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European Food Safety Authority

EXECUTIVE DIRECTOR

Parma, 24 MAY 2012
Ref. SG/DD/PB/OR/nm (2012) **out-6595981**

Mr P. Nikiforos Diamandouros
The European Ombudsman
Avenue du President Robert Schuman, 1
CS 30403
F-67001 Strasbourg
France

Complaint 0775/2010/ANA – your communication S2012-153408 of 11 April 2012

Dear Mr P. Nikiforos Diamandouros,

I hereby acknowledge receipt of your communication of 11 April 2012, received by the European Food Safety Authority (EFSA) on 24 April. In that letter, you outline the reasons why the documents identified as confidential by EFSA pursuant to Article 5(1) and (2) of the Ombudsman's implementing provisions and those identified as confidential in EFSA's final opinion cannot be considered by the Ombudsman in the context of the present procedure.

In order to allow the Ombudsman to take due account of all the documents submitted by EFSA in the context of the Complaint at issue here, EFSA contacted the third parties concerned by these documents, and with their agreement is now lifting the confidentiality claim related to certain of these documents, as attached to the present letter.

It follows that these documents can be taken into account in the context of Complaint 0775/2010/ANA. My services remain at your disposal for any clarification on these matters.

Yours sincerely,

Catherine Geslain-Lanéelle

Enclosures:

1. Annex IV (documents n. 19, 24, 26, 28, 33 and 40) of EFSA's communication ref. DD/AH/SG/rl (2010) – out- 5345394
2. Annex III of EFSA's communication ref. OR/DD/SG/rl (2012) – out – 6460928 - Note of the Legal and Regulatory Affairs Unit regarding a request pursuant to Article 16 of the Staff;
3. Annex IV of EFSA's communication ref. OR/DD/SG/rl (2012) – out – 6460928 - Decision of the Appointing Authority regarding a request pursuant to Article 16 of the Staff Regulations.

ANNEX II

(19)

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Parma, 29 May 2007
EFSA/GMO/348
Draft Minutes

MINUTES

SIXTH MEETING OF THE SELF TASKING WORKING GROUP "GUIDANCE FOR THE ASSESSMENT OF GENETICALLY MODIFIED PLANTS USED FOR NON-FOOD OR NON-FEED PURPOSES"

Meeting date:	31 May 2007 from 10.00 a.m. - 17.00 p.m
Venue:	Ministerie van de Vlaamse Gemeenschap, Boudewijnlaan 30, 1000 Brussel 05 Balkon 5 left
Participants	Christer Andersson, Ralph Bock, Paul Christou, Philip Dale, Marc De Loose, Anna Depicker, Sirpa Kärenlampi, Harry Kuiper, , Annette Pöting, Julian Ma, Dominique Masset, Pere Puigdomenech, Suzy Renckens, Reinhilde Schoonjans
Apologies	Detlef Bartsch, Howard Davies, Claire Halpin, Gijs Kleter, Uwe Sonnewald, Jeremy Sweet, Jean-Michel Wal Aurélie Andre, Pervin Bassaran, Paula Rey Garcia, Sebastien Goux, George Sakellaris, Charles Kessler, Alexis Nolte, John Purves, Michael Walsh,
Chair	Joachim Schiemann

#	Items
1.	Welcome, apologies for absence
2.	Adoption of the agenda (doc 2.1). *The agenda was adopted*
3.	Adoption of the minutes of the fifth meeting of the working group of October 2006 (doc 3.1) + go through the action items. *The minutes were adopted.*
4.	**Discussion on the Opinion** (doc 4.1) *The structure of the document was finally approved by the whole group. New text or proposals to be further discussed were directly entered into the text. Alternatively, new tasks were defined.*
5.	Case studies: what to present and how. *An extra subworking group is going to convene to work on this. (date set on 18 July 2007 in Brussels).*
6.	Stakeholders consultations. *Not discussed due to time constraints.*
7.	Any other business: *no issues particular issues were raised.*

(24)

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MINUTES OF THE SCIENCE MANAGEMENT MEETING OF 25 JUNE 2007

16:00 – 18:00 MEETING ROOM: DUS D 00/003

PARTICIPANTS

	PRESENT	APOLOGIES
CHAIR	Herman Koëter	
AFC	Dimitrios Spyropoulos	Torben Hallas-Moller
AHAW	Jordi Serratosa	
BIOHAZ	Tobin Robinson	Marta Hugas
CONTAM		Claudia Heppner
FEEDAP	Claudia Roncancio Peña (minutes)	
GMO	Suzy Renckens	
NDA	Pilar Rodriguez Iglesias	
PLH	Elzbieta Ceglarska	
PPR	Muriel Dunier-Thomann	
SCI COOP & ASSIST		Hubert Deluyker
ASS METH		
DATEX	Stefan Fabianson	
EM RISK	-	
PRAPER	Henning Bruno	
SCI COOP	-	
ZOONOSES	Pia Makela	
SC-AF	Djien Liem	
	Juliane Kleiner	
OTHERS	Dirk Detken and Mari Varho	

1) Draft minutes of the meeting of 11 June 2007

- Regarding the Declaration of Interest: the new templates, distributed by Hubert on Friday 8 June, have been modified and should not be considered as the final version (for further information see point 2 of the agenda).
- Herman invites all the HoU to complete and send the CDAC asap to HR (copy Herman).

2) DoI : Introduction of the revised format (Dirk Detken)

Herman provided feedback from the MB. Some modifications have been proposed on the general layout, as for example to include the footnotes directly in the table. Dirk thanked the HoUs for comments made on the new draft procedure for handling DoI's which had been circulated before

5) **Follow-up to the "Efficiency of Scientific work" discussions of 18th June and at the MB**

- Regarding the RoQ, Jane Richardson will make an inventory of some questions not included in the RoQ and also to increase functionalities of the RoQ.
- Stef will draft options for the future of the EFSA Journal.
- A brainstorming meeting will be organised for organisation of workload.
- As some panels preferred to have meetings outside Parma, each unit should found a balance between meetings in Parma and outside Parma.

6) **Harmonisation of opinions**

Due to the lack of time this point of the agenda will be discussed at the next meeting.

7) **Any other business**

Mari Varho volunteers to participate in a future Plenary meeting to inform the panel members on the financial rules..

ANNEX : Copy of the presentation made by Mari Varho.

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(26)

Parma, 2 August 2007
EFSA/GMO/359
Follow-up

EFSA Document Cover Page

Panel on :	**GENETICALLY MODIFIED ORGANISMS**
Working group :	Self task on "the assessment of allergenicity of genetically modified foods"
Subject :	**Follow-up**
Title :	**Follow-up of the working group meeting Self task on allergenicity assessment (16/07/2007 - Brussels)**
Submitted by :	**Ellen Van Haver**
Document for :	√ **Information** **Discussion** **Possible adoption**
Distributed to :	**All Panel's members** On √ **The Working Group members** On **3 August 2007**
Confidentiality level :	**Confidential** √ **For Restricted Use Only**

FOLLOW-UP OF THE WORKING GROUP MEETING SELF TASK ON ALLERGENICITY ASSESSMENT HELD ON 16 JULY 2007 (BRUSSELS)

AGENDA

PARTICIPANTS

GMO Panel and Working Group (WG) members:
Rob Aalberse, Karine Hoffmann-Sommergruber, Gijs Kleter, Martinus Lovik, Gabriel Peltre, Jean-Marie Saint-Rémy, Willem Seinen, Daniel Soeria-Atmadja and Jean-Michel Wal (Chair).

EFSA:
Suzy Renckens and Ellen Van Haver.

APOLOGIES:
Christer Andersson, Philippe Eigenmann, Ralf Einspanier, Clare Mills, John Warner.

1. WELCOME AND APOLOGIES FOR ABSENCE

The Chairman opened the meeting and welcomed all. Apologies for absence were received from some working group (WG) members as mentioned above.

Karine Hoffmann-Sommergruber was welcomed as new member of the WG.

2. DECLARATIONS OF INTERESTS

A new template for the annual declaration of interest (ADoI) was distributed to update the current declarations of WG members on the EFSA website[1]. Issues to be declared relate to activities of the past five years that might be relevant to the activities of this WG. Membership to or participation in ILSI meetings needs to be declared under item "VIII. Other membership or affiliation" or "item X. Other". An electronic version of the ADoI can first be sent to Ellen who will check for consistency.

3. DISCUSSION OF THE DIFFERENT CHAPTERS

Since last plenary WG meeting, different sub-WG meetings were held for the elaboration of the respective chapters. To aim of this WG meeting was to go through the different chapters and to identify gaps and redundancies.

Chapter 1 (General Intro):

The aim of this Chapter is to introduce the issues addressed by the other chapters of the document, without going into detail into the different topics. Furthermore, the scope of the document needs to be highlighted in the introduction (see further as 1.9), after the general description of food allergy.

1.1 Food allergy

The definition of food allergy was discussed and the text was amended (see document) and was put into context of (GMO) risk assessment. It was also noted that allergy may be defined differently in US and EU guidance documents, and that it might be useful to highlight these differences. Atopic and genetic predisposition was not by everyone preferred to have it in the definition of allergy as these terms are not that well defined, or alternatively, it needs to be explained in the glossary.
The definition of allergy should not be restricted to ingestion only, but should also take into account the possible contact with the mucosa, such as the exposure in the oral cavity.

The issue of coeliac disease does not fit in the section on Food allergy, but should be addressed later in the document.

1.2 IgE-mediated food allergy

A paragraph needs to be added on what is an adjuvant.

1.3 Food allergen

There is some discrepancy between section 1.3 (Food allergen) and following chapters. It is correct to mention that many proteins could become allergens, but this statement appears to be contradicted in other sections, which should be adjusted.

1.5 Measures of allergy and allergenicity

[1] http://www.efsa.europa.eu/en/science/gmo/gmo_working_groups.html

The title was amended to "Methods to assess allergenicity in patients". The paragraph on animal models was subsequently deleted. Animal models might have a role in testing substances for which no history of exposure and allergy exists as yet, but for which no patients are yet available.

The methodology described in 1.5 could also be used for post-market monitoring purposes, but the focus should however be on pre-market assessment in line with the general scope of the document.

Section 1.5 should be shortened as it is not necessary to address issues like reliability, predictivity and accuracy of the various tests, being already covered in the subsequent chapters.

1.6 What happens when a new food allergen is introduced into the diet?

The title should be modified and the section should move to the clinical chapter.

The examples of kiwi and lupin as cross-reactive allergens might not be representative for GMOs. The real issue is primary sensitisation which may takes years before it can be picked up. In addition, the conditions may vary, such as wide-scale use by/exposure to particular subpopulations (for instance sesame in Israeli children). Sensitisation to cypress following the exposure to diesel (adjuvanticity) could be included as an additional example (issue adjuvanticity to be addressed in the Clinical chapter).

Figure 1 could go out from the text and a sentence could instead be added mentioning that it takes years before sensitisation occurs.

1.7 Allergy in animals

Ad hoc experts could be asked to elaborate on this issue. Jean-Michel will approach experts with experience with allergy in farm animals.

1.8 GMO risk assessment and 1.9 Scope

The weight-of-evidence approach of the assessment of the allergenicity of GMO and the regulatory context is currently missing. It was however the intention to have an additional chapter preceding the Introduction chapter (see minutes of the meeting of 26/10/06), in which the terms of reference (covering the weight-of-evidence approach and the regulatory context), the mandate and scope of the document will be addressed.

At the end of the Introductory chapter, the sensitisation and elicitation potential, cross-reactivity and adjuvanticity need to be explained and the possible allergenicity of newly expressed proteins and whole food need to be added within the scope (1.9). It needs also to be clarified that the intrinsic allergenicity of the GMO can be altered because of the genetic modification even if it will not always be possible to include a tool for assessing whole foods in every chapter.

Chapter 2 on Clinical aspects

Jean-Marie introduced the revised version of Chapter 2.

It was noted that the language in for instance section 2.2 (Mechanisms) was quite technical, but also necessary for the understanding of the mechanisms of allergy. Terms used throughout the document should go into the glossary.

References should be provided at more instances in the chapter.

Specific comments:

- Some bullet points in "The cascade of events following the exposure to an antigen at mucosal level" (see "In summary,..." under section 2.2, pg 16) are not mentioned, or are not more elaborated in the text (such as the activation of the innate immune system). In addition, some more details should be provided about the mechanisms of non-IgE-mediated allergies.
- Immunogenicity of peptides (last paragraphs of section 2.2, pg 17): some parts regarding the binding of peptides by antigen-presenting cells might pertain more to pollen allergies than to food allergies. This is because it is suggested that peptides derived from digestion might bind directly to the surface of MHC cells without having been processed internally and being loaded on APC cells. This needs to be clarified.
- Section 2.3 suggests that all non-confirmed allergies besides confirmed IgE-mediated allergies (5%) would be non-IgE-mediated allergies, which would then amount to a prevalence of 25%. It was recommended modifying this text (pg 17).
- Section 2.3: Martinus will provide a reference for the statement that the prevalence of food allergies has increased (pg 18).
- Section 2.4: should clinical pictures be merged with mechanisms? Non-IgE mediated reactions are more diluted throughout the text. Delayed-type hypersensitivity, enterocolitis, enteropathies... are not described and should be added to the text.
- Section 2.4 (pg 20): coeliac disease, although non-IgE mediated, should be mentioned to be an allergy, because it is an adverse immune response to an external trigger (food). The mechanism needs to be discussed with regards to the scope of this document.
- Recommendations and conclusions should be added, for instance that special attention needs to be paid with regard to the allergenicity assessment for children (section 2.6), which is not specifically addressed in the GM plant guidance document. Kiwi could provide an interesting case with respect to *de novo* sensitization in particular segments of the population (e.g. children but also old people). The title "specific assessment for children" should therefore not be misleading.
- The issue of adjuvanticity and immunogenicity (IgG) should be covered as well (description of the issue/public health concern; tools how to assess). There is however no clear-cut relationship between non-IgE immune response to foods and IgE mediated reactions, about which Rob/Gabriel will provide a paragraph. Martinus will write an additional text on the issue of adjuvanticity.

Chapter 3: Structural aspects

Karin explained which changes had occurred since the last meeting. For example, text has been added on intracellular processing of plant proteins, which is an important factor that may affect the allergenicity of a protein.

The rationale might be made more clear by restructuring the text to clarify the relationship between protein structure and allergenicity. The implications of the current state of knowledge on the predicting capacity of allergenicity need to be addressed. If for instance no sequence homology has been found, there might still be a problem. It would be useful to extend the discussion on processing of glycan chains and cross-reactive carbohydrate determinants, and the implications of the newest insights into these issues. Another important question to be solved with the bioinformatics group is whether a protein that belongs to the same protein family as an allergen can be regarded a potential *de novo* allergen.

Jean-Michel noted that IFR-Norwich had done some/extensive studies on *in vitro* digestibility and recommended Gijs to approach Clare on this issue for the chapter on *in vitro* methods.

John also provided following comments via e-mail (16/06/2007):
... The final statements should include comments more applicable to GM. The issues about the effect of matrix and glycosylation etc make it important to point out that GM may therefore have knock on effects on allergenicity that extend well beyond the insert protein(s). This could either increase or decrease the allergenic potential of other proteins.
However, the plea should be for more research to understand both initial sensitisation and subsequent allergic reactions in relation to allergen structure, matrix etc and how this affects presentation to the immune system both in the gut and other organs such as inflammed skin and airway...

4. ANY OTHER BUSINESS

Comments from Norway on the possible adjuvant effect of Cry proteins:

EFSA has received comments from Norway on the possible adjuvant effect of Cry proteins within the framework of Regulation 1829/2003-GM food/feed applications and the corresponding opinions of the GMO Panel. Martinus explained the background (see also his e-mail from 13 July 2007) and clarified the remaining Norwegian concerns that have not been addressed in the opinions and the answers from the GMO Panel.

Before inviting an expert from Norway (Per Brandtzaeg) at a next working group meeting to discuss the issue of adjuvanticity, Jean-Michel will look for the text that was initially drafted by the GMO Panel for answering the comments from Norway.

ILSI-HESI meetings:

Some information was provided on parallel ILSI activities that have been taken place, or are going to take place in the near future.

5. DATE AND PLACE OF FUTURE MEETINGS

- 24 September 2007 in Brussels
- 14 or 26 November 2007 in Brussels (date to be confirmed, depending on the availability of experts that were not present).

6. ACTION ITEMS (BY 3 SEPTEMBER 2007)

The WG members are requested to provide i) the revised version of their own chapter with regards to the comments made during the WG meeting and ii) their written comments on the other chapters in advance of the meeting in order to facilitate the discussions at the next meeting. In addition, remaining issues of this meeting will be discussed, as well as Chapter 8, which needs to address the integration of the different approaches. The WG members are therefore asked to reflect on perspectives and recommendations and to draft corresponding text at the end of each chapter.

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European Food Safety Authority

Parma, 8 October 2007
EFSA/GMO/ **Draft Minutes**

MINUTES

THIRD SUBGROUP MEETING OF THE SELF TASKING WORKING GROUP "GUIDANCE FOR THE ASSESSMENT OF GENETICALLY MODIFIED PLANTS USED FOR NON-FOOD OR NON-FEED PURPOSES"

Meeting date:	18 July 2007 from 10.00 a.m. - 17.00 p.m
Venue:	Ministerie van de Vlaamse Gemeenschap, Boudewijnlaan 30, 1000 Brussel 05 Balkon 5 left
Participants	Ralph Bock, Annette Pöting, Julian Ma, Dominique Masset, Pere Puigdomenech, Suzy Renckens, Reinhilde Schoonjans, Jean-Michel Wal
Chair	Joachim Schiemann

#	Items
1.	Welcome, apologies for absence
2.	Adoption of the agenda . *The agenda was adopted*
3.	**To Agree on a general scheme that we follow for the evaluation of each case study.** *The Matrix in the ANNEX I, was updated with all the topics to be addressed. The matrix is based on what is mentioned in the text of the opinion (plant parts to assess, routes of exposure to take into account etc.), but new insights were gained e.g. the division of toxicity testing in systemic toxicity and local toxicity.*
4.	**Use the general agreed scheme for each case study** *There were topics for which the matrix was not relevant and then the reasoning was given. There where topics for which the GD is sufficient, innthis case the matrix was left blanc or by default "GD applies" was used. This was done for 3 case studies.The matrix was then to be abandoned and all the particulars of the matrix were incorporated in the sections "issues specific for this case study".*
5.	**Descriptions of the case studies were reworked where necessary**
6.	Stakeholders consultations. *Not discussed due to time constraints.*
7.	Any other business: *no issues particular issues were raised.*

European Food Safety Authority

Parma, 9 October 2007
EFSA/GMO/368
Follow-up

EFSA Document Cover Page

Panel on :	**GENETICALLY MODIFIED ORGANISMS**
Working group :	Self task on "the assessment of allergenicity of genetically modified foods"
Subject :	**Follow-up**
Title :	**Follow-up of the working group meeting Self task on allergenicity assessment (24/09/2007 - Brussels)**
Submitted by :	**Ellen Van Haver**
Document for :	√ **Information** **Discussion** **Possible adoption**
Distributed to :	**All Panel's members** On √ **The Working Group members** On **20 December 2007**
Confidentiality level :	**Confidential** √ **For Restricted Use Only**

European Food Safety Authority

FOLLOW-UP OF THE WORKING GROUP MEETING SELF TASK ON ALLERGENICITY ASSESSMENT HELD ON 24 SEPTEMBER 2007 (BRUSSELS)

AGENDA

PARTICIPANTS

GMO Panel and Working Group (WG) members:
Rob Aalberse, Karine Hoffmann-Sommergruber, Gijs Kleter, Martinus Lovik, Gabriel Peltre, Jean-Marie Saint-Rémy, Willem Seinen, Daniel Soeria-Atmadja, Jean-Michel Wal (Chair) and John Warner.

EFSA:
Suzy Renckens and Ellen Van Haver.

APOLOGIES:
Christer Andersson, Philippe Eigenmann, Ralf Einspanier and Clare Mills[1].

1. WELCOME AND APOLOGIES FOR ABSENCE

The Chairman opened the meeting and welcomed all. Apologies for absence were received from some working group (WG) members as mentioned above.

[1] Clare participated to the discussions of Chapter 3 by teleconference.

2. DECLARATIONS OF INTERESTS

Those Working Group (WG) members that have not yet updated their annual declaration of interest (ADoI) will receive an e-mail from EFSA to remind them to update their ADoI.

3. MINUTES OF 16 JULY MEETING – FOLLOW-UP

Comments on and follow-up of the minutes of 16 July:

- It needs to be emphasised that besides gastro-intestinal sensitisation, sensitisation can also occur via the non-gastro-intestinal tract, such as via inhalation and the skin.
- Allergy in animals (currently covered by Chapter 1.8): statements on allergy in animals (such as the statement that piglets are immune-competent) might need to be checked by an expert in the field. **Ralf Einspanier** will be asked whether he can check this issue and whether other experts need to be approached. Professor Chris Stokes from the Bristol Veterinary School has a lot of expertise with allergy in animals (see also below under Chapter 1).
- As the draft document is besides IgE mediated reactions also covering non-IgE immune responses to foods, it would be useful to explain the role of the different subclasses of IgG and their relationships with allergy, acknowledging that this is a contentious area (as Codex is for instance only focussing on IgE-mediated reactions). **Rob** will write a paragraph in Chapter 1 and **John** will address the possible clinical impacts of the different antibodies involved in the Clinical Chapter (see also below under Chapters 1 and 2).
- **Jean-Michel** will compile the different responses from the GMO Panel that have been used to address Member States comments on GMO applications that are related to adjuvanticity of Cry-proteins. This compilation will be useful to address the comments from Norway and to prepare a possible meeting with Norwegian experts by the end of this year.

4. DISCUSSION OF THE DIFFERENT CHAPTERS

As a follow-up to the last WG meeting of 16 July, it was the aim to discuss those chapters that were not discussed on 16 July, as well as the chapters that have been updated since last meeting, focussing on the new paragraphs.

Chapter 1 (General Intro):

- Rob suggested to write a text on epitopes for Chapter 1.3 as the definitions of epitopes used throughout the document are slightly different. In addition, there is no clear cut between linear and conformational epitopes and the impact of post-translational modifications. Epitopes within a protein molecule should be clearly distinguished from isolated peptide fragments. References to epitopes along the document need to be consistent with this text.
- As the draft document is besides IgE mediated reactions also covering non-IgE immune responses to foods, it would be useful to explain the role of the different subclasses of IgG and their relationships with allergy, acknowledging that this is a contentious area (as Codex is for instance only focussing on IgE-mediated reactions). **Rob** will write a short paragraph on this issue in Chapter 1.

- Allergy in animals (currently covered by Chapter 1.8): statements on allergy in animals (such as the statement that piglets are immune-competent) might need to be checked by an expert in the field. **Ralf Einspanier** will be asked whether he can check this issue and whether other experts need to be approached. Professor Chris Stokes from the Bristol Veterinary School has a lot of expertise with allergy in animals.

Martinus presented new text on **adjuvanticity** (Chapter 1.4) and the following issues need to be further elaborated (**Martinus**):
- Adjuvanticity of diesel particles has not been unequivocally demonstrated. Gabriel informed about his own research on diesel particles in lab animals, showing high adjuvanticity of various fractions. Martinus mentioned that ultra-fine particles, as chemically inert or reactive particles, can be adjuvants.
- A distinction will be made between compounds that have a direct and indirect adjuvant activity, including indirect effects through stimulation of uptake of allergens, e.g. by saponins in foods. Substances promoting gut permeability may stimulate allergy similar to Th2 adjuvants.
- It needs to be highlighted that adjuvanticity can be beneficial (Th1 response can decrease the risk of allergenicity) or negative (sensitising potential in the presence of adjuvants).
- Related topics, such as immune response modifier, and breaking of self-tolerance and induction of autoimmunity should not be addressed (as this would widen the scope).
- We need to think about recommendations on how adjuvanticity should be assessed. There is no definite test for the prediction of adjuvanticity as there is no definite test for the prediction of allergenicity.
- A specific Th2-adjuvant potential identified in a mouse-model might be regarded as a hazard or a warning signal and a Th2-response might then require further assessment. This issue can be further addressed as a recommendation/perspective (in Chapter 6 in the context of the whole GM plant, or in Chapter 7 on animal models).
- Th2-sensitising effects in mouse do however not necessarily induce an effect in man. Human exposure studies or post-market monitoring might therefore be needed.

Chapter 2 on Clinical aspects

John and Jean-Marie introduced shortly the Chapter on clinical aspects.

- The immunological vs. the clinical reactivity needs to be more explicit in the Introductory paragraph (**John**).
- As the draft document is besides IgE mediated reactions also covering non-IgE immune responses to foods, it would be useful to explain the role of the different subclasses of IgG and their relationships with allergy, acknowledging that this is a contentious area (as Codex is for instance only focussing on IgE-mediated reactions). **John** will address the possible clinical impacts of the different antibodies involved in the Clinical Chapter.
- The mechanisms of non-IgE mediated reactions are considered to be addressed explicitly enough in the text.

The following recommendations were shortly discussed:
- More sera from patients are needed but they need also to be well-characterised. Statistical calculations have been done showing that 60-70 well-characterised sera are needed based on variability. Since this might not be feasible, the WG has to consider the reliability of studies performed with a lower number of sera.

- Regarding post-market surveillance, descriptions of reporting systems performed in France, Norway, Germany, Switzerland and Austria can be provided.
- Infants are more susceptible towards allergenic reactions as their gastro-intestinal tract differs from adults. A specific assessment for children might therefore be recommended. It needs however to be discussed how this specific pre-market assessment needs to be performed. It might for instance be recommended that more research is needed on young animal models.

Chapter 3: Structural aspects

Clare (by teleconference) and Karin presented their latest version of Chapter 3.

The following issues were discussed and need to be further elaborated in the text (**Karin/Clare**):
- Chapter 3 needs to be more applicable to GM.
- A new paragraph will be included on regulating deliberately (by genetic modification) or naturally the amount of specific proteins in plants. This would accommodate the section on transgenic plants down-regulating allergenicity.
- Another sub-section on post-harvest modifications will be added, besides those on biosynthesis in the plant including post-translational modifications.
- Would certain scaffolds lead to sensitisation? The example was raised how to assess a protein that belongs to a protein family which comprises numerous common allergens, e.g. the cupin family, while there is no or low sequence homology, and consequently unlikelihood for cross reactivity, with known allergens. The potential of this protein for de-novo sensitisation remains the main concern which needs to be further checked, particularly if it is stable towards digestion. Testing in an animal model is however not yet a requirement.
- Additional issues may be considered in a multi-step *in silico* analysis, such as clusters of homology, conservation of potential epitopes, ... T cell epitopes may also be taken into account.
- It also needs to be defined what is the meaning of low sequence homology. 35% alignment using a 80-amino acid sliding window might indicate cross-reactivity. Below 25%, alignment might in many cases not be relevant.
- The relevance of the 3-D structure for predicting the allergenicity of proteins was discussed. The sequence homology using an 80-amino acid sliding window does not tell anything about the 3-D structure. Sequence similarity within a particular important domain might be more relevant.
- Another criterion to take into account is in which part of the plant the protein is expressed. For instance, many cupins do not occur in the edible part of the plant.
- A paragraph needs to be added to explain how to assign a new protein to a certain protein family. The Pfam database is used for this purpose. It needs however to be clarified that this is a general database for all proteins, but not for allergens (in contradiction to the allergen databases mentioned in Chapter 4). The issue whether protein folding might help in assigning a new protein to a protein family was debated.
- An introductory paragraph to Chapter 3 needs to explain the connection between Chapters 3 and 4. Chapter 3 addresses the structural features of a protein, whereas Chapter 4 provides details how to assess the sequence homology
- The issue on digestibility needs to be further elaborated (**Gijs**, Chapter 5).

Chapter 4: Bioinformatics for the risk assessment of GM foods as regards potential allergenicity

The Bioinformatics' Chapter was presented by Daniel.

- With bioinformatics, cross-reactivity rather than the sensitising potential is looked at.
- The sequence homology based on the 6 or 8 contiguous amino acids was discussed. Matches of 6 amino acids are not specific enough to perform serum screenings, but also identical stretches of 8 amino acids do not necessarily mean the identification of potential epitopes. It was concluded that homology searches based on 6 contiguous amino acids should not be performed. In a publication of Kleter and Peijnenburg[2], methods for epitope prediction are combined, by further screening the positive outcomes of the sequence homology with a minimal length of six amino acids for the presence of potential linear IgE-epitopes (35% homology in a sliding window of 80 amino acids). The question was however raised whether this multi-step approach should be systematically performed and what to do in the case of positive results at the different stages.
- The FASTA approach appears to be better than the linear sliding window. There was some discussion with regard to the minimum threshold level for FASTA. Recommendations should be made in order to pick up potential cross-reactivity with sufficient sensitivity and acceptable specificity. The level of false positives that is acceptable needs to be agreed upon. This might however be a regulatory decision and not a scientific question. 35% is the threshold currently accepted. See also the comments provided by Rob attached to these minutes.
- The question was raised which databases need to be mentioned in Chapter 4.4, and whether some of them deserve to be recommended. It should be explained why particular databases are mentioned and that these are examples. To select the most suitable database, we need first to decide on what kind of procedure we are going to recommend and whether the search should be conducted on all the proteins or whether some of the proteins could be excluded because of a low importance with regard to allergenicity.
- As there are many databases and algorithms offered by websites, uniformization should be recommended.
- The issue was raised whether it would be possible to add information on the estimates of the sensitivity/specificity of the different computational methods as described under Chapter 4.7. It will however be difficult to compare the different databases because they have been validated with different datasets with different underlying algorithms and methods.

Chapter 6 (In vitro analysis for potential allergenicity testing of whole GM plants)

The aim of Chapter 6 is to cover *in vitro* analysis of the whole GM plant and to analyse possible modifications in its intrinsic allergenicity due to unintended effects, whereas Chapter 5 addresses *in vitro* methods for the assessment of the allergenicity of newly expressed proteins. Chapter 6 particularly concerns plants that are known to be food allergens. It is focussed towards the analysis of the allergen repertoire of the GM plant as compared with that of the conventional one in order to assess whether some endogenous allergens may be over-expressed after the genetic modification. Attention needs to be paid to the natural variability of proteins. The study on whether the whole GM crop is more allergenic than the non-GM crop should then be conducted both from a qualitative and quantitative point of view.

The following gaps were identified and need to be addressed in the chapter (**Gabriel**):

- Extraction of proteins and sample preparation (e.g. soluble/insoluble proteins).
- Separation then identification of proteins/allergens (e.g. proteomic analysis).
- Quantitative determinations methods, (RAST/EAST and inhibition assays).

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[2] Kleter and Peijnenburg (2002). Screening of transgenic proteins expressed in transgenic food crops for the presence of short amino acid sequences identical to potential, IgE-binding linear epitopes of allergens. BMC Structural Biology 2002, 2:8.

- Profiling techniques, including glycomics, should be discussed with a careful attention to their relevance, appropriateness and validation obtained so far. Post-translational modifications of proteins as expressed in the plant need to be covered. Quantitative PCR of transcripts (transcriptomics) may also be an alternative sensitive method.
- The analysis of specific allergens in the whole crop should be carried out in analogy with the compositional analysis of the GM compared with the non-GM crop. The total spectrum of allergens, but also the glycosylation pattern needs to be looked at.

The difficulty of these methods is however that the outcome has to be interpreted correctly, and that the natural variation when comparing the non-GM with the GM crop needs to be taken into account. **Karin** will address this issue.

- Availability of sufficient number and volumes of sera in the case an allergen is expressed.
- Chapter 5 and 6 can cross-reference each other for methods that are relevant for both chapters (for instance ELISA, Western blot, proteomics).
- Micro-arrays and omics-technologies will be reviewed by **Gijs**.

5. DATE AND PLACE OF FUTURE MEETINGS

The next meeting is scheduled for 23 January 2008 in London (venue: Medical Research Council).

6. ACTION ITEMS (BY 10 JANUARY 2008)

The WG members are requested to provide i) the completed and revised version of their own chapter with regards to the comments made during the WG meeting and ii) their written comments on the other chapters in advance of the meeting in order to facilitate the discussions at the next meeting. Chapter 8, which needs to address the integration of the different approaches, will be discussed. The WG members are therefore asked to reflect on perspectives and recommendations and to draft corresponding text at the end of each chapter.

We will need to distinguish between three kinds of recommendations:
- Guidance to applicants: how to improve current practices
- Research gaps: recommendations for further research
- Recommendations to risk managers, for instance the need for databases and serum banks.

Rob provided some written recommendations regarding the assessment of the risk of potential cross-reactivity, which are attached to these minutes and will be discussed at the next meeting.

Annex: Recommendations regarding the assessment of the risk of potential cross-reactivity (Rob Aalberse, 24 September 2007)

1. The amino acid sequence of a significant number of "minor" allergens is not yet in the database. These will thus be invisible at the important in-silico checkpoint. It is important to apply proteomics to get better coverage of the allergen repertoire, particularly for food allergens.
2. The effects of post-translational modification should be fully incorporated into the risk assessment. This implies (1) removal from the allergen database of amino acids sequences of proteins for which IgE binding is completely due to post-translational attachment of glycans; (2) addition of information on posttranslational modifications that significantly affects IgE binding.
3. It is crucial that post-translational modification is investigated in the final host.
4. The current in-silico procedures for establishing potential cross-reactivity are imperfect, partially because reliable quantitative information on cross-reactivity is insufficient. A decision has to be made on the acceptability of false-negative hits (sensitivity versus specificity). A too strict adherence to sensitivity will result in an unreasonable number of false-positive hits, without completely avoiding all cross-reactivity risk.
5. The sensitivity/specificity profile for full identity over 6 (or 8) contiguous amino acids is poor. This analysis should not be advocated.
6. Partial identity of either a sliding window of 80 amino acids and/or full-length proteins is the preferred approach. The sliding window approach may be more appropriate if the target protein has (or is predicted to have) a multi-domain structure, as a single domain with similarity to a known allergen may escape detection if inserted into an otherwise non-allergenic protein. The 35% identity cut-off level is considered to be conservative and the use of a 50% identity cut-off has been suggested, but significant cross-reactivity may occur below 50% identity.

European Food Safety Authority

Risk Assessment Directorate

Risk Assessment Team Meeting 14 January 2008, 16:00 – 18:00

Meeting Report

Attendees

- Riitta Maijala (RM)
- Torben Hallas-Moller (THM)
- Per Have (PH)
- Marta Hugas (MH)
- Claudia Heppner (CH)
- Claudia Roncancio Pena (CRP)
- Suzy Renckens (SR)
- Pialr Rodriguez Iglesias (PRI)
- Elzbieta Ceglarska (EC)
- Muriel Dunier-Thomann (MDT)
- Tania Cavatorta (TC) - Secretariat

Acronyms

- AF: advisory forum
- EC: European Commission
- MB : Management Board
- MP: management plan
- MT: Management Team
- RAD: risk assessment directorate
- SC: scientific committee
- WP: work plan
- SCA: scientific cooperation and assistance

AGENDA	DISCUSSION AND DECISIONS
1. Goals of these meetings and minutes (secretary, approval, distribution)	The goal of these meetings is to enhance internal communication and collaboration as well as prepare together issues for further development of RA and EFSA. TC will take minutes of these meeting and after RM has accepted them, she will send a link to all staff. HoUs are asked to send issues for future agendas to TC. Draft agendas are shared with SCA Directorate and vice versa. SMM are in future taking place less frequently, possibly one Monday / month (to be determined together with SCA and SCAF). The acronym for these meetings is RAM.
2. Reporting in 2008, including progress indicators	Progress indicators mentioned in Table 1,2 and 3 of Work Plan 2008 need to be followed on the monthly basis. In order to do that, SCA (Jane Richardson) will help in preparing Excel sheets with macros etc. Jane will visit units and provide her assistance in this area. Draft tables were discussed. The existing table will be modified accordingly to the discussion: New line for mandates by month of acceptance (keep tracks when asking for more information to the applicants); new line for meetings organised by EFSA, one for participation in meetings organised by third parties, one for meetings with EC; presentations of EFSA staff as a separate line. The number of meetings will be counted as it is and not per days. Coadoption of opinion will be counted per each Unit which has worked on it. Jane will prepare an amended version which will then be discussed at next MTM. When MT has agreed on the outcome tables, Jane will further work with technicalities so that units could start filling in the information in January. **ACTION 14012008-01**: MDT will draft a paper concerning clear definition for statement, scientific opinion and scientific advise

3. CDAC practices and timelines	Have the staff CDAC ready by the end of the week. RM will ask HR clarification on promotion.
4. DOI (panels and WG), approach and future development	WG to be published asap, use of the new form. The electronic form will be explained to the experts by IT in plenary in April – May.
5. INEX report	Need to draft the planning. RM, EC, MH and CRP will produce a proposal how this would work. After that has been accepted, the INEX WG will be organised. **ACTION 14012008- 02** TC / RM will fix a meeting asap for the drafting group
6. Web and teleconferences	New IT system for web and teleconferences are available / will be availabe. The compensation to experts is still not yet defined. Finance and Alexandrine will find the solution how to pay and inform the units. Units have to take notes of all these teleconferences (duration, location, etc...)
7. AFC split	AFC call for experts to two new panels has been published. To THM by Friday 25th volunteers from Senior Scientific Staff (min Grade AD 8) for participation to evaluation groups. In addition, help in finding wise people for the external evaluation also to THM.
8. Future meetings day	These meetings will be held on Monday from 4.00 to 6.00 every two weeks
9. AOB	Add to each agenda the point: Interesting cases (scientific discussion) – 15 minutes. HoUs can send a message to Tania if they want to present an interesting case.

SUMMARY of ACTIONS

Ref	WHO	WHAT	BY
ACTION 14012008 -01	MDT	Draft a paper concerning clear definition for statement/scientific opinion and scientific advice	28/01/2008
ACTION 14012008 -02	TC / RM	Arrange first meeting for drafting plan for establishment of INEX	28/01/2008

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ANNEX III.

0775/2010/ANA
E2012-153028
CONFIDENTIAL

efsa
European Food Safety Authority

HEAD OF THE LEGAL AND REGULATORY AFFAIRS

Parma, 15 JUL 2011

NOTE TO THE ATTENTION OF THE EXECUTIVE DIRECTOR

concerning the resignation of a staff member from the Scientific Committee Unit and its intended change of occupation towards a nanotechnology industries representing organisation as envisaged new employer

I. Background

1. Facts

With a letter dated 30 June 2011 EFSA staff member David Carlander, currently employed in the SCOM Unit, indicates his intention to change employment and to take up a position as Director of Advocacy in the Nanotechnology Industries Association as of 16 September 2011. In this context he has been requesting CCP and by adjuvant means resigning with effect from 15 September 2011. According to its website (www.nanotechia.org),

"The Nanotechnology Industries Association, NIA, is the sector-independent, responsible voice for the industrial nanotechnologies supply chains. The NIA supports the ongoing innovation and commercialisation of the next generation of technologies and promotes their safe and reliable advancement.

The nanotechnology industries are made up of many varied companies all at different stages of their life cycle and with a variety of interests in the huge range of technologies that derive their benefit from the nanoscale.

Through the NIA's constant involvement in a number of international organisations, members of the Nanotechnology Industries Association are represented on globally influential fora, such the OECD Working Party on Manufactured Nanomaterials, and the OECD Working Party on Nanotechnology, as well as national and international advisory groups and standardisation committees.

[NIA] was formed in 2006 by a group of companies from a variety of industry sectors, including healthcare, chemicals, automotive, materials processing, and consumer products.

The NIA membership is made up of many varied companies, all of which at different stages of their life and with a variety of interests in the large range of technologies that derive their benefit from the nanoscale. In the NIA, these companies have a representative association to create a clear single 'voice' on behalf of the industries' views, to interface with governments, to be a source for consultation on regulation and standards, to engage with the public, to communicate the benefits of nanotechnologies, to interact with the media, and to inform the debate on nanotechnology".

2. Legal framework: Procedure according to Article 16 SR in case of resignation

The resignation as staff member is inter alia governed by Article 16 SR. This provision contains the requirement of prior information of the Appointing Authority (AA) before starting with the new activity. A 30 working days period is foreseen for the notification of any AA decision in reaction to the notification of the staff member's new occupational intentions. Without notification of such decision the implicit acceptance of the staff member's demand would be assumed. If the AA renders a decision, such decision can be (1) unrestricted

approval, (2) denial or (3) approval subject to specific conditions (conditions to be set at the discretion of the AA).[1]

II. Analysis

1. Resignation

In line with the current EFSA policy for CCP the requestor will not be granted such kind of special leave in case of taking up a professional assignment in the remit of EFSA. His initially conditional letter dated 30 June 2011 is therefore considered as a resignation as of 15 September 2011[2].

The notice period for resignation in the present case needs to be calculated in accordance with Article 47 point (b)(II) CEOS. Given that the requestor is currently employed as temporary agent with EFSA under a five years contract running since 16 May 2007, a three month notice period applies to the requestor. As the resignation was received on 30 June 2011, the requestor would be obliged to work until 30 September 2011.

However, the AA may consider, on request of the resigning staff member and in the context of a mutual agreement in the interest of the leaving staff member, the possibility of waiving the notice period in order to shorten it so that he would be allowed to work until 15 September 2011, included.

2. Assessment in relation to the application of Article 16

When assessing the case in relation to Article 16 SR, considerations in favour of the requestor could be guided by the formal facts of the FP7 funding of the intended projects of the staff member in question under his new employment or the NGO status of the envisaged new employer.

However, from a legal point of view the assessment needs to be performed in line with the scope of Article 16 SR. The purpose of Article 16 SR is to safeguard the legitimate (public) interests of the (former) public authority employer. As regards EFSA, the relevant legitimate interest — in the present case — is the scientific independence of the Authority, amongst others encompassing the aspect of public perception of the independence's safeguarding and EFSA's reputation as reference point of scientific excellence and independent scientific advice.

During the last three years of service the requestor has been working as Scientific Officer in the Unit providing scientific and administrative support to the Scientific Committee of EFSA (SCOM Unit). The competence for scientific questions related to nanotechnology is at EFSA statutorily allocated to the Scientific Committee. EFSA, and in particular its Scientific Committee, has been active in the field of nanoscience in the recent past.[3] Consequently the requestor has been working very closely in the area of principal nanotechnology questions and is in a position to be familiar with all relevant details (comprising valuable background knowledge) related to EFSA's scientific works and outputs with regard to nanomaterials, nanotechnology and nanoscience, i.e. a scientific opinion, a guidance document and different

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[1] The relevant second paragraph of Article 16 SR reads: *"Officials intending to engage in an occupational activity, whether gainful or not, within two years of leaving the service shall inform their institution thereof. If that activity is related to the work carried out by the official during the last three years of service and could lead to a conflict with the legitimate interests of the institution, the Appointing Authority may, having regard to the interests of the service, either forbid him from undertaking it or give its approval subject to any conditions it thinks fit. The institution shall, after consulting the Joint Committee, notify its decision within 30 working days of being so informed. If no such notification has been made by the end of that period, this shall be deemed to constitute implicit acceptance."*

[2] Cf. the third-to-last and the last paragraphs in the requestor's letter dated 30 June 2011.

[3] Cf. http://www.efsa.europa.eu/en/topics/topic/nanotechnology.htm.

scientific events (like a scientific colloquium or an event on nanotechnology in the food chain)[4]. Furthermore, the requestor has been responsible for the coordination of the Working Group of the Committee responsible for the drafting of EFSA's respective scientific outputs. In this position, he has been able to establish personal contacts with all the major experts active in the field and with those who had accepted working for EFSA on the above sensitive matters. The unit supporting the Scientific Committee has also been handling the feedback deriving from public consultations. Though not being member of the EFSA management, the requestor has been participating in several external conferences and events and thus attained visibility in relation to EFSA and nanotechnology stakeholders.

The intended new employer of the requestor is an industry orientated organisation representing industry interests in the field of nanotechnologies, consequently an actor and stakeholder in the remit of EFSA. Hence, in line with the provisions of the second paragraph of Article 16, the intended new occupational activity is related to the work carried out by the staff member in question during the last three years of service, namely as Scientific Officer in the Unit providing support scientific and administrative support to the Scientific Committee of EFSA, being the exclusively competent body dealing with nanotechnologies and nanoscience at EFSA. Already a general research of the focusing orientation of the *Nanotechnology Industries Association NIA* towards EFSA reveals the close interest of NIA in EFSA's remit and scientific works regarding nanotechnology and NIA's active participation, e.g. in form of comments during public consultations.[5]

In a crucial and sensitive area like nanotechnology — a field of activity that has the potential to become publicly as disputed as the GMO or cloning sector today — the legitimate interests of EFSA, in particular relating to its scientific independence and reputation could be seriously undermined, especially from the point of view of public perception.

Moreover there is a more than a purely abstract danger that the requestor, having worked for more than four years as Scientific Officer in the Unit supporting the nanoscience and nanotechnology works of the Scientific Committee of EFSA, could make use of his expertise and his contacts, in particular to the EFSA "internal" and external experts in the field of nanotechnology, in order to involve them in the framework of his envisaged new occupation. In the further course such scenarios could not only endanger EFSA's scientific independence and its reputation, but also its scientific excellence, as in the long run important experts might not be any longer available or eligible to act as scientific experts for EFSA in the fields of nanotechnologies and nanosciences, in case those experts would be involved directly or indirectly in NIA's activities.

Therefore the occupational activity intended by the requestor is pertinent to lead to a conflict with the legitimate interests of the Authority in terms of the second paragraph of Article 16 SR. EFSA is best advised to minimize any possible risks in this context — last but not least also with regard to the public perception and earlier criticism in relation to alleged "revolved door" cases.

In case of a non clear-cut approval, the second paragraph of Article 16 SR foresees exhaustively the following two alternative legal consequences:

- forbidding to undertake the intended new occupational activity within a two years period as of leaving the service at EFSA;

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[4] Cf. http://www.efsa.europa.eu/en/events/event/colloque091119.htm; http://www.efsa.europa.eu/en/supporting/doc/colloquiangovalfood.pdf; http://www.efsa.europa.eu/en/events/event/corporate101124a.htm

[5] Cf. e.g. http://www.nanotechia.org/global-news/efsa-publishes-new-guidelines-on-nanomaterials, http://www.nanotechia.org/nia-press/nia-encourages-efsa-to-support-sound-science-through-an-interactive-approach-to-risk-assessment, http://www.nanotechia.org/nia-press/nia-provides-comments-on-efsa-draft-opinion, http://www.nanotechia.org/news/global/efsa-publishes-scientific-opinion-on-the-potentia, http://www.nanotechia.co.uk/news/press/nia-comments-on-efsa-opinion.

- giving the approval subject to any conditions the AA "thinks fit" in view of the assessment of the concrete case.

III. Conclusions

1. Staff member David Carlander has resigned with effect from 30 September 2011. However, his request for resignation with effect already as of 15 September 2011 would require the consent of the AA.

2. As to the application of Article 16 SR and the respective assessment, from a legal point of view the intended new occupation is likely to lead to a conflict with the legitimate interests of the Authority, i.e. the scientific independence and the reputation of EFSA in view of the public perception of the envisaged unconditional and immediate switch to a nanotech industries organisation. The indicated intended activity should consequently be forbidden.

3. In case the AA nevertheless (e.g. in view of the FP7 funding of the intended projects or the NGO status of the new employer) would grant the approval for the new occupational activity, it should only be allowed under clear and strict conditions:
   - the requestor could be authorized to take up his desired new duties without (or with) restrictions, but only after a cooling-off period of a certain number of months (discretionary proposal: between 6 and 23 months),
   - the requestor could be prohibited to be the contact point with EFSA on behalf of his new employer (discretionary proposal: between 6 and 24 months),
   - the requestor could be prohibited to be directly or indirectly in contact with the Authority in relation to his new occupational remit throughout the period of two years, or
   - the requestor could be prohibited to make use of the EFSA experts (from the Scientific Committee and/or the Scientific Panels and/or the external experts database).

Dirk Detken

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ANNEX IV.

efsa
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EXECUTIVE DIRECTOR

Parma, 29/07/2011
Ref DD/CP/rl (2011) - out-5907984

David Carlander
Largo N. Palli 5/a
43121 Parma
Italy

Re: Your letter dated 30 June 2011 and procedure applicable under Article 16 of the Staff Regulations

Dear Mr Carlander,

With your letter dated 30 June 2011 you resigned from EFSA in order to take up a position as Director of Advocacy in the Nanotechnology Industries Association (aibsl) based in Brussels.

In line with Article 16 of the Staff Regulations, I have concluded that your future engagement as a Director of Advocacy in the Nanotechnology Industries Association is approved.

In order to be compatible with EFSA's legitimate interest you are requested during the period of one year after taking up the new assignment not to be the reference contact point for EFSA on nanotechnology-related issues, to not to approach EFSA staff to gain access to non-public documents and information, and to respect potential conflicts of interests that may arise for EFSA in case you would approach EFSA experts for work assignments for your new employer.

Please note that in line with applicable notice period as set out in Article 47(b)(ii) CEOS your last day of employment with EFSA will be the 30 September 2011.

I kindly seek for your written confirmation of your commitment and acceptance of the above conditions.

Yours sincerely,

Catherine Geslain-Lanéelle