TECHNICAL REPORT

Outcome of the consultation with Member States and EFSA on the basic substance application for chitosan hydrochloride and the conclusions drawn by EFSA on the specific points raised[1]

European Food Safety Authority[2]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The European Food Safety Authority (EFSA) was asked by the European Commission to provide scientific assistance with respect to the evaluation of applications received by the European Commission concerning basic substances. In this context EFSA's scientific views on the specific points raised during the commenting phase conducted with Member States and EFSA on the basic substance application for chitosan hydrochloride are presented. The context of the evaluation was that required by the European Commission in accordance with Article 23 of Regulation (EC) No 1107/2009 following the submission of an application for approval of chitosan hydrochloride as a basic substance. The current report summarises the outcome of the consultation process organised by the European Commission and presents EFSA's scientific views on the individual comments received.

KEY WORDS

Chitosan hydrochloride, basic substance, application, consultation, plant protection, pesticide

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[2] Correspondence: pesticides.peerreview@efsa.europa.eu

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SUMMARY

Chitosan hydrochloride is an active substance for which in accordance with Article 23(3) of Regulation (EC) No 1107/2009 the European Commission received an application from ChiPro GmbH for approval as a "basic substance". Regulation (EC) No 1107/2009 introduced the new category of "basic substances", which are described, among others, as active substances, not predominantly used as plant protection products but which may be of value for plant protection and for which the economic interest of applying for approval may be limited. Article 23 of Regulation (EC) No 1107/2009 lays down specific provisions for consideration of applications for approval of basic substances.

A consultation on the basic substance application for chitosan hydrochloride, organised by the European Commission, was conducted with Member States and EFSA via a written procedure in June – July 2012. Subsequently the applicant was invited to address the comments received in the format of a Reporting Table.

In March 2013 the European Commission requested the EFSA to provide scientific assistance with respect to the evaluation of applications received by the European Commission concerning basic substances. In particular, EFSA was asked to consider the comments received on the basic substance application for chitosan hydrochloride and the response of the applicant thereon, and to finalise the Reporting Table with its scientific views on the specific points raised in the commenting phase.

The current report therefore summarises the outcome of the consultation process organised by the European Commission and presents EFSA's scientific views on the individual comments received in the format of a Reporting Table.

A revised version of the application for approval of chitosan hydrochloride as a basic substance has been submitted in an appropriate format, in line with the guidance on the procedure for application of basic substances.

Considering the specification provided chitosan hydrochloride is not comparable with the material evaluated in the Scientific Opinion of the EFSA NDA Panel of the safety of glucosamine hydrochloride from *Aspergillus niger* as food ingredient (EFSA Journal (2009) 1099: 1–19). The substance is a polymer, consisting of the two units N-acetyl-D-glucosamine and D-glucosamine, with an averaged MW of 47000-65000 Da. The heavy metal content is ten times higher than the composition of chitosan hydrochloride described in the European Pharmacopeia 6.0.

A justification was provided for the comparability of chitosan hydrochloride with chitosan, for which a Scientific Opinion of the EFSA NDA Panel is available (Scientific Opinion on the substantiation of health claims related to chitosan and reduction in body weight (ID 679, 1499), maintenance of normal blood LDL-cholesterol concentrations (ID 4663), reduction of intestinal transit time (ID 4664) and *reduction of inflammation* (ID 1985) pursuant to Article 13(1) of Regulation (EC) No 1924/20061; EFSA Journal 2011;9(6):2214). However this Opinion "does not constitute, and cannot be construed as ..... a positive assessment of its safety" (Appendix B of the Opinion). It can therefore be concluded that for the material presented in this assessment there is no EU evaluation of its safety.

The toxicological data available do not allow drawing a conclusion on the toxicity of chitosan hydrochloride: the data provided in the application are not adequately reported and it is unclear whether they specifically refer to chitosan hydrochloride.

Since it could not be concluded that chitosan hydrochloride is of food grade quality and comparable with the material evaluated in the Scientific Opinion of the EFSA NDA Panel of the safety of glucosamine hydrochloride from *Aspergillus niger* as food ingredient (EFSA Journal (2009) 1099: 1–19), and considering that the available data were not sufficient to conclude on the toxicity of chitosan hydrochloride, a consumer risk assessment could not be completed.

The available evaluations of chitosan hydrochloride or related molecules as food ingredients do not contain any assessment of the potential environmental exposure. The potential maximum application rate of chitosan hydrochloride, according to the reported intended uses, will be 208 kg /ha. This rate is deemed to result in environmental exposures above natural levels and above levels resulting from other authorised uses. Relevant impurities, such as heavy metals, shall be considered in the environmental assessment. Based on available scientific literature chitosan hydrochloride may be expected to be highly persistent in soil (DT_{50} > 100 days). Half-life in estuary water is expected to be longer than 50 days. Further information would be needed to complete the exposure assessment of chitosan hydrochloride for use in plant protection.

The scientific information provided to address the risk to non-target species was not relevant, except for soil microorganisms. Therefore a conclusion could not be drawn in the area of ecotoxicology.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 1107/2009[3] (hereinafter referred to as 'the Regulation') introduced the new category of "basic substances", which are described, among others, as active substances, not predominantly used as plant protection products but which may be of value for plant protection and for which the economic interest of applying for approval may be limited. Article 23 of the Regulation lays down specific provisions to identify a substance as a basic substance with a view to ensure that such active substances that do not have an immediate or delayed harmful effect on human and animal health nor an unacceptable effect on the environment can be approved as "basic" and used for plant protection purposes.

Chitosan hydrochloride is an active substance for which, in accordance with Article 23(3) of the Regulation, the European Commission received an application from ChiPro GmbH for approval as a "basic substance".

The European Commission organised a consultation with Member States and EFSA on the basic substance application for chitosan hydrochloride, which was conducted via a written procedure in June – July 2012. The comments received were collated by the European Commission in the format of a Reporting Table. Subsequently, the applicant was invited to address the comments in column 3 of the Reporting Table. The comments received and the response of the applicant thereon, together with the application submitted by the applicant, were considered by EFSA in column 4 of the Reporting Table.

The current report aims to summarise the outcome of the consultation process organised by the European Commission and to present EFSA's scientific views on the individual comments received in the format of a Reporting Table.

The application and, where relevant, any update thereof submitted by the applicant for approval of chitosan hydrochloride as a "basic substance" in the context of Article 23 of the Regulation, is a key supporting documentation, therefore it is considered as a background documentation to this report and will also be made publicly available, excluding its appendices (ChiPro GmbH, 2011 and 2012).

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

On 6 March 2013 EFSA was requested to provide its scientific views on the specific points raised during the consultation process conducted on the basic substance application for chitosan hydrochloride. To this end, a Technical Report containing the finalised Reporting Table is prepared by EFSA. On the basis of the Reporting Table, the European Commission may decide to further consult EFSA to conduct a full or focussed peer review and to provide its conclusions on certain specific points.

[3] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ No L 309, 24.11.2009, p. 1-50.

EVALUATION

The comments received on the application for chitosan hydrochloride and the conclusions drawn by the EFSA are presented in the format of a Reporting Table.

The comments received are summarised in column 2 of the Reporting Table. The applicant's considerations of the comments, where available, are provided in column 3, while EFSA's scientific views and conclusions are outlined in column 4 of the table.

The finalised Reporting Table is provided in the Appendix of this report.

DOCUMENTATION PROVIDED TO EFSA

1. ChiPro GmbH, 2011. Chitosan Hydrochloride. Basic substance application submitted in the context of Article 23 of Regulation (EC) No 1107/2009. December 2011. Submitted by ChiPro GmbH. Documentation made available to EFSA by the European Commission.

2. ChiPro GmbH, 2012. Chitosan Hydrochloride. Basic substance application update submitted in the context of Article 23 of Regulation (EC) No 1107/2009. August 2012. Submitted by ChiPro GmbH. Documentation made available to EFSA by the European Commission.

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EFSA (European Food Safety Authority), 2009. Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from the European Commission on the safety of glucosamine hydrochloride from *Aspergillus niger* as food ingredient. *The EFSA Journal* (2009) 1099, 1-19.

EFSA (European Food Safety Authority) Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011; Scientific Opinion on the substantiation of health claims related to chitosan and reduction in body weight (ID 679, 1499), maintenance of normal blood LDL-cholesterol concentrations (ID 4663), reduction of intestinal transit time (ID 4664) and reduction of inflammation (ID 1985) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(6):2214. [21 pp.]. doi:10.2903/j.efsa.2011.2214. Available online: www.efsa.europa.eu/efsajournal.

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Sato, K., Azama, Y., Nogawa, M., Taguchi, G. & Shimosaka, M., 2010. Analysis of a change in bacterial community in different environments with addition of chitin or chitosan. J Biosci Bioeng 109, 472-8 (2010).

APPENDIX

COLLATION OF COMMENTS FROM MEMBER STATES AND EFSA ON THE BASIC SUBSTANCE APPLICATION FOR CHITOSAN HYDROCHLORIDE AND THE CONCLUSIONS DRAWN BY EFSA ON THE SPECIFIC POINTS RAISED

1. Purpose of the application

General				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
1)	General	EFSA: With regard to the identity, physical properties and methods of analysis it cannot be concluded from the summary document that the dossier fulfils the requirements of Article 4 of Regulation (EC) No 1107/2009.	Identity, physical properties and methods of analysis are provided in sections 2.2.1 - 2.2.7 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	Some additional information about the identity, physical properties and methods of analysis has been provided in the revised version of the application for approval of chitosan hydrochloride as a basic substance in the context of Regulation (EC) No 1107/2009 (August 2012). However, since there are no relevant EU evaluations available to show that the substance has no harmful effects on human or animal health, nor an unacceptable effect on the environment, Article 4 of Regulation (EC) No 1107/2009 fully applies. See also EFSA conclusion in comment 2.2(1).
2)		FR: The draft application to approve chitosan should follow the format indicated in the guidance on the procedure for application of basic substances in order to	The revised version of the application to approve chitosan hydrochloride follows the format indicated in the guidance on the procedure for application of basic	A revised version of the application for approval of chitosan hydrochloride as a basic substance has been submitted in an appropriate

General				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		be approved in compliance with Article 23 of Regulation 1107/2009 (SANCO/10363/2012 rev.3 March 2012). As Chitosan has been evaluated as a food grade by EFSA, a complete evaluation is maybe not necessary, even if the source and the process are different. A justification should be sufficient to confirm that specifications comply with those from US Pharmacopoeia, which are the reference used by EFSA in its evaluation.	substances. Specifications for the chitosan hydrochloride under evaluation here are provided in section 2.2.5 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	format, in line with the guidance on the procedure for application of basic substances[4]. It should be noted that there is no EFSA safety evaluation on chitosan hydrochloride. Considering the specification provided chitosan hydrochloride is not comparable with the material evaluated in the *Scientific Opinion of the NDA Panel of the safety of glucosamine hydrochloride from Aspergillus niger as food ingredient* (EFSA Journal 1099: 1–19. 2009). A justification is provided in section 2.2.5 for the comparability of chitosan hydrochloride with chitosan, for which a Scientific Opinion of the EFSA's NDA Panel is available (*Scientific Opinion on the substantiation of health claims related to chitosan and reduction in body weight (ID 679, 1499), maintenance of normal blood LDL-cholesterol concentrations (ID 4663), reduction of intestinal transit time (ID*

[4] European Commission, DRAFT Guidance on the procedure for application of basic substances to be approved in compliance with Article 23 of Regulation 1107/2009, SANCO/10363/2012

General				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				4664) and reduction of inflammation (ID 1985) pursuant to Article 13(1) of Regulation (EC) No 1924/20061, EFSA Journal 2011;9(6):2214). However this Opinion *"does not constitute, and cannot be construed as ..... a positive assessment of its safety"* (Appendix B to the Opinion). See also EFSA conclusion in comment 2.2(1).

2. Identity of the substance/product as available on the market and predominant use

2.1. Predominant Use				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

2.2. Identity and Physical and chemical properties of the substance and product to be used				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
1)	3. Specification of the substance, p. 2	EFSA: The applicant should clarify what is exactly the substance and should provide a detailed specification. Under point 3.1 the substance is defined as Poly-s-(1,4)-2-Amino-2-deoxy-D-glucose hydrochloride. However, as already noted by the applicant (Paragraph 5, p. 5 of the Application) "the term Chitosan embraces a multitude of derivatives, which differ with regard to their chemical-physical properties...", chitosan could not be regarded as a strictly defined chemical. The name chitosan is either used as a synonym of 1) Poly-D-Glucosamine or of 2) a polymer composed of D-glucosamin and N-acetyl-D-glucosamin. Thus the use of chitosan hydrochloride as a synonime of	Identity, physical properties, specifications, batch analysis and methods of analysis are provided in sections 2.2.1 - 2.2.7 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. A justification for the comparability of the chitosan from the EFSA assessment on food grade chitosan and the chitosan under consideration here is presented under section 2.2.5 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	Additional information for the identity has been provided in the revised version of the application for approval of chitosan hydrochloride as a basic substance in the context of Regulation (EC) No 1107/2009 (August 2012). It has been clarified that the substance is a polymer, consisting of the two units N-acetyl-D-glucosamine and D-glucosamine with an averaged MW of 47000-65000 Da. Therefore chitosan hydrochloride is not comparable with the material evaluated in the *Scientific Opinion of the NDA Panel of the safety of glucosamine hydrochloride from Aspergillus niger as food ingredient*, (EFSA Journal 1099: 1–

2.2. Identity and Physical and chemical properties of the substance and product to be used				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		Poly-s-(1,4)-2-Amino-2-deoxy-D-glucose hydrochloride is not always correct and could be misleading. There is no information provided for characterization (e.g. purity, content of impurities, degree of deacetylation, batch analysis) of the substance applied for approval. In order to consider the applied substance as comparable with the material evaluated in the *Scientific Opinion of the NDA Panel of the safety of glucosamine hydrochloride from Aspergillus niger as food ingredient*, where glucosamine hydrochloride is specified based on U.S. Pharmacopoeia, and the specification is supported by 5 batch analysis data *(*The EFSA Journal, 2009. **1099**: p. 6-7), a reasoned justification should be provided.		19. 2009), which is a monomer with a MW of 215.6 Da. A justification is provided in section 2.2.5 for the comparability of chitosan hydrochloride with chitosan, for which a Scientific Opinion of the EFSA's NDA Panel is available (*Scientific Opinion on the substantiation of health claims related to chitosan and reduction in body weight (ID 679, 1499), maintenance of normal blood LDL-cholesterol concentrations (ID 4663), reduction of intestinal transit time (ID 4664) and reduction of inflammation (ID 1985) pursuant to Article 13(1) of Regulation (EC) No 1924/20061*, EFSA Journal 2011;9(6):2214. It should be highlighted however that this Opinion on chitosan *"does not constitute, and cannot be construed as ..... a positive assessment of its safety"* (Appendix B to the Opinion). It should also be noted that the specification provided in section 2.2.5 (p.11) is slightly different (no chlorides have been specified and the heavy metals content is ten times higher) than the composition of

2.2. Identity and Physical and chemical properties of the substance and product to be used				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				chitosan hydrochloride described in the European Pharmacopeia 6.0. Furthermore, it should be noted that as the specification for heavy metals is given as a sum, no (eco)toxicological evaluation for the intended uses can be made. Therefore it is suggested that separate limits for the individual heavy metals should be set. It should be also clarified that by "impurities" in table 2.2.5 of the revised application actually total aerobic plate count, yeast and molds are meant.
2)		DE: Information/specification regarding the purity of chitosan hydrochloride and the identity and content of (possible) impurities is missing.	Information regarding purity, identity and possible impurities are provided in sections 2.2.5 - 2.2.6 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	See EFSA conclusion in comment 2.2(1).
3)		DE: It should be stated if information about analytical methods for chitosan hydrochloride and possible relevant impurities is available.	Information about analytical methods for chitosan and possible impurities are provided in section 2.2.7 of the revised version of the Proposal for approbation of basic substances, in the context of	Information about analytical methods has been provided in section 2.2.7 of the revised application (August 2012); the available analytical methods sufficiently cover the

2.2. Identity and Physical and chemical properties of the substance and product to be used				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
			Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	specification for chitosan hydrochloride (as presented in section 2.2.5 of the revised application). See also EFSA conclusion in comment 1(1).

2.3. Current, former and in case proposed trade names of substances/products as put on the market				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

2.4. Manufacturer of the substance/products				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

2.5. Type of preparation				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

2.6. Description of the recipe for the product to be used				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
4)	5.1 Application and effects of Chitosan hydrochloride in the protection of plants	DE: It is not clear whether chitosan hydrochloride or a 0.5 % solution thereof is placed on the market. Either information about the preparation (composition, name) or the recipe for the product to be used are missing.	Information on the preparation and recipe are provided in section 2.5 - 2.6 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	It has been clarified in sections 2.5 - 2.6 of the revised application (August 2012) that chitosan hydrochloride is water soluble powder, which is used by the end applicant to prepare an aqueous solution with a maximum concentration of 1% (w/w).

2.7. Function on plant protection				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

3. Uses of the substance and its product

3.1. Field of use				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
1)	3.1 Field of use	FR: The field of use must be specified		It has been clarified in the revised application (August 2012) that the field of use envisaged includes outdoor and field use (agriculture, horticulture), greenhouse, gardening and indoor use.

3.2. Effects on harmful organisms or on plants				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

3.3. Summary of intended uses				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
2)	5.1 Application and effects of chitosan hydrochloride in the protection of plants, p.7	EFSA: no table provided Information on the effects of chitosan hydrochloride is presented, however it is not clear what exactly are the intended uses.	A summary of intended uses is provided in section 3.3 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	A summary of intended uses is provided in the revised application. Chitosan hydrochloride is intended to be used for all crops as a plant elicitor.

3.3. Summary of intended uses				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
3)	3.3 Summary of intended uses	FR: A clear summary of intended uses has to be provided following the template in the document "Basic substance application model".	A summary of intended uses is provided in section 3.3 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	A summary of intended uses is provided in the revised application. It should be made clear that the units for the application rate are 'g/ha' and the in-use concentration is given in 'g/hL'. See also comment 3.3(2) above.

4. Classification and labelling of the substance

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5. Impact on Human and Animal Health

5.1. Effects having relevance to human and animal health arising from exposure to the substance/its products or to impurities				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
1)	General	EFSA: for the assessment of chitosan health effects no relevant EU evaluations are available: the EFSA NDA Panel assessment (2009) refers to the monomer D-glucosamine hydrochloride and not to the polymer; the BfR assessment is in German and as such cannot be assessed (only a summary is available); the US EPA 2008 assessment does not allow for an independent assessment of the mentioned data waivers. Limited toxicological data are available to define the hazard of chitosan.	Extensive information on chitosan health effects is provided in section 5.1 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. Among these information there is an EFSA assessment of chitosan health claims from June 2011. Extensive toxicological data on chitosan and its derivatives is provided in section 5.2 - 5.14 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. The most part of references provided here, has been provided already in the first draft of the application for registration of chitosan hydrochloride from December 2011.	See EFSA conclusion in comment 2.2(1). Chitosan hydrochloride is not considered comparable with the material evaluated in the *Scientific Opinion of the NDA Panel of the safety of glucosamine hydrochloride from Aspergillus niger as food ingredient*, (EFSA Journal 1099: 1–19. 2009). Concerning the EFSA assessment of chitosan health claims from June 2011 **(**EFSA Journal 2011;9(6):2214), it should be highlighted that this Opinion on chitosan *"does not constitute, and cannot be construed as ..... a positive assessment of its safety"* (Appendix B to the Opinion). Therefore, reference to these publications is not sufficient to address the toxicological profile of the active substance. The toxicological data provided in the revised application were not adequately reported. (It is not clear whether the monomer or the polymer was tested. Also the validity of the

5.1. Effects having relevance to human and animal health arising from exposure to the substance/its products or to impurities				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				studies (all published) cannot be judged.) Therefore, the data available do not allow to draw a conclusion on the toxicity of chitosan hydrochloride.
2)	General	EFSA: the identity of the compound chitosan has to be defined to further check its toxicological relevance in the frame of the definition of what a basic substance is.	Identity, physical properties, specications, batch analysis and methods of analysis are provided in sections 2.2.1 - 2.2.7 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	See EFSA Conclusion in comment 2.2(1). As it is currently provided, the specification is not precise enough (e.g. regarding heavy metals) to allow an appropriate evaluation to be performed.

5.2. Toxicokinetics and metabolism in humans				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.3. Acute toxicity				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.4. Short –term toxicity				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.5. Genotoxicity				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.6. Long-Term toxicity				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.7. Reproductive toxicity				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.8. Neurotoxicity				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.9. Toxicity studies on metabolites				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.10. Medical Data adverse effects reported in humans				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.11. Additional Information related to therapeutic properties or health claims				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.12. Additional information related to use as food				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.13. Acceptable daily intake, acute reference dose, acceptable operator exposure level				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

5.14. Impact on human and animal health arising from exposure to the substance or impurities contained in it				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

6. Residues

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
1)	6. Assessments of chitosan and D-glucosamine	EFSA: The crops and intended uses for CHITOSAN should be clarified. No risks to consumers envisaged, unless toxicological concerns are raised in the Phys-Chem or Tox. sections.	A summary of intended uses is provided in section 3.3 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. Further information on residues is provided in section 6. of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	Information on the intended uses is provided in the revised application of August 2012. Chitosan hydrochloride is intended to be used on all crops at a maximum rate of 4000 g/ha per application and per week, with a PHI of 0 day. Chitosan hydrochloride is not comparable with the material evaluated in the *Scientific Opinion of the NDA Panel of the safety of glucosamine hydrochloride from Aspergillus niger as food ingredient*, (EFSA Journal 1099: 1–19. 2009), and therefore, reference to this publication is not sufficient to address the toxicological profile of the active substance. The consumer risk assessment cannot be finalised and it is pending on the conclusion on the toxicity of the active substance chitosan hydrochloride.

7. Fate and Behaviour in the environment

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
1)	1.12. Fate and behaviour in the environment	EFSA: An EU evaluation relevant for environmental fate and behaviour assessment is not referred to so it is probably not available. Therefore derogation from Article 4 of the Regulation is not possible. Information on '*its fate and distribution in the environment, particularly contamination of surface waters, including estuarine and coastal waters, groundwater air and soil taking into account locations distant from its use following long-range transport need to have been addressed in the application*', as required by the Regulation.	An EFSA evaluation for chitosan as food is dated to June 2011. According to Regulation (EC) №1107/2009, Article 23 (1): "For the purpose of this Regulation, an active substance which fulfils the criteria of a 'foodstuff' as defined in Article 2 of Regulation (EC) No 178/2002 shall be considered as a basic substance." From this there should be no further need for environmental fate and behaviour assessment. However, as requested further information on the environmental fate of chitosan is provided in section 7 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. The most part of this information has been provided already in the first draft of the application for registration of chitosan hydrochloride from December 2011.	The available evaluations of chitosan hydrochloride or related molecules as food do not contain any assessment of the potential exposure of the environment to chitosan hydrochloride and corresponding environmental risk assessment, relevant to the proposed uses for plant protection. Therefore derogation from Article 4 of the Regulation (EC) No 1107/2009 is not possible with respect to environmental assessment. Information on '*its fate and distribution in the environment, particularly contamination of surface waters, including estuarine and coastal waters, groundwater, air and soil taking into account locations distant from its use following long-range transport need to have been addressed in the application*', as required by the Regulation.
2)	1.12. Fate and behaviour in the environment	EFSA: As indicated in the comments to 2.2 the chemical identity of the substance presented to be considered as a basic substance is not clearly specified. Without a clear specification of the	Identity, physical properties, specifications, batch analysis and methods of analysis are provided in sections 2.2.1 - 2.2.7 of the revised version of the Proposal for approbation of basic substances, in the	The substance chitosan hydrochloride proposed as a basic substance would need a specific exposure assessment since its specifications are not covered by substances assessed

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
		substance under consideration, an environmental risk assessment cannot be performed. Also it would not be possible to assess the relevance of an existing risk assessment (if available) under another EU legislation.	context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	previously. Explanatory note: As indicated in point 2.2(1), it has been clarified that the substance is a polymer, consisting of the two units N-acetyl-D-glucosamine and D-glucosamine, with an averaged MW of 47000-65000 Da. Therefore chitosan hydrochloride is not comparable with the material evaluated in the *Scientific Opinion of the NDA Panel of the safety of glucosamine hydrochloride from Aspergillus niger as food ingredient*, (EFSA Journal 1099: 1–19. 2009), which is a monomer with a MW of 215.6 Da. In addition, it should be also noted that the specification provided in section 2.2.5 (p.11) is slightly different (no chlorides have been specified and the heavy metals content is ten times higher) than the composition of chitosan hydrochloride described in the European Pharmacopeia 6.0.

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
3)	1.12. Fate and behaviour in the environment	EFSA: Intended agricultural uses are not clearly defined in terms of: -pest for which it is demonstrated to give protection -application technique (spraying, seed treatment etc…) -application rates (per application/per quantity of seed and per annum) -crops Without this information an environmental risk assessment cannot be performed. Also it would not be possible to assess the relevance of an existing risk assessment (if available) under another EU legislation with respect to the agricultural use. See comment in 3.3	A summary of intended uses is provided in section 3.3 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. Application techniques and application rates have been provided already in the first draft of the application for registration of chitosan hydrochloride from December 2011.	In the intended uses table (section 3.3 of the revised application) the application rate is ambiguous (see EFSA conclusion in comment 3.3(3)). If it is assumed that the table refers to 4000 g / ha (as indicated in section 6 of the application), this will result in an annual application of 208 kg/ha (52 x 4 kg/ha), since any possible crop is intended for plant protection purposes. No predicted environmental concentration in the different environmental compartments has been presented. No data on levels encountered in the environment as natural background level or as resulting of other authorised uses of this substance are presented. At these application rates levels of relevant impurities such as heavy metals may need to be considered in the environmental assessment. EFSA calculated worst case initial PEC for soil (based on an annual application of 208 kg/ha). PEC soil initial = 277 mg chitosan

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				hydrochloride / kg soil. Whereas no information is provided on the natural background level for chitosan hydrochloride and related compounds, this level would be clearly above any naturally existing level. Also, it is expected to be higher than levels resulting from the currently authorised uses of chitosan hydrochloride for purposes other than plant protection. No estimation of initial PEC_{SW} has been provided by the applicant. Since the use is proposed for any crop, an assessment would be needed to identify those crops, for which the proposed use will result in worst case with respect to surface water exposure.
4)	1.12. Fate and behaviour in the environment	EFSA: The applicant should provide a detailed summary of the papers presented to support the fate and behaviour assessment of chitosan in the environment. Papers should be classified according to the point that the applicant intends to address with them (soil environment, aquatic environment, air).	A summary of the environmental fate of chitosan is provided in sections 7.1 -7.2 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. Sections 7.3 - 7.5 provide data on the fate in soil, aqueous environments and air. However, detailed information and references on the degradation of chitosan in	The applicant has not provided a detailed summary of the papers presented to support the fate and behaviour assessment of chitosan hydrochloride in the environment. Papers have not been classified according to the point that the applicant intends to address with them (soil environment, aquatic environment, air), and were not

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
			various environments have been provided already in the first draft of the application for registration of chitosan hydrochloride from December 2011.	adequately summarised and assessed with regard to the experimental methods employed and the results obtained. No specific environmental endpoints have been derived. The assessment presented by the applicant is in a narrative review style. General statements are made, presumably supported by a number of quoted references. However, when references were checked by EFSA, it was found that in some cases the references quoted were not relevant or related to the statement they are presumed to support (e.g. in some cases the papers only refer to chitin and no data on chitosan hydrochloride are available). In other cases the references seem to contain relevant and reliable information, but it has not been appropriately presented in relation to the uses proposed. It is the EFSA's view that a number of the papers quoted in the revised application may contain information that could eventually be used to derive endpoints relevant to the environmental risk assessment of chitosan hydrochloride for use in

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
				plant protection. Nevertheless, no proper and detailed analysis has been presented to allow a sound risk assessment to be performed. From the available information it may be expected that chitin and chitosan polymers are highly persistent in soil: DT_{50} > 100 d. (See e.g. Ref 227 Sato *et al*., 2010). Other papers provided less precise quantification (e.g. Ref 236 Mayer *et al.*, 1996 indicates that it takes weeks to degrade 10 µg / mm^2 of chitosan film in the soil test system used in that study). For papers not published in English (e.g. Ref 1 Domsch, 1960), no English translation or summary has been provided. It is also noted that in the dossier a number of copies of the scientific papers presented to support the application are not complete (e.g. Ref 230 Okafor, 1966, Ref 234 Gray and Bell, 1962).
5)	1.12. Fate and behaviour in the environment	EFSA: A number of the references provided relate to chitin but do not provide any useful information in relation to degradation of chitosan in the environment.	Information on the same molecular structure of chitin and chitosan and the synergistic and consecutive enzymatic systems are responsible for the degradation of chitin and chitosan are provided in section 7.1 of the	See EFSA conclusion in comment 4 above.

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
			revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. However, detailed information and references on the degradation of chitosan in various environments have been provided already in the first draft of the application for registration of chitosan hydrochloride from December 2011.	
6)	1.12 Fate and behaviour in soil	EFSA: Available information on chitosan polimers indicates that they may be degraded by soil organisms. On the other side some chitosan polymers are known to be antimicrobial agents against a variety of microorganism. No quantitative information seem to be available on the rate of degradation of chitosan polymers in soil. This is likely also to depend on the specifications of each particular chitosan polymer in terms of polymeric chain average weight. Further information on the fate and behaviour of the chitosan under consideration in soil is needed to be able to perform an environmental risk assessment. Ground water risk assessment could be needed if the chitosan under consideration is not proved to have been already assessed as a food ingredient (see comment 2.2).	Information on the synergistic and consecutive enzymatic systems responsible for the degradation of chitin and chitosan are provided in section 7.1 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. Further degradation rates for chitosan in soil are presented in section 7.3. The determining factor for degradation rate is not molecular weight, but deacetylation as referenced in section 7.1. This is due to the molecular mechanisms of the degrading enzymatic systems. However, detailed information and references on the degradation rates and mechanisms of chitosan in soil environments have been provided already in the first draft of the application for	See EFSA conclusion in comment 4 above.

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
			registration of chitosan hydrochloride from December 2011.	
7)	1.12 Fate and behaviour in water	EFSA: No data or study presented in the application seems to be addressing the fate and behaviour of chitosan in aquatic systems. Further information on the fate and behaviour of chitosan in water and water/sediment systems may be needed to complete the aquatic exposure assessment.	Information on the synergistic and consecutive enzymatic systems responsible for the degradation of chitin and chitosan are provided in section 7.1 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. Further degradation rates for chitosan in water are presented I section 7.4. The determining factor for degradation rate is not molecular weight, but deacetylation as referenced in section 7.1. This is due to the molecular mechanisms of the degrading enzymatic systems. However, detailed information and references on the degradation rates and mechanisms of chitosan in water environments have been provided already in the first draft of the application for registration of chitosan hydrochloride from December 2011.	The data presented on the degradation of chitosan hydrochloride in aquatic systems only refer to an experiment in an estuary. Whereas no precise estimation of half-life was done in these experiments, it may give indications that in this system DT_{50} of chitosan hydrochloride > 50 d.
8)	1.12 Fate and behaviour in air	EFSA: According to the information provided by the applicant, chitosan is intended to be applied by spraying. Therefore, data on its persistence in air would be needed.	Information on the fate of chitosan solution in the air is provided in section 7.5 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to	No relevant scientific data are provided in relation to the persistence of chitosan hydrochloride in air. No estimation of the troposphere half-life or long-range transport of the

No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
			approve chitosan hydrochloride.	substance is available.

8. Effects on non target species

8.1. Effects on terrestrial vertebrates				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
1)	General, effect on non-target species	EFSA: It is noted that no data were available on non-target species and an EU evaluation relevant for ecotoxicological risk assessment is not referred to, so is probably not available. Therefore derogation from Article 4 of the regulation is not possible. Information on the effects to non-target organisms, according to the regulation, should be provided.	Information on non-target organisms is provided in sections 8.1 - 8.7 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride. However, large part of the information and references on effects on non-target organisms have been provided already in the first draft of the application for registration of chitosan hydrochloride from December 2011.	In the revised version of the application for approval of chitosan hydrochloride as a basic substance submitted in the context of Regulation (EC) No 1107/2009, no information was available for terrestrial vertebrates, aquatic organisms, non-target arthropods, terrestrial non-target plants or effects on biological methods of sewage treatment plants. Some information was referenced for bees and soil organisms, but the risk was not addressed. Overall, it is considered that the scientific information provided to address the risk to non-target species is not relevant, except for soil microorganisms.

8.2. Effects on aquatic organisms				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

8.3. Effects on bees and other arthropods species				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application
2)		DE: No information has been provided by the applicant with regard to effects on bees and other arthropods. It has not been reasoned that the substance is harmless for bees and other arthropods.	Information on the effect of chitosan on bees is provided in sections 8.3 of the revised version of the Proposal for approbation of basic substances, in the context of Regulation (EC) №1107/2009 to approve chitosan hydrochloride.	See EFSA conclusion in comment 8.1(1) above. Overall, the information available is not sufficient to conclude on the risk to bees and non-target arthropods.

8.4. Effects on earthworms and other soil macro-organisms				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

8.5. Effects on soil micro-organisms				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

8.6. Effects on other non target organisms (flora and fauna)				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

8.7. Effects on biological methods of sewage treatment				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

9. Overall conclusions with respect of eligibility of the substance to be approved as basic substance

Other comments				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

10. Other comments

Other comments				
No.	Column 1 Reference to Application Template	Column 2 Comments from Member States / EFSA	Column 3 Follow up response from applicant	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the application

No comments.

ABBREVIATIONS

µg	microgram
µm	micrometer (micron)
a.i.	active ingredient
a.s.	active substance
BfR	Bundesinstitut für Risikobewertung (The Federal Institute for Risk Assessment in Germany)
d	day
Da	dalton
DT_{50}	period required for 50 percent disappearance (define method of estimation)
EPA	Environmental Protection Agency (USA)
EU	European Union
g	gram
ha	hectare
hL	hectolitre
kg	kilogram
L	litre
LDL	low-density lipoprotein
mg	milligram
mL	millilitre
mm	millimetre
MW	molecular weight
NDA	Panel on Dietetic Products, Nutrition and Allergies (EFSA)
PEC	predicted environmental concentration
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
PHI	pre-harvest interval
PPP	plant protection product
w/w	weight per weight