regulation of food additives it is possible that the use of ENM's for technological purposes may be restricted to use in particular food groups. Although it may seem reasonable that the use of ENM's for nutritive purposes could similarly benefit by grouping in individual food categories, in practice it is not clear how this could be achieved. Although it is conceivable that ENM's will be particularly attractive for use in certain food categories, this is also currently the case for many innovative novel food ingredients which are dealt with on a case by-case basis. Hence a case-by-case approach would be preferable for ENM's.

3. Assess current knowledge and identify data gaps on ENM stability in various food matrices and in the gastro-intestinal tract.

There are few published reports investigating the stability of ENMs in food matrices or *in vivo.* Although work is carried out in both areas it is acknowledged that there will be little data available in the near future. The limited number of studies which have been carried out to date do not, in general, take account of the surface properties of ENM's and whether interactions with other nano particles or components in the gut (including the food matrix) may influence absorption properties (corona affect). Studies into organic micelles (including micro-sized) are of limited usefulness if they are broken down and their component parts are soluble as the effect that they have on the GI tract could be investigated using established risk assessment approaches.

4. Try to define crucial elements for a tiered risk assessment for soluble and endogenous ENMs (e.g. vitamins, nutrients).

A tiered risk assessment should start with characterization and include site and mode of activity), and there should be an awareness that ENMs can display unusual solubility characteristics (e.g. a fat soluble Vitamin C preparation). ENMs which are completely soluble in the gut could be assessed using established risk assessment procedures. ENM's requiring additional investigation could still be assessed by following the usual ADME (Absorption, Distribution, Metabolism, Excretion) approach, but it should be noted that differences could be observed in each of the four areas requiring investigation. As such, a tiered approach as per figure 1 could be followed. If at any stage throughout the ADME paradigm the ENM material is not behaving similar to the comparator product then a special risk assessment procedure applies.

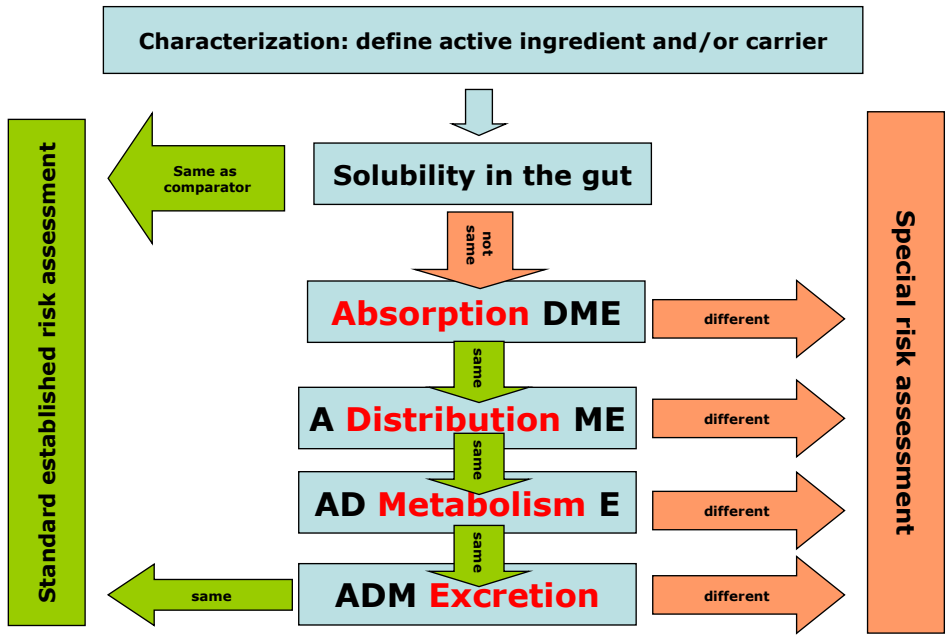

Figure 1: Elements for a tiered risk assessment for soluble nanomaterials.

5. Please list possible methods (advantages and disadvantages) to assess changes in bioavailability.

There is a lack of good quality data in this area but current methods to assess changes in bioavailability (e.g. quantifying levels in urine and blood) remain valid. Methods may need to be refined as a consequence of the use of relatively small quantities of ENMs and account needs to be taken of possible changes in bioavailability as a result of their nano-formulation.

6. Specify data requirements and discuss suitable methods to generate data for exposure assessment.

There are well established existing methods used to quantify exposure of novel foods and these approaches, commonly utilising data from food consumption surveys, and food composition databases can be utilised for the assessment of ENMs. This may require specific analytical methods to determine the extent and nature of the material in one or all proposed food matrices and if viewed to be of sufficient importance this could be evaluated for inclusion as a condition of approval.

III FINAL PLENARY DISCUSSION – CONCLUSIONS

The outcome of the discussion groups were presented in a final plenary session bringing together the different aspects. Several questions and comments during the final plenary session related to the European Commission's proposal for a new Novel Food Regulation, which provides definitions for the "traditional foods from third countries" and a "history of safe food use". The Commission representative clarified that extracts without a history of safe food use but derived from primary foods which have a proven history of safe food use, would not fall under the regulatory provisions for traditional foods. The Commission representative further addressed other rather regulatory questions beyond the remit of EFSA's tasks on risk assessment.

The group concluded that in compliance with the draft regulation, extensive compositional data on nutrients and other substances should be used to characterise the traditional food, and serve as a baseline for comparison for actual products to be marketed. The specifications based on batch testing by qualified laboratories using up to date analytical methods and recognized international standards, were essential elements for the characterisation of the food. Similarly, information on the production, the harvesting, quantitative consumption data, preparation of the food and its role in the diet of the country or origin, have to be considered. It was stated that anecdotal information on the previous consumption was insufficient, but should be demonstrated by reliable references which show previous consumption by a large part of the population. Such information could include sales figures by companies, information from government organisations, ethnobotanists and information from scientific publications. The presence of nutritive dietary constituents such as secondary plant metabolites, anti-nutritional factors and contaminants should be considered on a case-by-case basis.

Concerning exposure assessment, several options were mentioned with regard to estimates for the 'average consumer': using the mean intake of a similar food in food consumption surveys; where there is a functional ingredient, applicants could identify a specified daily intake for the target group and restrict intake by limiting the use level/ foods that can carry the ingredient, in conjunction with relevant legislation. A third approach would be to use a FFQ in conjunction with market data. Then, the risk manager/policy maker should make an *a priori* decision how to distribute amounts over foods and food supplements (e.g. 100 : 0 or 50 : 50 or 0 : 100), where after, the appropriate risk assessment procedure can take place. For the estimation of "a worst case", a number of assumptions have to be made, which increasingly magnify the error, especially when the ingredient may be present in a number of food formats. Assumption should be linked with the expected target group for the food, and to the average and high consumers within this group.

It was noted that existing food consumption surveys such as the UK rolling National Diet and Nutrition Survey programme and the Irish Diet and Nutrition Survey would provide essential tools for the intake assessment. EFSA informed the audience on its existing population survey database, which provides aggregated data for around 15 food categories from 19 countries. In addition, EFSA is currently considering establishing a pan European survey of individuals using a consistent methodology.

It was noted that following a pre-defined standard toxicological testing program may not be an appropriate approach for scientific, economical and for animal welfare reasons. The wide variety of different products including pure chemicals, chemical mixtures and complex food

would require a testing program suitable for the nature of the novel ingredients and should consider all existing information on it. Several participants stressed the importance that an EFSA Guidance on novel ingredients should be in-line with already existing guidance from EFSA (e.g. Guidance for botanicals, food additives, or feeding studies for GM food) and other international guidelines such as the OECD Guidelines. It was mentioned that in general an applicant should consider all toxicological tests, but not necessarily have to conduct them all if a scientific justification for the absence of tests can be provided.

The approach for the toxicological testing should consider the nature of the product, its origin, the production process, composition and specification, in particular the presence of critical substances, history of use - previous intake, as the intended/anticipated intake, target population and relevant evidence from existing scientific literature. It appeared that participants broadly agreed with some general principles which should be in line with existing guidelines.

It was thought that for complex foods, including botanicals and extracts which contain a large number of different substances, a 90-day study should be generally recommended for the testing program. Specific testing such as for chronic, reproductive and developmental, endocrinological, neurotoxicological and immunotoxicological effects and interaction with other foods or drugs should be based on specific considerations related to the nature of the novel ingredients, findings from other tests or from scientific literature or, if applicable, to establish the safety of specific target groups (e.g. children, pregnant women). Human studies might be recommended in specific cases, when the safety can not be established by representative animal model (e.g. ADME studies, supporting the safety of specific sensitive target population such as diabetic subjects).

Overall, the audience agreed that the individual testing program should follow a case- by-case approach considering all existing information of the novel ingredients.

For nanotechnology derived novel ingredients and novel food ingredients it was noted that existing methods can be a good basis for safety testing, but that these need to be adapted to take account of low level exposure to nanoparticles. It was considered unlikely that classical toxicology would be sufficient (i.e. treating a nanomaterial in the same way as a completely new chemical entity) unless the full ADME characteristics are similar and long-term animal tests should be a minimum requirement. The testing needs to take account of specific endpoints for nanomaterials. Also, ADME studies will require adapted analytical methods that can differentiate between the total amount of the chemical substance and its nanomaterial form.

Overall, the Colloquium provided a good level of debate among the experts from scientific bodies, industry, national and international agencies and authorities and other knowledgeable experts. It identified a number of important issues that will need to be reflected in the EFSA's guidance for the preparation of an application of novel foods. Before finalisation such guidance should be subject to a public consultation.

The development of effective guidance requires a delicate balance, providing sufficient information in order that applicants know what questions they need to answer, and what type of data will help to answer those questions, without being too proscriptive. The need for flexibility was highlighted in each of the discussion groups, considering the wide range of substances that might need to be considered as novel foods in future, including sources, production methods and functionalities that have not been considered before. Each product

will raise a range of different questions that will need to be addressed in the risk assessment. Guidelines will therefore need to be flexible in order to allow for future products that may raise unique issues in terms of characterisation, toxicology and exposure assessment.

It was accepted however that many of the issues that are relevant to the risk assessment of novel foods are common to other areas of risk assessment and, where possible, the requirements for novel foods should be consistent with the approaches that EFSA has already developed, or is developing, in other areas such as nanomaterials, botanicals, GM foods and food additives.