DELIVERABLE 6.1

Title: Food regulatory status of the substances intended to be used for the NanoPack active packaging system

Date: 31/03/2017

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Project funded by the European Commission within the Horizon 2020 Programme (2014- 2020)		
Dissemination Level		
PU	Public	X
PP	Restricted to other programme participants (Including the Commission Services)	
RE	Restricted to a group specified by the consortium (Including the Commission Services)	
CO	Confidential, only for members of the consortium (Including the Commission Services)	

This project has received funding from the European Union's
Horizon 2020 research and innovation programme under grant agreement No 720815.

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Document Change Log

Version	Date	Comments
v0.1	14.3.2017	First draft of document
v0.2	20.3.2017	Revised version based on the comments Ester Segal, Technion, Helle Buchardt Boyd, DHI and , Margrethe Winther-Nielsen, DHI
v0.3	28.3.2017	Revised version based on the comments of Simon van Dam, Agora
v1.0	30.3.2017	Final version, approved by Executive Board for submission to EC.

Document Distribution Log

Version	Date	Distributed to
V0.3	28.3.2017	All partners involved in the scientific Working Group
V1.0	28.3.2017	EUFIC for insertion of new logo and project graphics

Verification and approval

	Name	Date
Verification Final Draft by WP leader	Dr. Angela Störmer	28.3.2017
Approval Final Deliverable by coordinator	Prof Ester Segal	28.3.2017

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Table of Contents

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1 Executive Summary

NanoPack will demonstrate a solution for extending food shelf life by using novel smart antimicrobial surfaces, applied in active food packaging products. It will run pilot lines in operational industrial environments to manufacture commercially feasible antimicrobial polymer films. The project will employ natural Halloysite Nanotubes (HNTs) as carriers of bio-active compounds. At start of the project the food regulatory status of HNTs, possible modification substances and of the active compounds shall be evaluated.

The active components of the NanoPack system are the essential oils which act antimicrobially. In Europe, the candidate essential oils are listed and approved as flavouring substances but not for their antimicrobial application and will need specific approvals as food additives for this use. In the USA the candidate essential oils are either classified as generally recognized as safe (GRAS) or approved as synthetic flavouring substances. If used in concentrations not exceeding the concentrations in the applications as flavouring, approvals as flavouring components are considered as a good basis for approval as active components.

The halloysite nanotubes (HNTs) are related to the passive part of an active system and need to be in compliance with the Plastics Regulation (EU) No. 10/2011 in Europe. The halloysite mineral is a component of the mineral kaolin which is approved as an additive in the EU Plastics regulation but not as a nanomaterial. The nano-structure of the HNTs is considered to be no hindrance for approval because the HNTs are immobilised in the polymer and will not migrate into food. This will be experimentally verified within the NanoPack project. Only a part of the candidate modification substances is already approved as modificators for fillers. In any case, modified HNTs will need to be approved as food contact plastic additive.

Prior to issuing the Call for Proposals the need of food regulatory approvals for the use of anti-microbial systems in food packaging was considered by the EU as well as any potential need for adjusting the current governing regulatory regimes. NanoPack already considered and incorporated these issues into the design of the project. Necessary data for a dossier will be achieved in Work Package WP6 of the NanoPack project. The analyses of the finally developed materials will be designed such that they are suitable for the inclusion in dossiers for EFSA or FDA. The compilations of dossiers which shall be filed to EFSA are an integral part of the project. In order to exploit its full innovation potential, the approval process needs to be completed in order to introduce the NanoPack food packaging to the market. The food regulatory pre-evaluation at the beginning of the project did not identify major hindrances. The Consortium intends to periodically share information and results from the project during its lifetime with EU Commission (DG Sante), EFSA and FDA to allow these authorities a better understanding of the underlying technology and mode of action. Furthermore the Consortium plans to initiate an informal discussion with the authorities on the particular food regulatory aspects.

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2 General food regulatory background

2.1 European Union

2.1.1 Active packaging material

The polymer films that will be developed within NanoPack are intended to release bio-active compounds to the headspace of the food or the food itself in order to prolong the shelf life of the packed foods. Therefore the NanoPack product falls under the definition of an 'active' packaging material given in Art. 2 2.a) Framework Regulation (EC) No. 1935/2004 on materials and articles intended to come into contact with food. Art 4 of this Framework Regulation as well as the specific Regulation (EC) No 450/2009 on active and intelligent materials and articles intended to come into contact with foods apply.

According to Regulation (EC) No. 450/2009 only authorised substances may be used in components of active (and intelligent) materials and articles (Art. 5). Hereby, 'component' means an individual substance or a combination of individual substances which cause the active and/or intelligent function of a material or article, including the products of an *in situ* reaction of those substances; it does not include the passive parts, such as the material they are added to or incorporated into." (Art. 3 (c)). The components need to be included in the 'Community list' of authorised substances (Art. 5 1.). But this list has not been published by the EU Commission so far. Until the 'Community list' will be published and applied, national provisions in force concerning the composition of active and intelligent materials and articles apply. This means that it is necessary to submit applications for approval of components according to regulation 450/2009, but it might be possible to use such components according to national law.

EFSA has published opinions on the evaluation of various active systems (EFSA Journal). An EFSA opinion is the basis for evaluation of an active system according to the requirements of Art. 3 of Framework Regulation (EC) No. 1935/2004. Satisfying the requirements of Article 3 and, where they apply, Article 4 of Regulation (EC) No 1935/2004 for the intended condition of use is the base requirement for inclusion in the future Community list (Art. 6, Regulation (EC) 450/2009).

Released active substances which are already approved for use in food (e.g. as food additive) are exempt from inclusion in the 'Community list' if they will be used in full compliance with the relevant Community and national provisions applicable to food. Furthermore, it shall comply with the provisions of Regulation (EC) No 1935/2004 and, when applicable, its implementing measures. (Art. 5 2. (a) and Art. 9, Regulation (EC) 450/2009). The same is the case for substances which are added to or incorporated into active materials and articles by techniques such as grafting or immobilisation in order to have a technological effect in the food (Art. 5 2. (b)). In other words, if the substance is approved to be added into certain or all foods and the released substance complies with all rules given in the applicable food regulation, the substance will not be included in the 'Community list'.

The EU Guidance to the Commission Regulation (EC) No. 450/2009[1] specifies this requirement: If the released active substance performs a technological function on the food and the substance is not yet authorized, authorization under the legislation applicable to food additives needs to be requested. This means that the petition has to follow the EFSA data requirements for the evaluation of food additive applications[2] and the guidelines for submission for food additive evaluations[3] and will be evaluated by

[1] https://ec.europa.eu/food/sites/food/files/safety/docs/cs_fcm_legis_active-intelligent_guidance.pdf
[2] http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1188/pdf
[3] http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2760/pdf

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the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS). Summarising, it is a prerequisite for going into market with such an active system, that releases substances with technological function in or on the food are approved as food additives for use in these food types for which the active packaging system is intended.

Petitions for other active substances or components which shall be included in the 'Community list' for active materials and articles, have to follow the 'Guidelines on submission of a dossier for safety evaluation by the EFSA of active or intelligent substances present in active and intelligent materials and articles intended to come into contact with food'[4]. They will be evaluated by the EFSA Panel on food contact materials, enzymes, flavourings and processing aids (CEF).

2.1.2 Passive parts of the active packaging material

The passive parts of the active packaging are all substances that do not contribute to the active function. Passive parts are e.g. carrier substances but also the layer in which the active components are incorporated. This means in the case of incorporation of the active substances in a polyolefin layer that the polymer and the carrier substances have to comply with the Plastics Regulation (EU) No. 10/2011.

All monomers, other starting substances and additives need to be authorised and included in the Union list in Regulation (EU) 10/2011. For substances that are not yet included in the list, a dossier has to be submitted to EFSA following the guidelines for food contact materials[5]. It will be evaluated by the EFSA Panel on food contact materials, enzymes, flavourings and processing aids (CEF).

2.1.3 Food additives

Food additives are substances that are not normally consumed as food itself but are added to food intentionally for a technological purpose such as the preservation of food (Regulation (EC) No. 1333/2008, Recital 5). Food additives must be approved and used only if they fulfil the criteria laid down in Regulation No. 1333/2008. Food additives must be safe when used, there must be a technological need for their use, and their use must not mislead the consumer and must be of benefit to the consumer (Recital 7). Substances should not be considered as food additives when they are used for the purpose of imparting flavour and/or taste (Recital 5). But if flavouring substances are used as food additives, they fall under the scope of Regulation (EC) 1333/2008 (Art. 2 2.(e)).

Regulation (EC) 1333/2008 rules the approved food additives (Community lists), their uses and their labelling. Specifications, e.g. purity criteria, are laid down in Regulation (EU) 231/2012.

2.2 USA

Food additives are defined in Section 201, § 321 (s) of the Federal Food, Drug, and Cosmetic Act as "Any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food." Food additives need clearance from the US Food and Drug Agency (FDA). Substances that are generally recognized as safe (GRAS), "prior sanctioned," or not reasonably expected to become components of food (no migration exemption) are excluded from needing FDA clearance. General regulations for polymers or polymer additives are laid down in the Code of Federal Regulations 21 (21 CFR) (FDA). Since 1997 FDA clearances are provided mainly as Food Contact Notifications (FCN) which are proprietary to the notifier and the manufacturer/supplier listed in the FCN. The FCN is related only to

[4] http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2009.1208/pdf
[5] http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2008.21r/pdf

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the notified product but not to similar products from others. Active packaging materials are not specifically regulated but tackled within the system for all packaging materials.

3 Food regulatory status of Halloysite nanotubes (HNTs) and possible chemicals for HNT modification

3.1 European Union

3.1.1 Food regulatory background

The halloysite nanotubes (HNTs) are intended to be the carriers of the active substances (i.e. essential oils). HNTs are loaded with the essential oils and in a second step the loaded HNTs are introduced into a polymer (e.g. polyethylene) by melt compounding. The HNTs remain in the polymer, whereas the essential oils are intended to migrate to the headspace of the packaged food or the surface of the food. Thus, the essential oils are the active components as defined in Regulation (EC) No. 450/2009 and the HNTs belong to the passive part of the active packaging system.

Therefore, the applicable law for the HNTs is the Plastic Regulation (EU) 10/2011. The nanotubes or the modified nanotubes are considered to be plastic additives. Substances in nanoform need to be explicitly authorised (Art. 9 2.). The nanoform needs to be mentioned in the column "Specification" in Annex I of the Regulation.

3.1.2 Halloysite nanotubes (HNTs)

Halloysite is a clay mineral ($Al_2[(OH)_4/Si_2O_5] \cdot 2\,H_2O$) which is assigned to the kaolinite group. These are layered silicas, composed of a tetrahedric [SiO_4] and a octahedric [$Al_2(OH)_4O_2$] layer. In case of the HNTs, the layered silicate is not planar but forms rolls[6]. HNTs are naturally occurring materials and are mined.

HNTs are not yet authorised as components of plastic food packaging materials. They are not included in the 'Union list' of Plastic Regulation (EU) 10/2011. Other nanotubes, e.g. carbon nanotubes, are not included either.

The mineral kaolin (CAS 1332-58-7) is mainly composed of halloysite or kaolinite[6]. Kaolin is listed as additive in the 'Union list' of Plastic Regulation (EU) 10/2011 without specific restriction (FCM no. 410). But the authorisation is related to the bulk material only and not to a specification as nanomaterial.

3.1.3 Evaluation of candidate substances for HNT modification

In order to improve the properties of the HNTs, their chemical modification may be required. Possible modification reactions are adding of phosphonic acid derivatives and/or silanes.

The food regulatory status related to Plastics Regulation (EU) 10/2011 of the candidate substances is summarised in Table 1 and Table 2. SML means the specific migration limit in food or food simulant. Some of the substances are approved in combination with the modified additive/filler only. In this case, the approved substance is inserted in the column "Specification or remarks". In case of substances which are not listed in Regulation 10/2011, other toxicological data (especially on mutagenicity tests), if found, are added.

[6] Roempp (online), © 2017 Georg Thieme Verlag KG

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Table 1: Phosponic acid candidate substances and their food regulatory status in Plastics Regulation (EU) No. 10/2011 or other relevant data for evaluation

Substance name	CAS	Union list 10/2011	FCM No.	SML [mg/kg]	Specification or remarks
Ethylphosphonic acid	6779-09-5	no			
Butylphosphonic acid	3321-64-0	no			
Vinylphosphonic acid	1746-03-8	no			
n-Octylphosphonic acid	4724-48-5	additive	483	0.05	
[Aminotris(methylenephosphonic acid), penta sodium salt]	2235-43-0				titanium dioxide, coated with a copolymer of n-octyltrichlorosilane and [aminotris(methylenephosphonic acid), penta sodium salt], FCM 805[7]

Table 2: Silane candidate substances and their food regulatory status in Plastics Regulation (EU) No. 10/2011 or other relevant data for evaluation

Substance name	CAS	Union list 10/2011	FCM No.	SML [mg/kg]	Specification or remarks
Hexadecyltrimethoxysilane	16415-12-6	no			ECHA: OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test) negative
Trichloro(hexyl)silane	928-65-4	no			
Chloro(dimethyl)octadecyl-silane	18643-08-8	no			
Chlorodimethylethylsilane	6917-76-6	no			
Trichloro(hexyl)silane	928-65-4	no			
Chloro(dimethyl)octylsilane	18162-84-0	no			
Vinyltriethoxysilane	78-08-0	Monomer/ starting substance	142	0.05	Only to be used as a surface treatment agent
3-Aminopropyltriethoxysilane	919-30-2	Monomer/ starting substance	377	0.05	Residual extractable content of 3-aminopropyltriethoxysilane to be less than 3 mg/kg filler when used for the reactive surface treatment of inorganic fillers. SML = 0,05 mg/kg when used for the surface treatment of materials and articles.
Vinyltrimethoxysilane	2768-02-7	Monomer/ starting substance	453	0.05	

[7] EFSA opinion http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2008.816/pdf

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Table 2 (continuing): Silane candidate substances and their food regulatory status in Plastics Regulation (EU) No. 10/2011 or other relevant data for evaluation

Substance name	CAS	Union list 10/2011	FCM No.	SML [mg/kg]	Specification or remarks
[3-(Methacryloxy)propyl] trimethoxysilane	2530-85-0	Monomer/ starting substance	788	0.05	Only to be used as a surface treatment agent of inorganic fillers
n-Octyltriethoxysilane	2943-75-1				titanium dioxide reacted with octyltriethoxysilane, FCM 873[8]
n-Octyltrichlorosilane	5283-66-9				titanium dioxide, coated with a copolymer of n-octyltrichlorosilane and [aminotris(methylenephosphonic acid), penta sodium salt], FCM 805[7]

3.1.4 Evaluations by German BfR

A search was performed in the Database BfR Recommendations on Food Contact Materials[9] for the substances that are not included in the Plastics Regulation (EU) No. 10/2011. None of the substances was found in the database.

3.2 USA

The HNTs are not expected to be released from the packaging material. Therefore, the "no migration exemption" might be applied. The modification agents are expected not to be completely bound to the HNTs and to migrate at least in traces out of the packaging material. Thus, the modification agents need a FDA clearance. To summarise, the modified HNTs will need a Food Contact Notification (FCN) when intended to be marketed in USA.

Kaolin is affirmed as GRAS when used in the manufacture of paper and paperboard that contact food according to 21 CFR §186.1256 'Clay (kaolin)'. Neither the phosphonic acids nor the silanes from the tables above are listed in 21 CFR[10].

[8] EFSA opinion: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2003/pdf
[9] https://bfr.ble.de/kse/faces/DBEmpfehlung_en.jsp?filter=clear; search by CAS No.
[10] Search by List of Indirect Additives Used in Food Contact Substances: https://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/IndirectAdditives/ucm115333.htm

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4 Food regulatory status of active substances

4.1 European Union

4.1.1 Food regulatory background

The active antimicrobial substances are essential oils. The main application of essential oils is flavouring, i.e. imparting flavour and/or taste. In this application the essential oils are not regarded as food additives but regulated by Regulation (EC) 1334/2008 and the 'Commission list' (Annex I) of approved flavouring substances which was established in the amendment Regulation (EU) No 872/2012, lastly amended by Regulation (EU) 2016/1244. The intended effect in the NanoPack project is acting antimicrobially. In this application the essential oils fall under the definition of food additives and are therefore under the scope of Regulation (EC) 1333/2008.

In the community lists of food additives of Regulation (EC) 1333/2008 (last amendment 2016/1776) essential oils are not yet included. Only extract from rosemary is listed as an antioxidant for specific applications. But in this case the phenolic compounds (carnosol, carnosol acid) are the relevant ingredients rather than the essential oils. Flavouring components can be removed before use of rosemary extracts as an antioxidant[6].

All flavouring substances in Annex I of Regulation (EC) 1334/2008 have been evaluated by EFSA (CEF panel) for safety or former evaluations e.g. by JECFA have been adopted by the panel. The toxicological data basis for evaluation of existing flavouring compounds does not necessarily correspond to the requirements for evaluation of a new food additive. In the case of NanoPack, where the essential oils are used as active antimicrobial ingredients, the concentration in the food will not exceed the concentrations when these materials are added as flavouring compound or in the form of herbs but shall be intended to act at lower concentrations, which do not affect the sensory properties of the food. Therefore, listing of the substances as approved flavourings is considered as a basis for future approval as active components.

4.1.2 Evaluation of candidate active substances

The candidate essential oils with antimicrobial activity are thymol, carvacrol, citral, menthol, linalool, geraniol and essential oils from spices (e.g. rosemary oil). The single substances, i.e. defined chemical substances with flavouring properties are 'flavouring substances' according to the definition in Art. 3 2. (b) of Regulation (EU) 1334/2008. All these six flavouring substances are listed without specific restriction of use in Annex I of Regulation (EU) 1334/2008 (see Table 3). Preparations from spices or herbs (or other foods) are flavouring preparations (definition Art. 3 2. (d) (i)). Rosemary oil is obtained from a food (rosemary) 'by appropriate physical, enzymatic or microbiological processes either in the raw state of the material or after processing for human consumption by one or more of the traditional food preparation processes listed in Annex II' [of the Regulation]. Extraction, rectification and distillation fall under these 'traditional' preparation processes (amongst others). Those flavouring substances if gained from food may be used for flavouring without being listed in Annex I (Art. 8).

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Table 3: Listing in Annex I of Regulation (EU) 1334/2008, (last amendment Regulation (EU) No. 2016/1244). Footnotes referring to the evaluation documents are appended additionally to column 9.

-1	-2	-3	-4	-5	-6	-7	-8	-9
FL-Nr.	**Chemical name**	**CAS-Nr.**	**JECFA-Nr.**	**CoE-Nr.**	**Purity**	**Restric-tion of use**	**foot note**	**evaluated by**
2.012	Geraniol	106-24-1	1223	60	≥ 95 %			EFSA[11]
2.013	Linalool	78-70-6	356	61	≥ 95 %			JECFA[12]
2.015	Menthol	89-78-1	427	63	≥ 95 %			JECFA[13]
4.006	Thymol	89-83-8	709	174	≥ 95 %			EFSA[14]
4.031	Carvacrol	499-75-2	710	2055	≥ 95 %			EFSA[14]
5.020	Citral	5392-40-5	1225	109	≥ 95 %			EFSA[11]

Thymol, carvacrol, citral, geraniol are classified in toxicity 'Class I' with a threshold of concern of 1800 µg/person/day according to the EFSA opinions. All four substances are evaluated by JECFA as "No safety concern at current levels of intake when used as a flavouring agent" or by EFSA "No safety concern at estimated level of intake as flavouring substance based on the MSDI[15] approach". The EFSA Panel had agreed to this JECFA conclusion in all four cases. All the four substances are considered not to be genotoxic. For all four substances genotoxicity studies are reported in the EFSA opinions.

Linalool is evaluated by JECFA with an acceptable daily intake (ADI) of 0-0.5 mg/kg b.w. (corresponds to 30 mg/person/day [16]) and Menthol with an ADI of 0-4 mg/kg b.w. (corresponds to 240 mg/person/day).

Thymol and carvacrol have been evaluated by the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) to be safe for all animal species at a maximum level of 5 mg/kg complete feed[17].

[11] EFSA (2013): Scientific Opinion on Flavouring Group Evaluation 72, Revision 1 (FGE.72Rev1): Consideration of aliphatic, branched-chain saturated and unsaturated alcohols, aldehydes, acids, and related esters evaluated by the JECFA (61st meeting) structurally related to branched- and straight-chain unsaturated carboxylic acids, esters of these and straight-chain aliphatic saturated alcohols evaluated by EFSA in FGE.05Rev21. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). EFSA Journal 2013;11(10):3392
[12] http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=4144
[13] http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=1519
[14] EFSA (2008) Flavouring Group Evaluation 58 (FGE.58). Consideration of phenol derivatives evaluated by JECFA (55th meeting) structurally related to ring substituted phenolic substances evaluated by EFSA in FGE.22 (2006). Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in contact with Food (AFC). EFSA Journal (2008) 711, 1-50
[15] EU MSDI: Amount added to food as flavour in
(kg / year) x 10E9 / (0.1 x population in Europe (= 375 x 10E6) x 0.6 x 365) = µg/capita/day.
[16] Conventionally body weight (b.w.) of 60 kg assumed
[17] EFSA (2012). "Scientific Opinion on the safety and efficacy of phenol derivatives containing ring-alkyl, ring-alkoxy and side-chains with an oxygenated functional group (chemical group 25) when used as flavourings for all species (EFSA Panel on Additives Products or Substances used in Animal Feed)." EFSA Journal **10**(2): 2573

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4.2 USA

Citral (2,6-dimethyloctadien-2,6-*al*-8, gera-nial, neral), geraniol (3,7-dimethyl-2,6 and 3,6-octadien-1-*ol*), linalool (linalol, 3,7-dimethyl-1,6-octadien-3-*ol*) are generally recognised as safe (GRAS) in the USA according to 21 CFR §182.60 'Synthetic flavoring substances and adjuvants'. Menthol is generally recognized as safe when obtained from Mentha spp. according to 21 CFR §182.20 'Essential oils, oleoresins (solvent-free), and natural extractives (including distillates)'. In this chapter rosemary is listed as well. Carvacrol and thymol are listed in CFR 21 §172.515 'Synthetic flavoring substances and adjuvants' with the restriction to be 'used in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice'. A food contact notification with active antimicrobial application of these substances does not exist.

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5 Conclusions & Next Steps

The active components of the NanoPack system are the essential oils which act as antimicrobials. In Europe, the candidate essential oils are listed and approved as flavouring substances but not for their antimicrobial application. They will need specific approvals for this use. In the USA the candidate essential oils are either classified as generally recognized as safe (GRAS) or approved as synthetic flavouring substances. If used in concentrations not exceeding the concentrations in the applications as flavouring, approvals as flavouring components are considered as a good basis for approval as active components.

The halloysite nanotubes (HNTs) are related to the passive part of an active system and need to be in compliance with the Plastics Regulation (EU) No. 10/2011 in Europe. The halloysite mineral is a component of the mineral kaolin, which is approved as additive in the EU Plastics regulation but not as nanomaterial. The nano-structure of the HNTs is considered to be no hindrance for approval because the HNTs are immobilised within the polymer and are not expected to migrate into food. This will be experimentally verified within the NanoPack project. Only a part of the candidate modification substances are already approved as modificators for fillers. In any case, modified-HNTs will need to be approved as additive.

Prior to issuing the Call for Proposals the need of food regulatory approvals for the use of anti-microbial systems in food packaging was considered by the EU as well as any potential need for adjusting the current governing regulatory regimes. Innovative solutions will need food regulatory approvals in the sensitive area of food packaging materials. They are not approved yet because of their novelty. The use of essential oils as antimicrobial agents is discussed in several research papers but not yet brought to market in the EU or the USA.

NanoPack already considered and incorporated these regulatory issues in the design of the project. Necessary data for a dossier will be achieved in Work Package 6 of the NanoPack project. The analyses of the finally developed materials will be designed such that they are suitable for the inclusion in dossiers for EFSA or FDA. The compilations of dossiers which shall be filed to EFSA are an integral part of the project. In order to exploit its full innovation potential, the approval process needs to be completed prior to introducing the NanoPack food packing to the market.

The food regulatory pre-evaluation at the beginning of the project did not identify major hindrances. The Consortium intends to periodically share information and results from the project during its lifetime with EU Commission (DG Sante), EFSA and FDA to allow these authorities a better understanding of the underlying technology and mode of action. Furthermore the Consortium plans to initiate an informal discussion with the authorities on the particular food regulatory aspects.

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